Community Approach Targeting Cirrhosis and Hepatocellular Carcinoma (CATCH): a new model of care for people living with chronic hepatitis B and C virus infection

Diana Jane Lewis

MBBS, FRACP

ID: 19435452

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School of Medicine, Nursing and Health Sciences

Eastern Health Clinical School

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Abstract

Background:

Australia has committed to eliminating chronic hepatitis B (CHB) and chronic hepatitis C (CHC) as public health threats by 2030.[1, 2] To meet these goals, rates of diagnosis, linkage into care and treatment need to increase significantly. Gaps in knowledge regarding the care of people living with CHB and CHC within Australia have occurred due to studies being performed in specific cohorts such as patients managed within a hospital system, extrapolation of data or those who develop the outcome of interest. Outside of these cohorts, the prevalence of cirrhosis; those with CHB who should be considered for antiviral therapy and who require hepatocellular carcinoma (HCC) surveillance is unknown. Rates of linkage into care with appropriate monitoring and treatment and risk of liver-related outcomes is also unknown due to the same limitations.

Aims:

The CATCH study is a prospective study of a new model of care with a community cohort of people living with CHB and/or CHC aimed at assessing whether (1) it can identify patients with cirrhosis or at higher risk of complications; (2) determine rates of adherence with medical management; and (3) determine the risk of liver-related outcomes.

Methods:

People living with CHB and/or CHC were prospectively recruited from 21 primary care practices around Victoria, Australia. With clinical, biochemical and liver stiffness measurement (LSM) assessment, the risk of advanced liver disease and/or complications were determined. Where appropriate, patients were referred onwards to a non-general practitioner (GP) specialist for management. For comparison, a standard of care (hospital-based management) cohort of patients was also recruited.

Results:

People living with CHC from a community cohort had a similar and high prevalence of cirrhosis (18.3%, based upon LSM and ultrasound findings) to a hospital cohort of patients (23.6%, p = .06). People living with CHB had a lower prevalence of cirrhosis in the community cohort (2.9% versus 8.9%, p = .01), however, the two cohorts had a similar percentage (~70%) of patients who had one of cirrhosis, in a hepatitis phase or needing HCC surveillance. People living with CHB and/or CHC from the community cohort were generally from lower

socioeconomic status than the hospital cohort. Overall, the community cohorts were less adherent with lower (1) repeat attendance rates within CATCH; (2) retention in non-GP specialist care; (3) HCC surveillance rates and (4) antiviral treatment rates. The CHC community cohort had a similar incidence of liver-related outcomes to the hospital cohort (HCC, decompensation and/or death due to liver disease), however, there were lower rates of HCC diagnosis in the community cohort.

Conclusion:

Community people living with CHB and/or CHC have similar risks for morbidity and mortality compared to a hospital cohort, however, lower adherence rates with medical management may have a negative impact on morbidity and mortality. Community management of people living with CHB and/or CHC needs to be explored further with changes to the models of care with a multi-pronged approach to meet the 2030 goals in Australia.

Declaration

This thesis is an original work of my research and contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature: Diana Lewis

Name: Dr Diana Jane Lewis

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Publications

No publications are presented within this thesis.

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Contribution of others to this thesis

Assoc. Professor John Lubel and Assoc. Professor William Kemp conceived the concept, designed and obtained funding for the CATCH study.

Assoc. Professor John Lubel, Assoc. Professor William Kemp and Professor Amanda Nicoll critically revised this thesis.

Dr Stephen Bloom set up the CATCH study and contributed to patient recruitment and data collection.

Dr Kelly Trezise contributed to the coding required for data cleaning and analysis.

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List of Abbreviations

ABS	Australian Bureau of Statistics
AFP	Alpha-fetoprotein
ALD	Alcoholic liver disease
ALT	Alanine transaminase
APRI	AST to platelet ratio index
ARFI	Acoustic radiation force impulses
ASHM	Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine
AST	Aspartate aminotransferase
AUROC	Area under the receiver operator curve
BCLC	Barcelona Clinic Liver Cancer
BMI	Body mass index
CAP	Controlled attenuation parameter
CATCH	Community Approach Targeting Cirrhosis and Hepatocellular carcinoma
CHB	Chronic hepatitis B virus infection
CHC	Chronic hepatitis C virus infection
CI	Confidence interval
CPS	Child–Pugh Score
CR	Complete response
CT	Computed tomography
DAA	Direct acting antiviral
DEB-TACE	Drug-eluting bead transarterial chemoembolisation
DNA	Deoxyribonucleic acid
DSM	Diagnostic and Statistical Manual of Mental Disorders
EASL	European Association for the Study of the Liver
ECM	Extracellular matrix
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
ECRU	Eastern Clinical Research Unit
FIB4	Mean fibrosis index based on four factors
FN	False negative
FOB	Faecal occult blood
FP	False positive
FRAGP	The Fellowship of the Royal Australian College of General Practitioners
FTA	Failure to attend
GGT	Gamma-glutamyl transferase
GP	General practitioner
HBeAg	Hepatitis B e-antigen
HBsAg	Hepatitis B surface antigen

HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
HVPG	Hepatic venous pressure gradient
INR	International normalised ratio
IQR	Interquartile range
IU/L	International units per litre
IVDU	Intravenous drug use
LFT	Liver function tests
Li-RADS	Liver Imaging Reporting and Data System
LSM	Liver stiffness measurements
METAVIR	Meta-analysis of Histological Data in Viral Hepatitis
MRE	Magnetic resonance elastography
mRECIST	Modified Response Evaluation Criteria in Solid Tumours
MRI	Magnetic resonance imaging
ms	Median stiffness
MWA	Microwave ablation
NAFLD	Non-alcoholic fatty liver disease
NBCSP	National Bowel Cancer Screening Program
NCSP	National Cervical Screening Program
NPV	Negative predictive value
OR	Odds ratio
PBS	Pharmaceutical Benefits Scheme
PCR	Polymerase chain reaction
PD	Progressive disease
PEI	Percutaneous ethanol injection
PHN	Primary health networks
PICF	Patient information and consent form
PPV	Positive predictive value
PR	Partial response
PWID	People who inject drugs
RFA	Radiofrequency ablation
RNA	Ribonucleic acid
ROC	Receiver operator curve
S100	Section-100
SBRT	Stereotactic beam radiology
SD	Standard deviation

SEIFA	Socio-Economic Indexes for Australia
SIR	Standardised incidence ratio
SIRT	Selective internal radiation therapy
SVR	Sustained virological response
SWE	Shear wave elastography
TACE	Transarterial chemoembolisation
TARE	Transarterial radiation therapy
TE	Transient Elastography
TGA	Therapeutic goods administration
TN	True Negative
TP	True Positive
US	Ultrasound
WHO	World Health Organisation
XL	Extra-large

Chapter 1. Introduction

Australia has committed to eliminating CHB and CHC as public health threats by 2030.[1, 2] The targets are to:

- Diagnose 90% of people living with CHB and/or CHC
- Treat 80% of patients eligible for treatment
- Achieve a 65% reduction in deaths due to complications of CHB and/or CHC compared to 2015

Despite this, these target aims are very unlikely to be met in Australia by 2030.[3]

To improve health outcomes for people living with CHB and/or CHC, multiple steps are required. Patients need to be diagnosed, aware of their diagnosis, linked into medical care to have appropriate monitoring and surveillance for complications such as HCC and finally treatment for the underlying disease if appropriate. There are multiple gaps that occur in care for patients, so to address this, the CATCH study was developed as a new model of care for people living with CHB and/or CHC in Australia. This new model of care was a community management program to detect patients who are at a higher risk of complications, many of which relate to the development of fibrosis and subsequently cirrhosis which in turn can lead to worse health outcomes with risk of decompensation, HCC and death. Determining the degree of fibrosis is therefore a critically important component of clinical management. Detection of fibrosis and cirrhosis can be performed in many ways including biopsy, elastographic methods and using biomarkers or risk scores which consider a combination of risk factors for cirrhosis and/or serological tests. Although liver biopsy is considered the gold standard, it is an imperfect test with relatively infrequent, yet significant risks; it is thus no longer used as the standard assessment for diagnosis of cirrhosis.[4] Indirect biomarker algorithms use a combination of clinical and biochemical features that are associated with higher risk of progression to or as a feature of cirrhosis. These indirect biomarker algorithms include aspartate aminotransferase to platelet ratio index (APRI), mean fibrosis index based on four factors (FIB4) and Forn's Index. There are numerous methods of measuring liver stiffness using elastography techniques: transient elastography (TE), shear wave elastography (SWE), acoustic radiation force impulses (ARFI) and magnetic resonance elastography (MRE).[5] All of these methods produce a wave within the liver that displaces tissue, the speed of which is translated into liver stiffness measurements (LSM) which correlates with the degree of fibrosis within the liver.[5] The application of these techniques is painless and acceptable to patients.[5,

6] TE using FibroScan® has also shown to be cost effective: it is less expensive than liver biopsy [7] and has also been shown to increase rates of HCC diagnosis via diagnosis of cirrhosis with subsequent appropriate HCC surveillance.[8] People living with CHB with certain viral and host immune characteristics or cirrhosis benefit from antiviral treatment and treatment for CHC is widely available in Australia. Both CHB and CHC have very effective treatments with very clear treatment guidelines for both of these diseases in Australia.[9, 10] These guidelines also include appropriate HCC surveillance for patients who are at risk of developing this complication.[11]

There are multiple gaps in knowledge that exist regarding the care of people living with CHB and/or CHC within. Firstly, the percentage of people living with CHB and/or CHC who have factors that are associated with increased risk of morbidity and mortality is unknown. The existing knowledge regarding the prevalence of cirrhosis in Australia is based upon studies of specific populations such as patients managed within hospital settings, current patients who inject drugs (PWID), war veterans or refugee populations. Previous results from the CATCH study have shown a similar prevalence of elevated LSM as measured by FibroScan® in a CHC community cohort compared to a CHC hospital cohort of patients.[7, 12] There were lower rates of elevated LSM in a CHB community cohort compared to a CHB hospital cohort.[7] However, other measures of fibrosis including ultrasound and indirect biomarker algorithms have not been explored. Additionally, the percentage of people living with CHB who are at risk of HCC or who are in a viral phase where antiviral therapy should be considered (hepatitis phase) is also unknown outside of PWID, hospital cohorts or based upon extrapolation of overseas data.[13-19] It is also unclear whether these community patients adhere to monitoring and treatment.[20, 21] Lastly, although the overall risk of liver-related outcomes due to CHB and CHC is known, this knowledge is also based upon pre-existing literature assessing specific populations.[13, 22-26]

The aim of this thesis is to explore and highlight areas that could be targeted to improve patient care. This was done via a community management program aimed at detecting patients who have factors associated with morbidity and mortality and comparing this trial cohort of patients (community cohort) with a current standard of care (hospital cohort). This was explored by (1) determining how many patients had a high probability of cirrhosis as assessed by FibroScan® and ultrasound, were in a hepatitis phase of CHB infection or at risk of HCC; (2) assessing adherence with medical appointments, HCC surveillance and antiviral treatment and (3) determining the risk of liver-related outcomes. This research aims to highlight areas

where gaps in patient care occur and thus where changes to patient care can be made to meet the 2030 goals.

Chapter 2. Literature Review and Rationale Behind the Development of the CATCH Study

This chapter will first discuss CHB and CHC infection: pathophysiology, extent of disease in Australia and implications for patients who have these diseases. Secondly, complications of CHB and/or CHC will be discussed, including the development of liver fibrosis/cirrhosis, determining the extent of liver fibrosis and the risk of and surveillance for HCC. Thirdly, the management of CHB and CHC will be discussed, exploring different models of care for these diseases in Australia. It will then highlight the information gaps that exist within the cascade of care for management of people living with CHB and/or CHC. Finally, the rationale behind the development of the CATCH study will be discussed, along with the research aims and hypotheses.

2.1. Literature Review

In 2016 the World Health Organisation (WHO) committed to eliminating CHB and CHC a public health threats, with targets of reducing new infections by 80% and reducing mortality by 65% by 2030.[27] The Australian Government has endorsed this with its Third National Hepatitis B Strategy[1] and Fifth National Hepatitis C strategy.[2] Despite these strategies, these targets are unlikely to be met without improving methods of prevention and increasing rates of testing and treatment.[3]

2.1.1. Chronic hepatitis B liver disease

Hepatitis B virus (HBV) infection can cause chronic infection and can lead to liver cirrhosis and HCC. Prevention, diagnosis, monitoring of the disease and its complications and treatment is a vital part of health care.

2.1.1.1. Hepatitis B virus infection: acute and chronic infection

HBV is a blood borne virus that can lead to acute or chronic infection. Acute HBV infection is a short-term illness (less than six months) that occurs after exposure to HBV.[28] Patients with acute HBV either clear the virus or go on to develop CHB, which is usually a lifelong infection.[28] The risk of developing *chronic* HBV infection relates to the age of exposure: the younger the age the higher the risk of developing CHB, with rates of chronic infection of 90% in neonates down to 5% in adults after acute infection.[28] There are currently no treatments

available to prevent an acute infection becoming a chronic infection. The remainder of this thesis will focus on CHB rather than acute HBV infection when discussing this virus.

2.1.1.2. Chronic hepatitis B in Australia

There are estimated to be over 230,000 people living with CHB in Australia in 2020.[29] Although rates of new diagnoses of CHB have decreased over the last 5 years due to vaccination programs,[30] CHB is the still most common blood born virus in Australia and disproportionately affects specific populations: 72% of people living with CHB in Australia are either born overseas (61%) or are Aboriginal or Torres Straight Islanders (11%).

2.1.1.3. Hepatitis B virus transmission

HBV can be transmitted in many different ways: vertically, from mother to child at time of birth; or horizontally, from vaccination programs using unsterile equipment; scratches and biting; contaminated blood products; shared injecting equipment; and from sexual contact.[28] The most common method of transmission worldwide is vertically.[28]

2.1.1.4. Prevention of chronic hepatitis B

CHB can be prevented. Vaccination programs are highly effective with efficacy of 80-100% in preventing infection after exposure when the full vaccination course is given.[31] Vaccination rates are very high in patients born in Australia: 95% of infants aged 12 months have been vaccinated.[30] Vaccination against CHB is also highly cost effective.[32] Maternal screening programs and subsequent appropriate and timely HBV management during pregnancy lowers the risk of vertical transmission to a newborn baby to negligible.[31] This involves treatment with antivirals for the mother if required, based on e-antigen (HBeAg) and viral load, and, in the newborn, passive (hepatitis B immunoglobulin) and active vaccination.[31] Without medical care, rates of vertical transmission can be as high as 90%, but with appropriate medical care the risk is less than 1%.[31] Other methods that reduce transmission include needle and syringe exchange programs for patients who inject drugs[33] and screening of blood products.[34]

2.1.1.5. Diagnosis of chronic hepatitis B

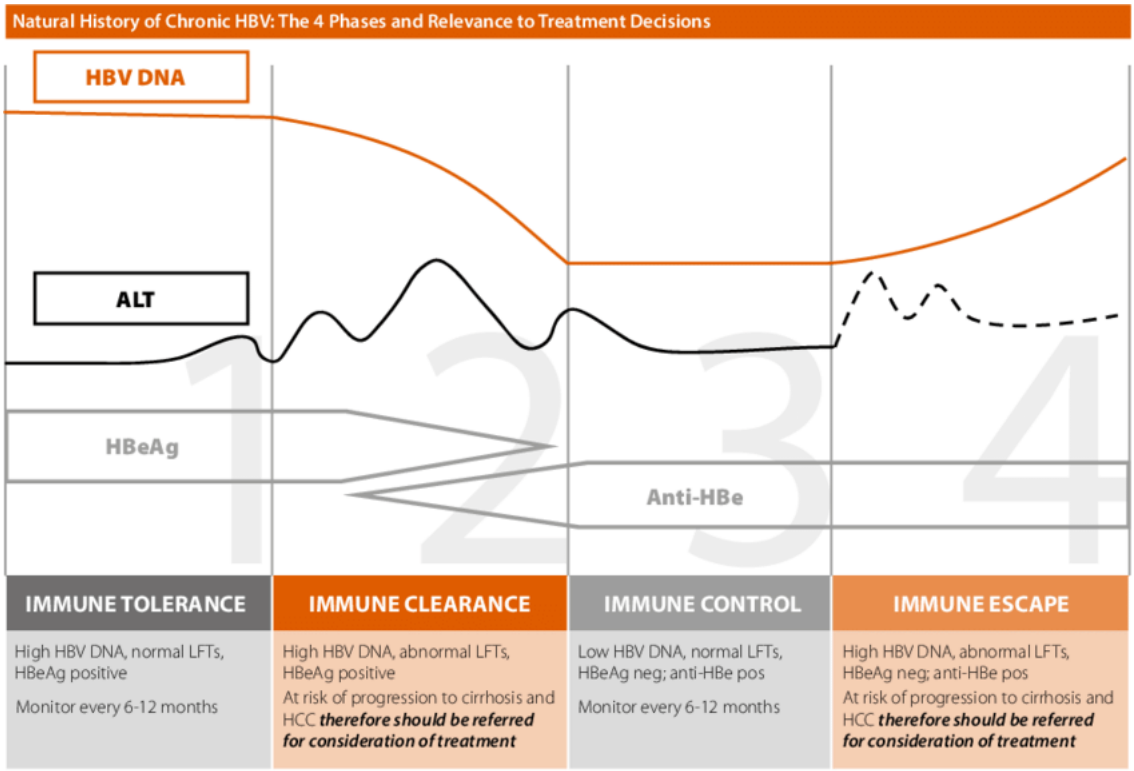
High-risk populations should be screened for CHB, including patients born in countries with high CHB prevalence, infants born to mothers with CHB, patients who have been incarcerated or patients who inject drugs, as well as many other populations.[35] CHB is diagnosed with serological testing for hepatitis B surface antigen (HBsAg).[35] If HBsAg is detected, this

indicates current infection and further testing is required to determine the disease phase which guides management decisions.

2.1.1.6. Phases of disease

CHB infection is typically classified into four phases depending on HBeAg status, viral load and alanine transaminase (ALT) levels (Figure 2-1).[36] The European Association for the Study of the Liver (EASL) classifies these phases based on eAg status as well as whether there is infection where hepatic necroinflammation is absent or hepatitis where necroinflammation is occurring.[37] The natural history of CHB infection is to transition from phase 1 (HBeAg positive infection) to phase 4 (HBeAg negative hepatitis) over time; however, patients can move backwards through phases, and, in some cases, don't clearly fit into one of the defined phases.[36, 38, 39] It is important to monitor which phase patients are in regularly as these phases help to guide management and treatment decisions. Those in the HBeAg positive hepatitis and HBeAg negative hepatitis can have significant hepatic-necroinflammation occurring and are at higher risk of fibrosis progression.[36] Treatment with antivirals can prevent this progression of fibrosis: typically, treatment is offered during these two aforementioned phases when ongoing hepatic inflammation is occurring.[9] The old terminology of 'carrier state' (HBeAg negative infection) of CHB is no longer used, as it can create a false reassurance that CHB does not require regular assessment; most adults with CHB are in the HBeAg negative infection and often do not have regular appropriate follow-up.[9] Transition to a more active phase of infection (hepatitis) may therefore be missed. Patients in any of the phases of CHB require regular follow-up as they may move into a phase where hepatic-necroinflammation occurs and thus may require treatment to prevent the development of fibrosis.[9] Historically, the accepted ALT cut-off was based upon the accepted lab suggested result, often 30-50 IU/mL depending on the analyser equipment used; multiple studies have suggested that the upper limit of normal should be lower than this at 19 IU/L for women and 30 IU/L for men.[40-42] This cut-off has superiority over conventional values for detecting those at risk of fibrosis[40] with evidence of increased liver-related mortality with increases in ALT, especially in people living with CHB.[43]

Figure 2-1 Phases of chronic hepatitis B virus infection



Reprinted from: "Australasian Society for HIV Medicine. Decision-making in HBV. Darlinghurst: Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM), 2013"; HBV: hepatitis B virus; DNA: Deoxyribonucleic acid; ALT: alanine aminotransferase; HBeAg: hepatitis b e antigen positive; Anti-HBe: hepatitis B e antigen negative; LFTs: liver function tests; HCC: hepatocellular carcinoma

Phase 1: HBeAg positive infection/immune tolerance
Phase 2: HBeAg positive hepatitis/immune clearance
Phase 3: HBeAg negative infection/immune control
Phase 4: HBeAg negative hepatitis/immune escape

In Australia in 2019, modelling data suggested that the majority of people living with CHB were in the HBeAg negative infection (46.1%), followed by the HBeAg positive infection (23.3%).[13] There were 23.7% of patients in a hepatitis phase where antiviral therapy should be considered.[13]

2.1.1.7. Health implications for people living with chronic hepatitis B

There are health implications for patients diagnosed with CHB as this infection can lead to cirrhosis as well as HCC.[22] It is estimated that 5.8% of people living with CHB in Australia have cirrhosis: this is based upon modelling data and specific populations such as patients managed within a hospital setting.[13] People living with CHB also have a higher mortality than those without CHB, mostly due to liver-related disease.[22] If left untreated, the risk of death due to complications of CHB is estimated to be between 15-25%, however, with

monitoring and appropriate treatment, complication rates are much lower.[23] People living with CHB should have regular assessments to determine the disease phase, degree of liver fibrosis and risk of HCC.[9] This regular monitoring should include yearly viral load and six monthly liver function tests (LFTs).[9] Depending on these investigations, antiviral treatment can be initiated to prevent progression of fibrosis and also decrease the risk of HCC [9] and, in people living with CHB who are at risk of HCC, regular HCC surveillance should be performed.[18]

2.1.1.8. Summary

Whilst vaccination is critical for the long-term eradication of CHB, the critical issues currently are diagnosis as well as appropriate management of people living with CHB.

2.1.2. Chronic hepatitis C

Although CHC is a distinctly different virus to CHB and has different prevention strategies, diagnosis and management, it also has similar outcomes. CHC can also lead to the development of liver fibrosis and cirrhosis and leads to increased risks of HCC.

2.1.2.1. Hepatitis C virus infection: acute and chronic infection

Hepatitis C virus (HCV) infection can be classified into acute and chronic infection. Acute infection is within the first six months of infection. Some patients with acute HCV infection can be infected with the virus for only a short amount of time, but the majority (50-80%) of patients go on to develop chronic infection.[44] The benefit of treatment for acute HCV infection in the current era of HCV treatment is unclear. If spontaneous clearance has not occurred by six months, by definition the person has chronic HCV (CHC) and treatment can then be initiated.[10] Currently the Medicare pharmaceutical benefits scheme (PBS) only funds HCV treatment for people living with *chronic* infection.[45]

2.1.2.2. Chronic hepatitis C in Australia

Despite access to new curative therapies, CHC is still prevalent in Australia with over 130,000 people living with this disease in 2020.[46] During 2017/18 there were 583 deaths attributable to CHC in Australia and 66 liver transplants due to CHC liver failure or CHC related HCC.[47]

2.1.2.3. Hepatitis C virus transmission

HCV is a blood borne virus and is most commonly acquired parenterally through sharing of needles and syringes with intravenous drug use (IVDU, 99%),[21] or blood transfusions (rare since screening commenced in 1990).[48] It is also acquired via vertical transmission (rare); healthcare exposure (rare); sexual intercourse (rare, more common in men who have sex with men); tattoos with non-sterile equipment; sharing razors and other sharp personal objects; and organ donation (rare).[21, 44]

2.1.2.4. Prevention of chronic hepatitis C

Although there is no vaccine to prevent CHC, there are other ways to lower the rates of CHC transmission. In Australia, there are strict guidelines for medical procedures, blood product testing and tattoo parlours which significant lowers the risk of transmission. There are also needle and syringe exchange programs which lowers the risk of transmission during IVDU.[33] There is also evidence that treating people living with CHC who currently inject drugs lowers the risk of that person transmitting CHC to other patients.[49]

2.1.2.5. Diagnosis of chronic hepatitis C

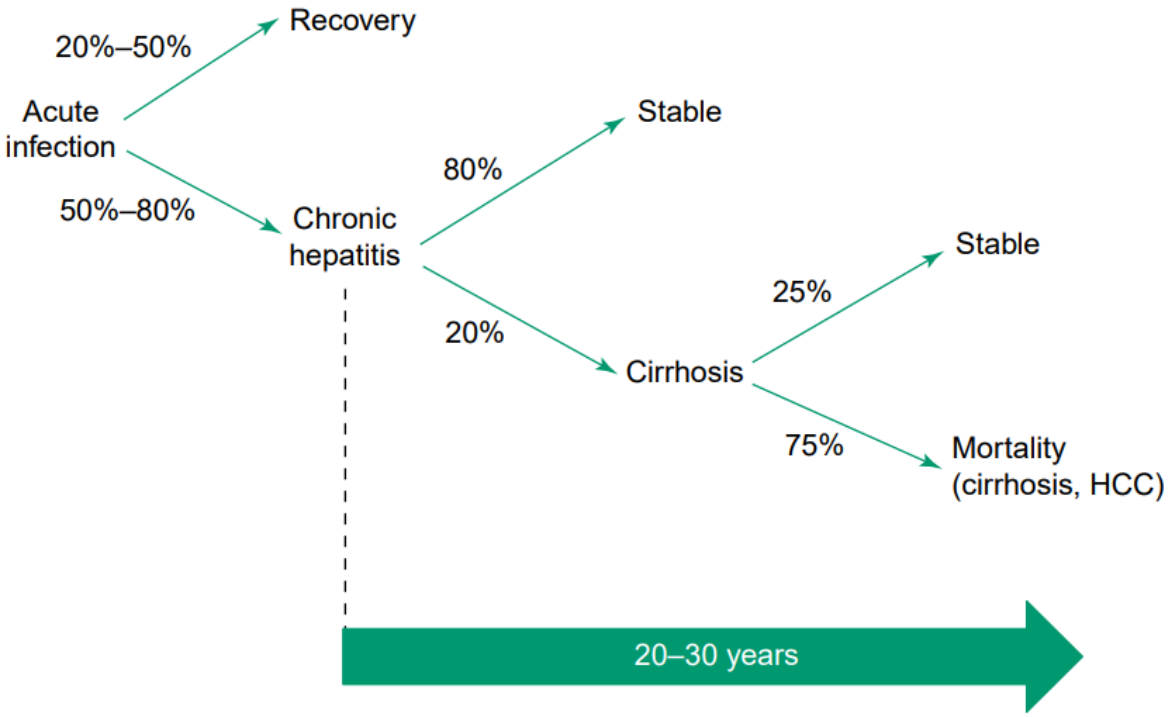
Whilst hepatitis C antibody is used as a screening test,[50] definitive diagnosis requires HCV polymerase chain reaction (PCR) testing which detects the presence of the actual virus.[50] PCR testing is utilised, usually 12 weeks after treatment to check for sustained virological response (SVR) or cure.[10]

2.1.2.6. Chronic hepatitis C pathophysiology

People living with CHC are at risk of developing cirrhosis, such that approximately 20% will develop cirrhosis after 20 years of infection (

Figure 2-2).[44]

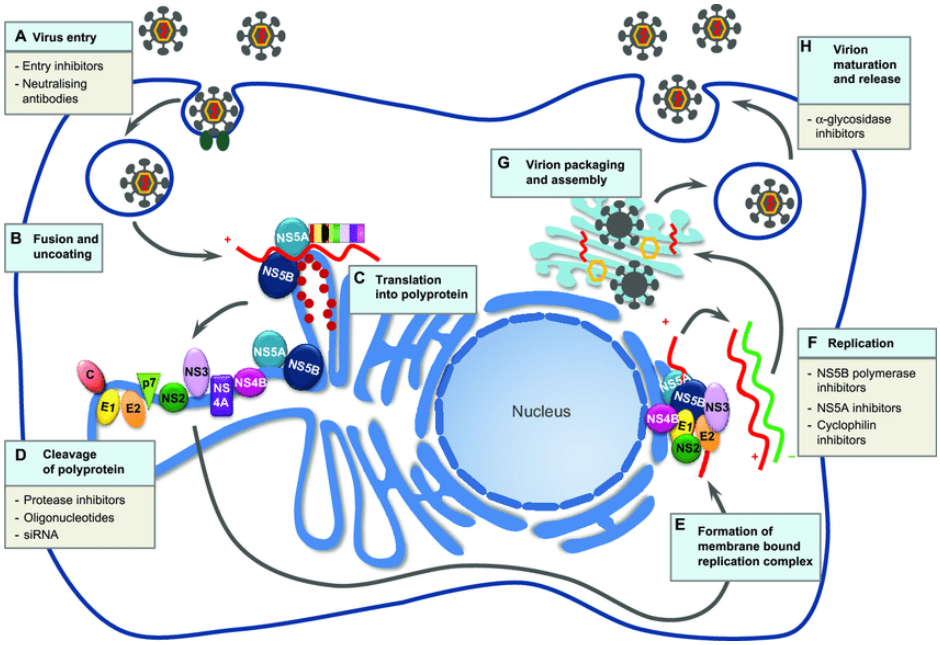
Figure 2-2 Schematic representation of the natural history of hepatitis C virus infection



Reprinted from: Pawlotsky, J.-M., *Pathophysiology of hepatitis C virus infection and related liver disease.* Trends in Microbiology, 2004. **12**(2): p. 96-102.

Detailed characterisation of the HCV replication has allowed new medications to be developed that directly inhibit replication pathways. HCV is a single stranded ribonucleic acid (RNA) virus which enters hepatocytes through a receptor complex (Figure 2-3).[51] Once in the cell, the RNA is released into the cell cytoplasm with translation and transcription occurring through multiple steps, followed by viral release from the cell.[51] Each of these steps are potential targets for inhibition of replication. These replication pathways have been used to develop drugs that specifically inhibit the replication of HCV, known as direct acting antivirals (DAA).[51]

Figure 2-3 Hepatitis C virus lifecycle and potential targets for direct acting antivirals



Reprinted from: Holmes, J. and A. Thompson, Interferon-free combination therapies for the treatment of hepatitis C: current insights. Hepatic Medicine: Evidence and Research, 2015. 7: p. 51-70.

2.1.2.7. Health implications for people living with chronic hepatitis C

CHC is an important disease to diagnose and treat as people living with CHC have a higher all-cause mortality compared to those without CHC.[22, 24-26] They are at risk of developing liver fibrosis, cirrhosis and are at increased risk of HCC.

Although very different diseases, both CHB and CHC are diseases that can lead to the development of liver fibrosis, cirrhosis and HCC. Assessment of the degree of fibrosis and risk of HCC to determine the best management is part of best practice in managing both diseases. The next section will focus on the development, health implications and determining the degree of liver fibrosis.

2.1.3. Liver Fibrosis

Liver fibrosis and cirrhosis have implications for patient management and outcomes. The development of fibrosis, the ability of the liver to regenerate and complications of cirrhosis will be discussed here. Assessment of/testing for fibrosis will then be discussed.

2.1.3.1. Development of liver fibrosis

The liver has an excellent capacity for repair after injury, and single, even severe episodes of inflammation may leave no long-term damage. However, repeated, or ongoing episodes of

liver inflammation can result in the development of liver fibrosis and cirrhosis. Once cirrhosis has developed, there is an increased risk of HCC and liver decompensation. The rates of progression of fibrosis depend on underlying disease factors, co-existing causes of hepatic necroinflammation and patient genetic factors. Treatment of the underlying condition can prevent this fibrosis progression. There are multiple conditions that can lead to the development of liver fibrosis, including CHB and CHC,[52, 53] as well alcohol consumption [53] and metabolic and autoimmune diseases of the liver.[53] People living with CHB and/or CHC are at higher risk of cirrhosis if there are other factors that contribute to fibrosis development, such as dual infection, alcohol use, obesity or male gender.[44] Male gender is probably related to a combination of immune response differences along with hormonal differences demonstrated by increased rates of fibrosis development in post-menopausal women compared to pre-menopausal women.[54] Most of these conditions have treatment options which are very effective at preventing the progression of liver disease. Some diseases have more limited treatment options such as alcohol use or non-alcoholic liver disease (NAFLD). In the absence of treatment, these liver diseases can progress to cirrhosis with subsequent risk of liver-related outcomes such as decompensation (hepatic encephalopathy, ascites and coagulopathy as well as variceal bleeding) and death.[55, 56] With treatment of the underlying disease, regression or reversal of fibrosis may occur. Paired biopsy studies on people living with CHB have shown regression of fibrosis after 1 year of antiviral therapy [57] and studies of people living with CHC have also shown reversal of fibrosis after anti-viral treatment.[58]

The development of fibrosis and subsequent cirrhosis occurs through multiple mechanisms; inflammation, necrosis of hepatocytes and excessive extracellular matrix (ECM) deposition.[56, 59] The ECM of the liver usually undergoes constant remodelling, however, in the presence of inflammation, due to many complex interplaying factors, ECM starts to accumulate, leading to fibrosis and eventually cirrhosis.[60] Cirrhosis is the end stage of fibrosis development with nodule formation and eventual loss of liver function. Once cirrhosis occurs, further structural and functional changes may follow leading to portal hypertension.[61] The development of portal hypertension has clinical implications. It is usually only after portal hypertension develops that liver-related outcomes occur.[61]

Overall survival in patients with cirrhosis is mainly based upon the extent of portal hypertension and degree of decompensation. The Child Turcotte Pugh score (CPS) is used to determine the extent of decompensation using factors that assess liver function as well as clinical features of decompensation: albumin, bilirubin, international normalised ratio (INR)

and the presence and severity of ascites and hepatic encephalopathy.[62, 63] This algorithm classifies patients into CPS of A, B or C, with A being preserved liver function and C being quite advanced decompensation.[62] The CPS can predict overall survival in patients with cirrhosis as well as the risk of post-operative complications.[62, 64, 65]

Diagnosing cirrhosis and the degree of fibrosis is important: early diagnosis of fibrosis or cirrhosis has been shown to improve outcomes by implementing treatment or behavioural change to reduce the underlying hepatic inflammation.[66] Monitoring for complications also improves outcomes: surveillance for HCC is an important part of care with significant benefits in improving outcomes with appropriate surveillance.

2.1.3.2. Other factors that contribute to fibrosis development

Although CHB and CHC can lead to the development of liver fibrosis on their own, other co-factors can also contribute to the development of fibrosis. Having more than one underlying disease may cause more rapid progression of fibrosis development.

2.1.3.2.1. Alcohol

Australian guidelines recommend drinking no more than four standard drinks on any one day and no more than ten standard drinks per week to reduce the risk of alcohol related disease.[67] Despite this, 16.8% of Australians are drinking more than this.[68] Recommended alcohol intake differs between country guidelines and at-risk alcohol intake definitions in clinical studies are also all different. At-risk alcohol intake leads to a host of health issues including increased risk of cancer and liver cirrhosis; this section will focus on alcohol and viral hepatitis and interactions between these factors. Alcohol contributed to 4.5% of the total burden of disease and injuries in Australia in 2015.[68]

Alcohol intake has a negative impact on liver disease in people living with CHB; with heavier consumption of alcohol having the highest risks. Higher quantity of alcohol intake increases the rate of progression of fibrosis in people living with CHB [69] and increases the risk of HCC in people living with CHB.[69] Heavy alcohol intake also increases the risk of HCC in people living with CHB related cirrhosis.[69, 70] Risk of death from cirrhosis and HCC in people living with CHB is also increased with heavy alcohol consumption.[71]

Alcohol is also an independent risk factor for cirrhosis in people living with CHC:[72] rates of progression to cirrhosis range from 2 to 6 times higher in those who drink alcohol at at-risk levels compared to those who do not.[73, 74] Risk of HCC is also higher in people living with

CHC and at-risk alcohol intake compared to those with either of these alone: alcohol abuse alone can increase HCC risk by 5-fold; CHC alone can increase HCC risk by 20-fold; and having both of these risk factors can increase HCC risk by up to 100-fold.[75, 76]

In people living with CHB and/or CHC, alcohol intake has a deleterious effect on liver specific health outcomes.

2.1.3.2.2. Tobacco

In Australia, 11% of patients smoke cigarettes daily and 23% are ex-smokers.[68] Pack-year history is used as a measure of lifetime volume of use; it is calculated by multiplying the packets of cigarettes smoked daily and the number of years smoked (assuming 20 cigarettes in a pack). Previous studies have shown that a 15 pack-year smoking history is the cut-off point for low risk and high risk of smoking related health outcomes.[77] Nicotine is also highly addictive: one study found that 67.5% of patients transitioned from use to dependence.[78] Nicotine contributed to 9.3% of the total burden of disease and injuries in Australia in 2015.[68]

Smoking may also have a deleterious effect on liver fibrosis; biopsies studies of people living with CHC had higher degrees of fibrosis in smokers than in non-smokers.[79-82] The data surrounding the effect of smoking on liver fibrosis in people living with CHB is conflicting; one biopsy study showed no effect [82] but other studies have found higher risk of more advanced fibrosis and lack of fibrosis regeneration after therapy using non-invasive measurements of liver fibrosis.[83, 84] There is also a causal association between smoking and liver cancer [85, 86] and specifically an increased risk of HCC in people living with CHB and/or CHC.[87] Smokers also have higher rates of HCC recurrence after curative therapy.[88]

2.1.3.2.3. Dual infection

Dual infection with CHB/CHC is associated with increased rates of liver-related outcomes. The prevalence of dual infection with CHB and CHC varies between 5-20% in people living with CHB and 2-10% in people living with CHC.[89, 90] Those with dual infection are more likely to be younger, male, have a history of multiple blood product transfusions or IVDU or have human immunodeficiency virus (HIV) infection.[89, 90] People living with dual CHB/CHC infection have a more severe clinical course with faster fibrosis development and higher rates of cirrhosis,[91-93] decompensation[93] and HCC.[94, 95] Discussion regarding hepatitis delta and HIV dual/triple/quadruple infection is beyond the scope of this thesis.

2.1.3.2.4. Obesity

Obesity leads to increased risk of mortality as well as higher risk of hypertension, dyslipidaemia, diabetes and cardiovascular disease.[96, 97] Obesity also leads to increased risk of NAFLD which itself can lead to cirrhosis.[98] Obesity is a risk factor for cirrhosis development and is also a risk factor for death due to liver disease.[98, 99] Obesity also leads to increased risk of HCC especially when obese at a younger age [100, 101] and, in people living with CHB or CHC, obesity was an independent risk factor for HCC.[102, 103] However, in CHB patients receiving entecavir, one study found obesity had no effect on HCC rates.[104] Studies have shown that people living with CHC have a higher prevalence of obesity than those without these infections [105] and the HCV itself has been directly implicated in insulin resistance and diabetes development.[106] Obesity is very common: in Australia, 31% of adults were classified as obese, with higher rates of obesity in lower socioeconomic status areas at 38%.[68] Obesity and overweight contributed to 8.4% of the total burden of disease and injuries in Australia in 2015.[68]

2.1.3.3. Other factors that may have an impact on morbidity and mortality in people living with viral hepatitis

2.1.3.3.1. Cannabis

In Australia, 36% of patients have used illicit cannabis in their lifetime (not including medically prescribed cannabis).[68] The impact of cannabis use on liver fibrosis is conflicting; studies have shown higher risk of advanced fibrosis on biopsies with daily cannabis use [107, 108] and other studies have shown no impact of cannabis on fibrosis or progression of fibrosis, including a meta-analysis.[109, 110] There is minimal clinical data looking at cannabis and its effect on HCC risk. Cannabis also has other impacts on morbidity, with higher rates of schizophrenia and more severe disease in patients with a predisposition to this and has also been associated with altered brain development with cognitive impairment and higher rates of not finishing high school.[111] It has also been associated with increased risk of anxiety and depression.[112] Approximately 9% of patients who use cannabis become addicted.[78] Epidemiological data also suggests that cannabis may act as a gateway drug for other drugs and cannabis has effects on dopamine receptors in the brain which have effects on rewards and addictive behaviours.[111] However, this has not been definitely proven and it may be that patients who are more susceptible to drug use behaviours may start with cannabis because it

can be more easily accessible.[111] Cannabis contributed to 0.2% of the total burden of disease and injuries in Australia in 2015.[68]

2.1.3.3.2. History of intravenous drug use

PWID have much higher rates of negative health outcomes including death due to overdose and CHB, CHC and HIV infections. PWID have higher rates of CHB at 4% compared to 0.9% of the whole population of Australia;[113] and very high rates of CHC at 50% in one study from Melbourne, Victoria.[114] The lifetime risk of non-fatal overdose is approximately 41.5% in PWID.[115] There are also specific risks with non-viral injecting-related injury and diseases including infections such as cellulitis, osteomyelitis and infective endocarditis, with lifetime prevalence ranging between 6-69%.[116, 117] PWID are also at higher risk of more severe complications and other health outcomes due to higher rates of other health conditions, homelessness and higher rates of lower socioeconomic status.[118] Other risks that are higher in PWID include risk taking behaviours during drug use such as unprotected sexual intercourse leading to higher rates of sexually transmitted infections.[119] In Australia, 1.5% of the population aged 14 years and over reported ever injecting drugs and 0.3% reported having used within the prior 12 months.[68] Males had higher rates of use within the prior 12 months compared to females.[68] Unsafe injecting practices contributed to 0.5% of the total burden of disease and injuries in Australia in 2015.[68]

2.1.3.3.3. History of psychiatric diagnosis

In Australia, 20% of patients reported an active mental health disorder within the previous 12 months and 46% reported every having a mental health disorder.[120] Mental health contributed to 24.5% of the total burden of disease and injuries in Australia in 2015.[68] People living with a mental health disorder have the lowest rate of doing paid work compared to cancer, cardiovascular, major injury, diabetes or arthritis.[121] Average life expectancy is also shorter in those with severe disease, mainly due to other untreated comorbid conditions with a life expectancy reduced by up to 20 years.[122] People living with mental health disorders also have higher rates of drug use[123] and people living with CHB and CHC have higher rates of mental health disorders.[124]

2.1.3.4. Summary

There are many causes of liver fibrosis including CHB and CHC with many complex interplaying factors. Dual infection, at-risk alcohol intake and obesity are associated with

higher rates of liver-related outcomes. People living with CHB and/or CHC also have higher rates of psychiatric diagnoses and drug use which themselves are also associated with poorer health outcomes. Determining the degree of fibrosis is an important part of management to determine the best treatment options.

2.1.4. Determining the degree of fibrosis

The degree of liver fibrosis has implications for disease treatment and management. Patients with advanced fibrosis or cirrhosis have worse outcomes without treatment of the underlying disease.[66] Monitoring for complications of cirrhosis also leads to better health outcomes for example with appropriate surveillance for HCC and oesophageal varices which leads to earlier diagnosis and lowering the risk of major bleeding events.[66] Consequently, the ability to determine the degree of liver fibrosis in someone with liver disease is a vital part of patient care. Fibrosis assessment allows prognostication and the introduction of appropriate and timely treatment and adequate surveillance strategies. The main methods for determining or estimating the degree of fibrosis include liver biopsy, imaging – including elastography methods and serological markers. In the section below, each of these methods will be examined.

2.1.4.1. Liver biopsy

The current gold standard for the assessment of the severity of liver fibrosis is biopsy and histological assessment of the liver. A liver biopsy is performed by taking a sample of the liver using a needle; this sample is then processed and graded by a pathologist. There are many histopathological scoring systems for fibrosis: in people living with viral hepatitis, the 'Meta-analysis of Histological Data in Viral Hepatitis' (METAVIR) system is one of the most widely used.[125-127] This system grades fibrosis in five increasing levels from F0, being no fibrosis to F4, indicating cirrhosis.[126, 128] Although liver biopsy is gold standard, there are issues around diagnosis of fibrosis and risks of a biopsy. There are significant risks associated with liver biopsy: 20% of patients report significant pain, major complications such as life threatening bleeding can occur in 0.5% and there is a mortality rate of 0.01%.[4] There are also issues surrounding the diagnosis of the degree of fibrosis on biopsy: ideal liver biopsies for fibrosis staging should be 20mm in length and contain 11 portal tracts.[129] Biopsies not meeting these specifications are more likely to inaccurately grade the degree of fibrosis as less severe: in biopsies more than 3cm in length, 49.7% were classified as mild fibrosis (F0 or F1)

compared to 86.6% in biopsies less than 1cm in length.[130] Some liver diseases are non-homogenous, and fibrosis itself can also be non-uniform throughout the liver, resulting in inaccuracies, as only 1:50,000 of the liver is assessed.[129] Liver histology is also imperfect with intra- and inter-observer variability between reporting pathologists,[131, 132] as well as sampling error.[133, 134] Despite these limitations of liver biopsies, there are clear benefits to liver biopsies. Biopsies can detect disease activity levels and detect other liver diseases that can impact disease progression, such as NAFLD.[131] Liver biopsy is useful for determining the degree of fibrosis and underlying liver diseases, however, due to the risks and limitations they have limited applicability on a population scale and are not suitable for regular monitoring of disease progression or regression. For these reasons, other techniques for estimating the degree of fibrosis are now more widely used.

2.1.4.2. Elastography

Elastography is a form of medical imaging used as an alternative to liver biopsy. Elastography uses physical shear waves and measures the speed of movement of these waves within the liver. Like sound waves, shear waves move more quickly in harder or stiffer tissue and more slowly in softer tissue. Elastography methods interpret the wave speed and uses this to report LSM.[5] Liver stiffness increases during the development of fibrosis as a result of ECM and vascular architectural change (discussed in section 2.1.3.1). The stiffness of the liver tissue correlates with the degree of liver fibrosis; a higher stiffness indicates more fibrosis.[5]

Elastography can be measured in different ways: TE (FibroScan®), SWE, ARFI or MRE; all these methods have their own benefits and limitations, but all are very safe and well tolerated which improves their applicability. Interpretation of results needs to consider a few different factors. Firstly quantification of fibrosis can vary considerably within the same histological architectural stage and this can reduce the correlation between the stage of disease as determined by liver biopsy and the liver stiffness as assessed with elastography.[5, 55, 135, 136] The variation in elastography readings within histological grades may also be due to issues with correlating a continuous variable (LSM results) with a categorical fibrosis grade. Other factors can also increase liver stiffness without an increase in fibrosis: inflammation, fatty deposition, cholestasis and venous congestion can increase liver stiffness.[137, 138] Also, there is increased portal blood flow after eating, which increases liver stiffness; consequently elastography should ideally be performed fasting.[139, 140] Elastography results are also not comparable between different elastography methods given different techniques and thus different cut-off points for different fibrosis levels.[137, 138] When interpreting elastography

results, the underlying disease and co-factors should be taken into account as well as the method of elastography.[137, 138]

2.1.4.2.1. Transient elastography (TE) with FibroScan®

TE is measured using a FibroScan® machine. This device emits mechanical shear waves and measures the propagation of the transmitted impulse by ultrasound. The speed of the shear wave provides an estimate of LSM which correlates with the degree of liver scarring.[6] Ten measurements are taken and the median result in kilopascal (kPa) is reported.[6]

The reliability and quality of a FibroScan® result is determined by three factors: image quality, percentage success rate (>60% is acceptable) and a low interquartile range (IQR) to median stiffness (ms, IQR:ms, <30% is acceptable).[141-143] FibroScan® comes with 3 different sized probes: the medium or M probe which is the most commonly used one; a small or S probe, which is mostly used in children, and an extra-large (XL) probe, which is more sensitive and has a deeper focal length and depth of measurement.[144] The M probe uses a higher frequency shear wave where the wave travels a shorter distance, so, in patients with obesity, it is less likely to be able to give a result due to greater skin to liver capsule distance.[144] The XL probe, with a lower frequency overcomes this barrier in patients with a greater skin to liver capsule distance.[144] Early Fibroscan® machines required the skin to liver capsule distance to be measured using an ultrasound to determine skin to capsule distance and thus which probe to use, however, modern Fibroscan® machine have this feature integrated which tells the operator which probe to use. In those with a skin to capsule distance of less than 20mm the M probe is used; if more than 25mm the XL probe is used; it is our practice that in those 20-25mm the M probe is used initially and moved to the XL probe if unable to get good quality measurements.[141, 145] Use of the XL probe has been shown to reduce failure rates and obtain more reliable results in obese or overweight patients.[144, 146] An ultrasound is also commonly used to determine the best location for the transducer probe, to avoid structures which may interfere with the assessment.

Measurement of LSM using FibroScan® can accurately predict the degree of fibrosis in people living with CHB [6, 147-149] and CHC.[6, 141, 150-152] For each disease, LSM cut-offs have been determined to indicate the degrees of fibrosis.[153] Optimal cut-off points for CHB and CHC were determined in early studies of FibroScan®. An LSM of more than 7.1kPa indicates significant fibrosis (≥F2) is likely with a positive predictive value to 95% in people living with CHC[150] and 80% in people living with CHB.[148] An LSM of more than

12.5kPa has a positive predictive value of 77% for cirrhosis in people living with CHC.[150] A cut off point of 11kPa was the optimal cut off point for diagnosis of cirrhosis in people living with CHB with a positive predictive value of 38% but a sensitivity of 93%.[148] Using a cut-off point of 18.2kPa increased the positive predictive value to 67% but the sensitivity dropped to 57%.[148] FibroScan® overall has good accuracy: it has a very high area under the receiver operator curve (AUROC) at 0.97 meaning it is very accurate in differentiating between patients with and patients without cirrhosis.[154]

FibroScan® also correlates with liver-related outcomes. A higher LSM is associated with an increased chance of liver-related outcomes. A study of 845 people living with CHC and/or CHB found that a LSM of 17kPa was the best cut-off liver-related outcomes and liver-related deaths.[155] Fibroscan® can predict portal hypertension measured by hepatic venous pressure gradient measurements (HVPG); HVPG measures portal pressures which correlate with liver related outcomes. HVPG measurements correlate with LSM measured by Fibroscan®[156, 157] with a LSM cut-off of 21kPa for predicting significant portal hypertension in one study[157] and 25kPa in another study.[158] LSM measured by Fibroscan® can also predict the presence of oesophageal varices:[6, 156, 159, 160] an LSM cut-off value of 17.6 kPa had a sensitivity of 90% [156] and, in another study, a LSM cut-off of 12.5kPa had a 76% sensitivity for the presence of oesophageal varices.[159] Fibroscan® can also predict whether oesophageal varices are clinically significant where varices are large or have signs that they are high risk of bleeding: a LSM cut-off of 27.5kPa had a negative predictive value of more than 90% for clinically significant oesophageal varices [6] and another study found LSM of <19kPa was predictive of the absence of clinically significant varices.[160] Fibroscan® also predicts the development of oesophageal varices over time [161] and can predict the risk of oesophageal variceal bleeding.[6, 161] Combining Fibroscan® with platelet counts have also been shown to have a high negative predictive value for varices requiring treatment when the LSM is less than 20kPa and platelets more than $150x10^9$/L,[162] meaning patients who meet this criteria can avoid a screening gastroscopy. FibroScan® also correlates with the development of liver decompensation with ascites, coagulopathy or encephalopathy.[161, 163] It can also determine the risk of development of and outcomes of HCC in both CHB and CHC as well as other causes of liver disease.[6, 161, 164] Patients with a higher LSM measured by FibroScan® had much higher rates of HCC with a hazard ratio (HR) of 16.7 using an LSM cut-off point of 10kPa and a HR of 45.5 using a cut-off of 25kPa.[165] Similar results have been repeated in studies of different liver disease aetiology including CHB and CHC with increasing

rates of HCC development with increasing LSM measured by FibroScan®.[6, 161, 164, 166] FibroScan® also correlates with HCC recurrence after curative resection.[167] FibroScan® is cost effective when used as a tool to determine those at risk of HCC taking into account the subsequent costs of HCC surveillance and treatment.[7] FibroScan® predicts overall survival and liver-related survival.[168] It can also predict response to CHC treatment: one study of 74 patients found that those with an LSM >12kPa had a relative risk of 2.44 of failing to achieve a SVR with CHC treatment.[169] Another study showed that an LSM >21kPa measured using FibroScan® had the highest chance of relapse after DAA therapy.[170] In addition to the clinical utility of FibroScan®, other benefits include the devices' ability to estimate the degree of fat within the liver using controlled attenuation parameter (CAP) values. This is potentially useful in assessing patients for and with NAFLD.[171, 172] FibroScan® is rapid to perform and easy to learn.[142] It also has good reproducibility with excellent intra and inter observer agreements with an intra-class correlation coefficient of 0.98 indicating a high correlation between proceduralists.[141, 173] There are some limitations to FibroScan®; obesity can make measurements harder, especially in those with a higher skin to capsule distance that the XL probe cannot overcome.[146] If there is bowel overlying the liver or ascites, measurements are either less reliable or they fail.[174, 175] Nonetheless, despite these limitations, it is the most widely used and validated elastography technique.[176]

To summarise, FibroScan® can accurately estimate the degree of liver fibrosis and risk of liver-related complications. It is cost effective and is the most widely used elastography technique.

2.1.4.2.2. Acoustic radiation force impulses (ARFI)

ARFI is an ultrasound based elastography technique where the elastography system is integrated within a standard ultrasonography device.[177] The elastography measurement is able to be targeted within a specific user-specified region of interest within the liver.[177] The machine emits a short duration acoustic pulse which generates localised displacements within the liver; the time of peak displacement is measured at a single point within the liver and thus the velocity of the shear wave allows for an assessment of liver stiffness.[177] Unlike FibroScan® which expresses LSM in kilopascals, by convention ARFI uses meters per second.[177]

ARFI has been shown to predict the degree of liver fibrosis in people living with CHB [178] and CHC.[178] A meta-analysis found that, in people living with CHB or CHC, ARFI had an

AUROC of 0.91 in differentiating between those with and without cirrhosis indicating it is a very accurate test.[154, 179, 180] Another meta-analysis for multiple aetiologies of liver disease found very similar accuracy.[180]

The extent that ARFI is able to predict liver outcomes is unclear with conflicting studies, one study found ARFI measurements can accurately estimate the degree of portal hypertension as measured by HVPG [181] but another study found negative results for this.[182] The ability of ARFI to predict oesophageal varices also has conflicting evidence: ARFI measurements in those with and those without oesophageal varices were found to be similar in one study [183] although other studies have found that ARFI can predict the presence and degree of varices.[184-186] Conflicting data for ARFI and HCC also exists with both negative studies [183] and positive studies.[184, 187] Another study found that ARFI could predict those who were at higher risk of decompensation.[188] In all of the studies where ARFI and its correlation with outcomes had a positive result, the AUROC was quite low, ranging from 0.54 to 0.60 indicating that although there is a correlation ARFI was able to differentiate between those with and those without disease quite poorly.[183-188] Although ARFI may correlate with liver-related outcomes, further research regarding this aspect is required.

One of the benefits of ARFI is that it is integrated within a standard ultrasound device and thus can be performed during ultrasonography.[177] ARFI measurement location can also be specified by the user, resulting in greater control in avoiding vessels and other structures optimizing reliability.[189] It also be performed in patients with ascites and obesity.[189] It does have a learning curve [190] but with excellent interobserver reproducibility.[189, 190] ARFI can help to differentiate between those with and those without cirrhosis, but, so far, correlation with liver-related outcomes has conflicting data and thus requires further research.

2.1.4.2.3. Shear wave elastography (SWE)

SWE is performed using a specially designed ultrafast ultrasonic scanner that generates shear waves by focusing ultrasound at a given location; the speed of these shear waves are then measured.[191] It is performed similarly to ARFI but the difference is that SWE measures the waves in a bidimensional area or box shape rather than a single point.[191]

SWE is able to distinguish those with and those without cirrhosis accurately with a high AUROC of 0.94-0.97[191, 192] It can also predict liver-related outcomes with higher SWE results being correlated with higher rates of oesophageal varices,[193] decompensation [193] and HCC.[194]

SWE has benefits and limitations. Similar to ARFI, it can be performed in patients with ascites and obesity although with some limitations to the degree of ascites or obesity.[195] Similar to ARFI, the region of interest can be specified by the operator.[191] One of the limitations to SWE is that unreliable or invalid scans occur in 30% of patients with a body mass index (BMI) >30kg/m^2.[195] SWE also has a high interobserver variability, especially in inexperienced operators,[196, 197] and requires a higher degree of training and expertise compared to FibroScan®.[197, 198]

To summarise, SWE is useful to determine those at risk of having cirrhosis and those at risk of decompensation and HCC, although does require some training and is less useful in patients with obesity.

2.1.4.2.4. Magnetic resonance elastography (MRE)

MRE is a technique that uses magnetic resonance imaging (MRI) to assess the mechanical properties of the liver. It uses a mechanic driver to cause low frequency mechanical shear waves within the liver, it then measures the speed of the wave using MRI and then processes the information to produce an elastogram and LSM results.[137]

MRE is able predict the presence of and degree of fibrosis, as well as liver-related outcomes. MRE can distinguish between a normal liver and one with fibrosis,[138, 199-201] measurements correlate accurately with the degree of fibrosis [138, 202, 203] based on biopsy studies of multiple patients with different causes of liver disease.[137] MRE results also correlate with liver-related outcomes, including HCC development,[204, 205] hepatic decompensation [205] and overall survival rates.[205] Higher LSM results measured using MRE are also associated with decompensation in those with compensated cirrhosis.[206] MRE LSM results are also an independent predictor of HCC recurrence amongst patients with HCC that were treated.[207] MRE LSM also predicts the development of post-hepatectomy liver failure after resection of HCC.[208]

MRE has some benefits and limitations compared to other methods of elastography; unlike the other elastography methods, MRE is not affected by obesity (as long as the person can fit into the machine) nor ascites, nor is it affected by having bowel loops between the liver and the abdominal wall.[209] It also produces information about the distribution of fibrosis within the liver as it measures fibrosis within the whole liver.[5] It can also provide cross sectional imaging which adds extra information.[5] Although there are clearly significant benefits of MRE, there are limitations for this test. It cannot be performed in patients with morbid obesity

where they are too large to fit into the diameter of the machine.[210] It also cannot be performed in someone with a contraindication to an MRI such as non-MRI compatible pacemakers, cochlear implants or other implantable devices.[210] Other factors to consider include claustrophobia [210] and that the person also has to be able to hold their breath for at least 10 seconds.[5, 210] MRE is also not easily accessible. It is not portable, there are limited machines available and it is more costly than other methods of elastography.[211] MRE is a good option for fibrosis assessment in patients where it is available and there are no contraindications. To summarise, MRE is useful in estimating the degree of fibrosis and can also predict outcomes but has some limitations, mainly in accessibility.

2.1.4.3. Imaging with ultrasound

Ultrasound is a vital tool in the assessment of liver disease; however, it does have some limitations. The features of cirrhosis on ultrasound include a nodular liver edge, caudate lobe hypertrophy and signs of portal hypertension including altered hepatic venous flow and splenomegaly or decompensation with ascites. One of the issues with ultrasound is that micronodular cirrhosis may not have a nodular appearing liver macroscopically and patients with early cirrhosis are unlikely to have portal hypertension.

Ultrasound has been shown to have a variable sensitivity in detecting cirrhosis: in people living with viral hepatitis, ultrasound findings of a nodular liver edge had a sensitivity of 74% for cirrhosis but with a positive predictive value of only 24%.[212] In another study of a group of patients with high prevalence of cirrhosis (45%) the sensitivity was 87.5% and specificity was 81.5%.[213] Another study found that liver surface nodularity on ultrasound had a sensitivity of 54.2% but a positive predictive value of 86.6%, and finding any sign of cirrhosis on ultrasound had a sensitivity of 73% but a positive predictive value of 54%.[214] Ultrasound has also been shown to overestimate cirrhosis. In patients whose ultrasound demonstrated findings of cirrhosis without signs of portal hypertension, subsequent liver biopsy found only 68% had histological evidence of cirrhosis.[215] However conventional ultrasound of the liver does have significant benefits in liver disease. It is used in surveillance for HCC and it can detect signs of portal hypertension as well as fatty liver. Ultrasound is thus quite variable in detection and confirmation of cirrhosis but has a definite role in the management of liver disease.

2.1.4.4. Serological markers – indirect biomarker algorithms

Liver fibrosis may also be estimated using a combination of patient factors as well as serological tests. Patient factors include age, in which increasing age indicates a longer duration of disease and thus damage; and gender where male gender is often associated with higher risk of cirrhosis. Serological tests include markers of hepatic inflammation such as aspartate aminotransferase (AST), ALT and alpha fetoprotein (AFP). Other serological tests use markers of fatty liver and thus potential damage and include ALT, gamma-glutamyl transferase (GGT) and cholesterol. Markers of impaired liver function includes albumin as well as AST: ALT is elevated in the setting of decreased hepatocyte function as clearance rates of AST are decreased. Markers of hypersplenism occurring due to portal hypertension include platelet counts. Combining some of these markers in algorithmic form have been done in many ways, all of which have benefits and limitations.[216-218]

2.1.4.4.1. Aspartate aminotransferase to platelet ratio index (APRI)

APRI is one of the most commonly used serological based test for fibrosis in CHC. APRI is calculated using AST and platelets, assuming 35 is the upper limit of normal for AST:

$$APRI = (AST \div 35) \div platelets \times 100$$

AST: international units per litre (IU/L), Platelets: $x10^9$/L

APRI was originally developed in a cohort of people living with CHC but has since been validated in other diseases. It has been incorporated into the Australian guidelines for treatment of CHC where a result of less than 1 indicates a low probability of cirrhosis and that GP treatment may be appropriate.[10] In people living with CHC, an APRI of less than 0.5 indicates a very low probably of fibrosis, 0.5-1.5 indicates a moderate amount and greater than 1.5 indicates a higher probability of advanced fibrosis.[217, 219] A meta-analysis of 40 studies found that an APRI cut-off of 1.0 in people living with CHC was probably the ideal cut-off for cirrhosis based on sensitivity and specificity.[216] APRI has also been studied and validated for predicting the risk of cirrhosis in people living with CHB.[220, 221] APRI has an AUROC of 0.735 in determining those with cirrhosis, indicating it is average at determining between those with and those without cirrhosis.[222] A similar cut-off point of 1 is recommended by the WHO for cirrhosis risk stratification in people living with CHB.[9] One of the issues with APRI is that there are significant errors with this test; other causes of thrombocytopenia such as immune thrombocytopenia rather than from portal hypertension can falsely elevate results. A large degree of hepatic necroinflammation elevates AST levels which doesn't always

correlate with decreased hepatic function, rather is a sign of significant inflammation. One study of people living with CHB found that the standard APRI cut-offs of 1.0 and 2.0 misclassified 45% of patients as incorrectly having no cirrhosis.[221] There are thus limitations with APRI where a result of more than 1 does not necessarily indicate advanced fibrosis or cirrhosis. APRI is also able to differentiate between those with those with and those without severe portal hypertension in people living with CHB or CHC as measured by HVPG with an AUROC of 0.740.[223] APRI does correlate with liver-related outcomes: a meta-analysis of studies that included people living with CHB and/or CHC found that a high APRI correlated with higher rates of HCC development.[224] It has been suggested that APRI is most useful in areas without access to other forms of fibrosis assessment such as remote areas of Australia.[9] APRI is useful but does have significant limitations and should be interpreted with caution.

2.1.4.4.2. Mean fibrosis index based on four factors (FIB4)

FIB4 was originally developed to estimate the degree of liver fibrosis in a cohort of people living with CHC and HIV co-infection.[225] This is calculated using the following formula:

$$FIB4 = (age \times AST) \div (platelets \times \sqrt{ALT})$$

Age: years, AST: IU/L, Platelets: $x10^9$/L, ALT: IU/L

The standard accepted cut-off of below 1.45 has a negative predictive value (NPV) of 90% for excluding advanced fibrosis or cirrhosis (F3/F4) although with a positive predictive value of only 39% for cirrhosis; a cut-off of above 3.25 has a high specificity (96%) for cirrhosis and a NPV of 88%.[225, 226] Similar cut-off points have been found in people living with CHC or CHB mono-infection.[217]

Although FIB4 was originally developed in people living with CHC/HIV coinfection, it has been validated in other liver diseases. In people living with CHB mono-infection, FIB4 has an AUROC of 0.8450 in predicting those with cirrhosis; this means it is average to good at distinguishing between those with cirrhosis and those without.[222, 227] FIB4 has conversely also shown poor results in other studies of people living with CHB: one study found that 41% of patients with cirrhosis were incorrectly classified as having no cirrhosis using the standard accepted cut-off points.[221] In people living with CHC mono-infection, FIB4 is moderately accurate in predicting those with cirrhosis with an AUROC of 0.874, indicating that it is good at distinguishing between those with and those without cirrhosis.[217] FIB4 is adequate at differentiating between those with those with and those without severe portal hypertension in people living with CHB or CHC as measured by HVPG with an AUROC of 0.744.[223] FIB4

has also been shown to correlate with risk of HCC in people living with CHB [228] and CHC [229, 230] with increasing FIB4 associated with increased HCC risk.

FIB4 is thus useful in determining the risk of cirrhosis and HCC risk in people living with CHB and/or CHC although should be interpreted with caution.

2.1.4.4.3. Forn's index

Forn's index was originally developed in a cohort of people living with untreated CHC infection.[218] Forn's index is calculated using the following formula:

$$Forn's\ index = 7.811 - (3.131 \times \ln[platelets]) + (0.781 \times \ln[GGT]) + (3.467 \times \ln[age]) - (0.014 \times cholesterol)$$

Platelets: x10^9/L, GGT: IU/L, Age: years, cholesterol: mmol/L

Forn's index has a high AUROC at 0.879 for differentiating between patients with and without cirrhosis indicating a high diagnostic accuracy.[217] In the original study, the optimal cut-off point for excluding those with advanced fibrosis was 4.2, and this had a NPV of 96% for significant fibrosis.[218] The utility of the Forn's index in diagnosis of cirrhosis in people living with CHC has also been validated in other studies.[217, 231] Forn's index does not perform as well in people living with CHB with an AUROC of 0.7 for differentiating between those with and those without cirrhosis.[232] Forn's index can also predict the grade of oesophageal varices in patients with cirrhosis,[233] although, in people living with CHB or CHC, it is poor at differentiating between those with those with and those without severe portal hypertension as measured by HVPG with an AUROC of 0.690.[223] Forn's index also correlates with HCC risk [234] and, after resection of HCC, can predict HCC recurrence and mortality.[235]

Forn's index has clinical utility for differentiating between patients with and without cirrhosis and risks of liver-related outcomes, although like the previous tests, has some inaccuracies.

2.1.4.4.4. 4AGP

4AGP was developed as part of the CATCH study and is part of Dr Bloom's thesis.[7] It comprises four variables beginning with 'a' and one of each of "g" and "p". 4AGP is calculated using the following formula:

$$4AGP = (0.16 \times AFP) - (0.2 \times albumin) + (0.2 \times AST) + (0.05 \times age) + (1.51\ if\ male) - (0.01 \times platelets)$$

AFP: alpha-feto protein, ug/L, Albumin: g/L, AST: IU/L, Age: years, Platelets: x10^9/L

It was developed using binary logistic regression boot strap analysis to identify factors that were predictive of an LSM ≥12.5kPa in people living with CHC.[236] The optimal cut-off point for determining patients with an LSM ≥12.5kPa was ≥ -4.32, with an AUROC of 0.922.[236] The 4AGP and LSM correlation was repeated with a validation cohort of people living with CHC within the CATCH study with very similar results.[236] 4AGP has not been studied to determine whether it can predict liver-related outcomes and has not been studied in people living with CHB.

2.1.4.5. Serological markers – direct biomarkers

Development of liver fibrosis and regeneration of the liver is dynamic: there is a cycle of ECM deposition and degradation. There are direct biomarkers which are serological measures of fibrosis and regeneration. These direct biomarkers have been studied individually but are most used in combination with other factors and variables to predict those at risk of cirrhosis. Hyaluronic acid is the most well-known direct biomarker and has repeatedly been shown to have a high diagnostic accuracy for predicting advanced fibrosis or cirrhosis.[237, 238]

2.1.4.5.1. Hepascore®

One example of combined panel of direct biomarkers and other factors is Hepascore® which is a validated predictor of liver fibrosis in CHC. Hepascore® includes bilirubin, GGT, hyaluronic acid, alpha 2 macroglobulin, age and gender.[239]

2.1.4.5.2. The Enhanced Liver Fibrosis (ELF) score

The ELF score is another logarithmic algorithm of of direct markers including hyaluronic acid, N-terminal peptide of procallagen III and tissue inhibitor of matrix metalloproteinase 1.[240] The ELF score has a high negative predictive value for advanced fibrosis (AUROC 0.81) and a moderately high positive predictive value for cirrhosis (AUROC 0.78),[241] although is less accurated in diagnosing cirrhosis in Asian patients living with CHB.[242] The ELF score has also been shown to predict liver related events[243-246] and can predict portal hypertension as measured by HVPG.[247] A prospective study of 3012 patients with NAFLD that were referred for hospital outpatient management were risk stratified using FIB4 followed

by the ELF score if needed. This study found significant benefits with unnecessary referrals decreasing by 88%.[248]

These direct biomarkers algorithms aren't used in everyday practice as they are not funded more by Medicare so there is an out-of-pocket cost for the patient.

2.1.4.6. Comparisons of different ways to measure liver fibrosis

The different methods to assess fibrosis all have benefits and negatives, and the differences in accuracy and reliability between these methods will now be discussed.

FibroScan® and acoustic radiation force impulses:

FibroScan® is either similar or possibly more accurate than ARFI in diagnosing fibrosis or cirrhosis.[249-251] One study suggested FibroScan® was superior with a correlation coefficient of 0.70 compared to 0.64 in ARFI [250] and another study found that FibroScan® was better at diagnosis of cirrhosis but very similar in differentiating between different degrees of liver fibrosis.[251] Another study found them to have very similar AUROC in people living with CHB and/or CHC.[178] In regard to failure rates, FibroScan® failure rates are higher [249, 250] with one study having rates of 2.6% compared to 0% in ARFI,[250] however, ARFI has higher rates of unreliable test results at 16% compared to 5.9% in FibroScan®.[250] One meta-analysis that suggested that FibroScan® had higher failure and higher unreliable result rates, had many studies that used only an M probe without an XL probe for FibroScan®.[249] FibroScan® failure rates are lower when the XL probe is available [195] and FibroScan® using the XL probe is superior to ARFI for obese patients.[195] ARFI also has conflicting evidence about its ability to determine risks of liver-related outcomes as discussed above. FibroScan® is thus likely to be superior to ARFI, but only if an XL probe is available.

FibroScan® and shear wave elastography:

Studies have also shown conflicting evidence when comparing SWE and FibroScan® accuracy. SWE is likely to be similarly accurate to FibroScan® in diagnosis of cirrhosis [250-252] Conflicting data exists in these two modalities ability to differentiate between different degrees of fibrosis with SWE having been shown to be superior in one study,[250] and FibroScan® being superior in another study.[251] SWE also has lower scan success rates than FibroScan® at 79% versus 92% [252] with similar comparable failure rates in other studies,[250] however, unreliable results rarely happen with SWE.[250] Thus data regarding SWE and FibroScan® is conflicting.

FibroScan® and magnetic resonance elastography:

MRE is superior to FibroScan® in determining the degree of fibrosis and diagnosing cirrhosis, and MRE had the highest AUROC indicating it was best able to distinguish between those with and those without disease compared to FibroScan®.[200, 252, 253] MRE also had the highest coefficient of repeatability indicating best correlation with biopsy.[200] MRE had similar success rates to FibroScan® at 91% and 92% respectively.[252] MRE is superior to FibroScan® but the biggest limitation is accessibility and cost of MRE.

Acoustic radiation force impulses and shear wave elastography:

SWE and ARFI also have conflicting evidence regarding which test may be superior; one study found that SWE was superior to ARFI in determining the degree of fibrosis but these two tests were similar in diagnosing cirrhosis.[250] Another study found that SWE was superior in diagnosis of cirrhosis but inferior in determining the degree of fibrosis.[251] Another study found that SWE was more accurate for cirrhosis but the two tests were fairly even for the diagnosis of the degree of fibrosis.[254] SWE, however, has higher failure rates than ARFI.[250]

Magnetic resonance elastography and acoustic radiation force impulses:

MRE is superior to ARFI in patients with NAFLD and obesity, although in non-obese patients with NAFLD these two tests were very similarly accurate.[255] A meta-analysis has also suggested that MRE is superior to ARFI for all stages of fibrosis but especially in diagnosis of early stages of fibrosis.[256]

Magnetic resonance elastography and shear wave elastography:

In determining the degree of fibrosis and cirrhosis, MRE is likely to be superior to SWE [252, 257] and MRE has consistently higher success rates than SWE.[252, 257]

Elastography and indirect biomarkers:

Elastography tests are consistently more accurate than indirect biomarkers at determining the degree of fibrosis. APRI is inferior to MRE,[200] FibroScan®,[150, 159, 200] and ARFI.[258] FIB4 is also inferior to FibroScan®.[259] Forn's index may be superior to APRI and FIB4 in regards to prediction of cirrhosis and significant fibrosis,[217] although APRI is likely to be superior in differentiating between those with and those without clinically significant portal hypertension.[260] APRI and FIB4 are similar in the accuracy in fibrosis degree with a Spearman's rank correlation coefficient of 0.43 and 0.51 respectively;[227] this

is much a much lower number than elastography methods in previous studies indicating they may be inferior in determining degrees of fibrosis. APRI and FIB4 are also not as cost effective as FibroScan® to inform treatment decisions in people living with CHB.[261]

Combining tests:

So far in this section, the different methods of elastography had been discussed: combining tests has been shown to be more accurate than using one test alone. Combining ARFI and TE was shown to have a higher AUROC than using one of the tests alone.[154] Combining MRE, FibroScan® and APRI results has a very high correlation with the degree of fibrosis, higher than any of these 3 alone.[200] Combining FibroScan® and APRI is also better at diagnosis of cirrhosis than FibroScan® alone.[200] Elastography using ARFI is more accurate than APRI at estimating the degree of fibrosis in people living with CHC; however, combining the two measures was more accurate again.[258] APRI was inferior to FibroScan®, again, combining these two is more accurate that using one measure alone.[150] One other study found that combining ARFI, APRI and patient characteristics was more accurate than any one method alone,[262] and combining APRI and FIB4 is more accurate than using one of these alone.[226] Australian guidelines for FibroScan® suggest interpreting LSM results in a clinical context by combining the LSM results with a pre-test clinically assessed probability for cirrhosis.[263] Using multiple methods of fibrosis assessment is more reliable than relying on one test alone and this is usually performed in clinical practice.

2.1.4.7. Cost effectiveness

FibroScan® is also more cost-effective when compared to SWE, indirect biomarkers and direct biomarkers. It was the only cost-effective method of fibrosis assessment that increased survival time in patients subsequently diagnosed with HCC based on diagnosis of cirrhosis and appropriate HCC surveillance.[7, 8]

2.1.4.8. Summary

To summarise, there are many effective tests for fibrosis. Although liver biopsy is gold standard, it has quite a few drawbacks with risks of the procedure and missed pathology. MRE is likely to be the most accurate to determine the degree of liver fibrosis; however, it is not portable and this, combined with the cost, limits the use of this test. Data suggests that FibroScan® is equivalent or even superior to ARFI and SWE in diagnostic accuracy, especially if an XL probe is available. FibroScan® also has the most validation data regarding its ability to predict the risk of liver-related outcomes and has been shown to be cost effective. There is

a learning curve with all these tests and expertise of the user is an important consideration. Combining tests and clinical suspicion rather than using one result in isolation is likely the optimal method for accuracy; however ultimately, the choice of which method(s) to use is based on availability and local expertise.

Assessment of the degree of fibrosis is an important part of health care. Increasing degrees of fibrosis have increasing risks of complications including HCC. Those with cirrhosis are at risk of HCC, however HCC can also occur in people living with CHB and NAFLD without cirrhosis. Determining those at risk of HCC is important as surveillance in those at risk improves outcomes.

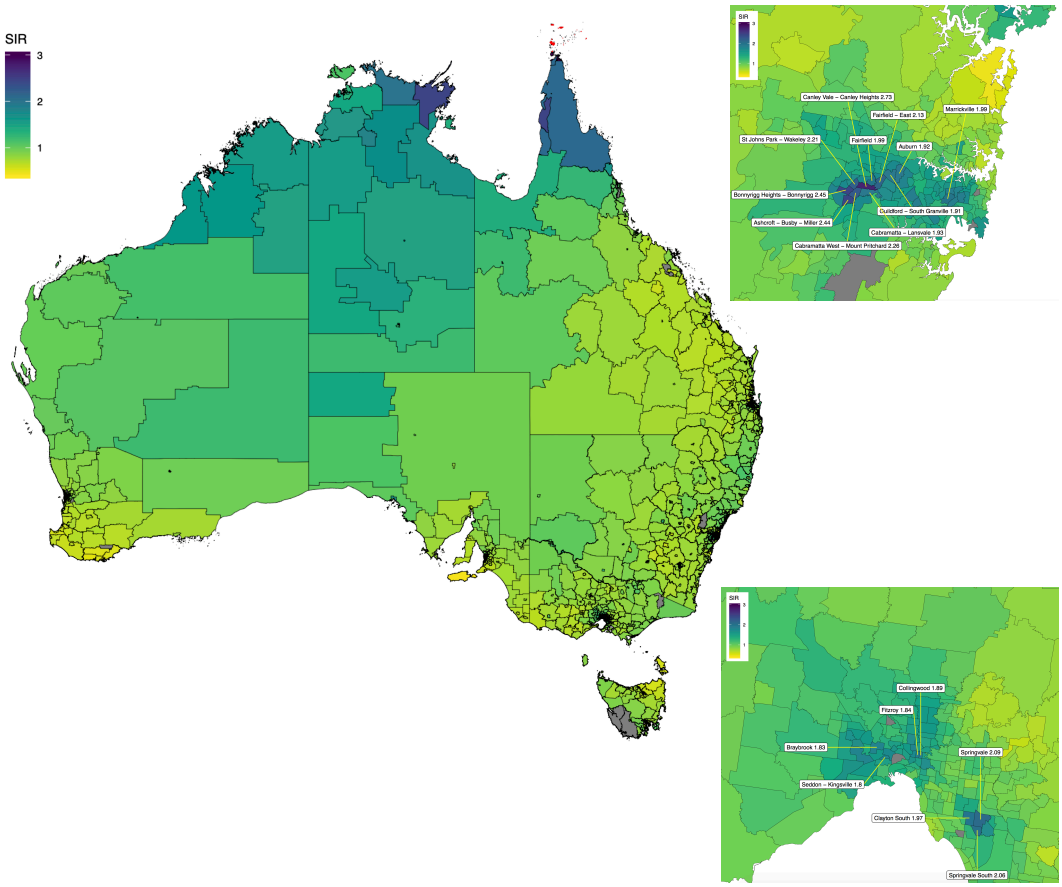
2.1.5. Hepatocellular carcinoma

Primary liver cancer includes HCC (70-82% of all liver cancer cases)[264, 265] and cholangiocarcinoma as well as other rare primary liver cancers.[265] Primary liver cancer is now the fifth most commonly diagnosed cancer worldwide and is the second highest cause for cancer related deaths.[265-267] HCC is responsible for the most rapid increase in liver-related deaths in Australia over the last 4 decades,[268] although survival time over this same period has increased due to improvements in surveillance and treatment.[269] In Australia, it is estimated that 2297 patients will have died from liver cancer in 2020.[270] The risk factors for HCC and indications for and how to perform surveillance will now be discussed.

2.1.5.1. Risk factors for hepatocellular carcinoma

HCC is most commonly diagnosed in patients with cirrhosis, with data from Melbourne, Australia, showing that 83% of patients diagnosed with HCC had cirrhosis.[18] The most common risk factors for HCC in Australia in a 2018 study was CHC (41%), alcohol related liver disease (39%) and CHB (22%).[18] Male gender had a much higher risk of HCC with 80% of HCC cases in Australia being in men. More recent Australian data has shown that CHB has become a less common aetiology with ALD and NAFLD becoming more common.[7] A high percentage of HCC cases in Australia occur in patients born overseas (45%) [269] and HCC incidence is highest in areas of low socioeconomic status with the highest incidence in very remote areas of Australia (Figure 2-4).

Figure 2-4 Standardised incidence of hepatocellular carcinoma in Australia, 2005-2014



Reprinted from Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. Melbourne: Gastroenterological Society of Australia, 2020. SIR: standardised incidence ratio, the ratio of the observed number of cases to the expected number of cases for age-specific rates in 5-year age bands.

2.1.5.1.1. Cirrhosis

HCC is most commonly diagnosed in patients with cirrhosis, where there is approximately a 2-7% incidence per year.[266, 267] The majority (83%) of all cases of HCC occur in patients with cirrhosis, with HCC in non-cirrhotic livers occurring predominantly in CHB or NAFLD.[18]

2.1.5.1.2. Non-Cirrhotic chronic hepatitis B

People living with non-cirrhotic CHB infection are also at risk of developing HCC depending on age, gender, ethnicity, family history and viral factors and surveillance is recommended based on a combination of these.[271] Males have higher risk of HCC than females based on certain genetic factors, and increasing duration of infection (and thus age) also leads to higher risk of HCC.[272] However, HCC is approximately 17 times more common

in people living with CHB *with* cirrhosis than CHB *without* cirrhosis.[272] As a result, those with CHB who should be screened with a 6 monthly ultrasound include:

- Anyone with cirrhosis
- Asian males over the age of 40 years
- Asian females over the age of 50 years
- Africans over the age of 20 years (increased risk at a younger age due to the presence of aflatoxins, and possibly due to different Hepatitis B genotype)[272]
- Anyone with a family history of HCC

Although there are HCC risk scoring systems for white people living with non-cirrhotic CHB on antiviral treatment,[273, 274] the risk of HCC and thus surveillance of HCC in white people living with untreated non-cirrhotic CHB infection is not clear.

2.1.5.1.3. Family history

Family history also increases the risk of HCC but the evidence is complex with cofounding factors as there are usually shared risk factors such as CHB or alcohol intake.[11, 275] Guidelines suggest surveillance for anyone with a first degree relative diagnosed with HCC, however, if the family member with HCC has a risk factor for HCC but the patient does not, then the risks are unknown but likely much lower.[11, 275] It is also unclear at what age family members should be screened.[11, 275]

2.1.5.2. Surveillance for hepatocellular carcinoma

Surveillance for HCC is a vital part of medical management in patients who are at risk of HCC. Surveillance is performed by liver ultrasound with or without AFP every six months.[11, 271] Six months appears to be the best interval based on cost and likelihood of early diagnosis of HCC.[276] Cost effectiveness of HCC surveillance is based on the severity of the underlying liver disease and the incidence of HCC: in patients with cirrhosis, a threshold of annual HCC incidence of 1.5% is the cut-off for cost-effectiveness for surveillance. In non-cirrhotic patients meeting age/gender/ethnicity CHB criteria, the cut-off is lower at 0.2% annual incidence as treatment options are wider given preservation of liver function.[277] Table 2-1 summarises those patients who should undergo surveillance and their estimated annual incidence of HCC.

Table 2-1 Populations where surveillance for hepatocellular carcinoma is recommended

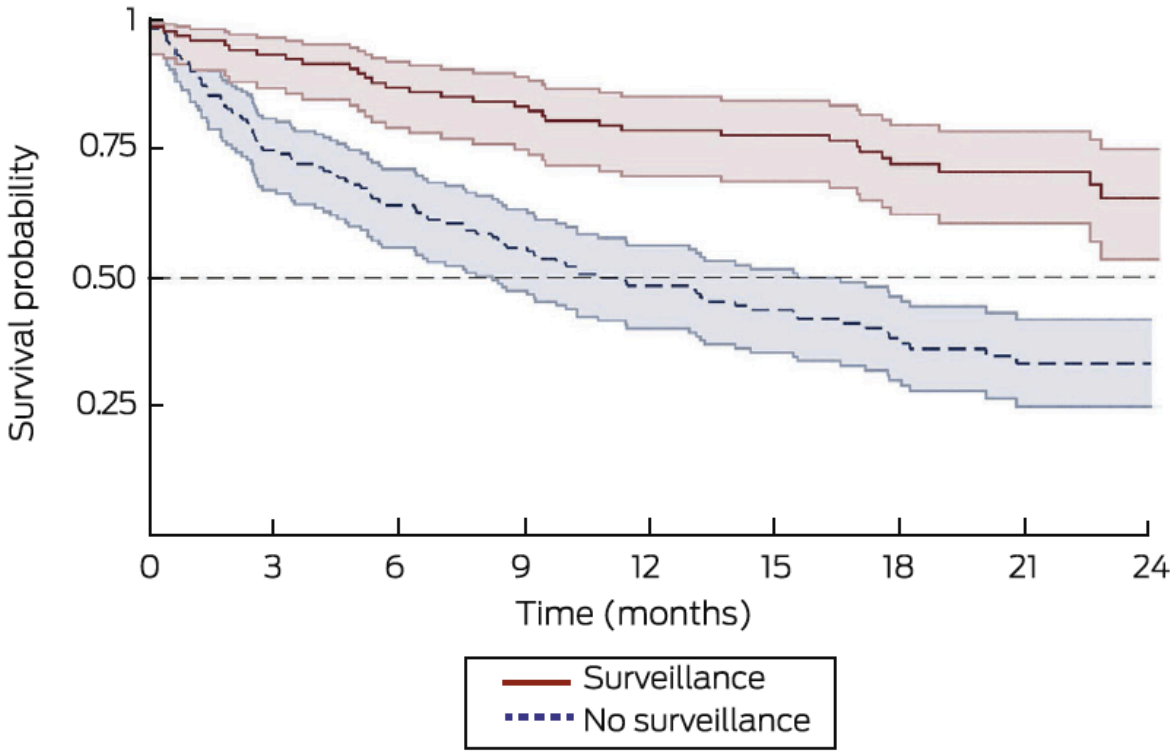
Population	Estimated incidence
Anyone with cirrhosis: Any cause without decompensation Any cause with decompensation where liver transplant would be considered	2-7%
HBV non-cirrhotic:	
Asian females >50 years	0.3-0.6%
Asian males >40 years	0.4-0.6%
Africans >20 years	Variable*
Non-Asian/non-African females >50 years	Unknown*
Non-Asian/non-African males >40 years	Unknown*
Family history HCC	Unknown*

*variable or unknown but likely to have an incidence above the cost-benefit threshold; Data from Diaz-Gonzalez A, Forner A. Surveillance for hepatocellular carcinoma. Best Pract Res Clin Gastroenterol 2016; 30: 1001- 1010.

2.1.5.3. Benefits of hepatocellular carcinoma surveillance

Surveillance for HCC in those who are at risk has significant benefits. Surveillance has been shown to increase the chance of diagnosing HCC at an earlier and potentially curable stage, with those who did not have surveillance being more likely to have larger and more advanced disease at presentation.[18, 276, 278] Patients who undergo HCC surveillance are also more likely to have curative therapy with reported rates of curative therapy in 46.5% of those diagnosed during routine surveillance compared to 7.5% in those not having surveillance.[278] One other study showed that, of those who were offered curative treatment, 60% were in a surveillance program, whereas of those whose treatment was palliative, only 30% were in a surveillance program.[18] Surveillance for HCC with a 6 monthly ultrasound also leads to improved survival.[18, 276, 278] Figure 2-5 shows the survival curve from Hong et al [18] comparing those who were having surveillance and those who were not having surveillance at time of HCC diagnosis, there is a clear survival benefit with surveillance. Given the issues surrounding surveillance and lead time bias where there is an overestimation of survival due to earlier detection of cancer during surveillance, one study looked at this specifically and found that although short term mortality benefit is likely affected by lead time bias, there is definite long term survival benefit with surveillance for HCC.[276]

Figure 2-5 Kaplan Meyer curve: survival by participation in hepatocellular carcinoma surveillance



Reprinted from: Hong, T.P., et al., Surveillance improves survival of patients with hepatocellular carcinoma: a prospective population-based study. Med J Aust, 2018. **209**(8): p. 348-354

2.1.5.4. Harms and limitations of hepatocellular carcinoma surveillance

Although there is benefit to HCC surveillance, there are limitations and potential harms for patients, including false positive and false negative results, costs of tests to both the patient and Medicare, the risks of investigations and psychological impacts of surveillance and its results. False positive results or indeterminate nodules often lead to extra investigations, some of which have risks. Computed tomography (CT) is associated with radiation exposure, cost and contrast nephropathy. The risk contrast nephropathy can be as high as 25% in hospitalised patients with cirrhosis who have had a CT.[279] One study of 999 patients at risk of HCC who were having HCC surveillance found 18.7% of patients required further investigations for indeterminate nodules that were subsequently found to be benign.[280] One other study found 27.5% of patients undergoing HCC surveillance had CT or MRI or liver biopsy for false positive results.[281] One point to note from both of these studies is that there were high rates of early HCC diagnosis.

There is limited data regarding psychological and financial harms of HCC surveillance, however, there is evidence for these harms with other cancer surveillance programs.[282, 283] Overdiagnosis can also occur with detection of dysplastic nodules, indolent HCC or HCC in a patient with high risk of mortality from other health issues. High grade dysplastic nodules can have similar radiological features to HCC on imaging.[284] HCC has a very poor 5 year survival (15%) and thus is regarded as a generally aggressive cancer, however, there are some HCCs that are more indolent especially in patients with non-viral causes of cirrhosis.[285] Despite these limitations and potential harm, the consensus is that HCC surveillance is beneficial. There are also other limitations to HCC surveillance as patients need to be identified to be at risk of HCC and then have appropriate surveillance.

The sensitivity of ultrasound for HCC surveillance also varies, with higher rates of false negatives in patients with obesity and thus poorer liver views. The sensitivity varies from 87% in those with a BMI <30 compared to 76% in those with a BMI >30.[286] Another study found that almost 20% of ultrasounds for HCC surveillance were inadequate with higher failure rates (more than 30%) in patients with BMI >35, cirrhosis due to NAFLD and Child Pugh C cirrhosis.[287] To overcome this limitation, imaging with CT or MRI has been suggested as an alternative. MRI was superior to ultrasound and CT for early HCC diagnosis, however, it is expensive, has long scan times and is not easily accessible.[288] An abbreviated MRI which is shorter (20 minutes) and thus lower cost has also been found to be superior to ultrasound for early HCC diagnosis.[289, 290] Although not yet part of standard care, HCC surveillance with an abbreviated MRI may be an option in the future, especially in those at higher risk of missed lesions on ultrasound. Longitudinal AFP monitoring has been shown to be accurate when the pattern of AFP is assessed.[291, 292] Other HCC tumour markers have been studied but have not met the requirements for cancer surveillance.[293]

2.1.5.5. Participation in hepatocellular carcinoma surveillance

Surveillance participation rates are very variable but are often quite low. Definitions of participation vary between studies from ever having had an ultrasound up to having an ultrasound every six months exactly which makes comparison of studies difficult. There are varying but generally quite poor rates of appropriate HCC surveillance in patients who are at risk of HCC: rates of surveillance worldwide range from 1.7% to 33%.[294-298] Even countries with national HCC surveillance programs are in place have low rates of surveillance.[294, 295, 297] Rates are poor even in patients with cirrhosis and thus at high risk of HCC. One study in the United States of America found that only 14% of people living with

CHB and cirrhosis had surveillance.[298] Even of those actively participating in surveillance programs, the frequency of ultrasounds is low: one study in China found that patients only completed 58.2% of the surveillance ultrasounds offered.[278] One other Unites States of America study also found that, of patients at risk of HCC, only 6.7% of patients had complete surveillance with an ultrasound every six months, 59.6% had inadequate surveillance and 33.7% had never had an ultrasound.[297]

In Australia, there is a paucity of data regarding participation rates and adherence rates in HCC surveillance programs. One single centre study found that only 10% of people living with CHB at risk of HCC had had an ultrasound within the preceding seven months.[299] One small Australian study of 22 patients at risk of HCC found that 46% had had an ultrasound within the last six months, but none had had the recommended frequency over the preceding two year period.[300] One other Australian study that looked at patients diagnosed with HCC found that only 38-40% were undergoing appropriate surveillance at time of HCC diagnosis.[18, 301] Of the 60% who were not in a surveillance program, the majority had an indication for surveillance: cirrhosis (76%) or non-cirrhotic HBV (11%) and of those with cirrhosis, 60% were not known to have cirrhosis prior to the diagnosis of HCC.[18]

Critical to the success of a surveillance program is optimisation of participation rates, factors associated with lack of participation in surveillance programs has been studied. There are lower rates of surveillance in those with non-cirrhotic CHB compared other indications. This data suggests that those who were having appropriate surveillance were less likely to be Australian born or Asian. White patients born outside of Australia had the highest rates of surveillance.[18] In overseas studies, factors associated with lower rates of HCC surveillance included younger age,[302] lower socioeconomic status,[294, 297, 302] lower frequency of clinic visits (either community or hospital based) and being managed by a doctor other than non-GP specialist.[298] Lack of awareness of diagnosis and thus risk was also associated with lower rates of surveillance.[302]

There have also been studies assessing different methods to improve HCC surveillance rates. In Australia, a chronic disease management system that provides clinical information system and patient self-management support has been shown to increase HCC surveillance rates.[303] Similar findings have also been found in overseas studies with rates of ultrasound within the preceding 12 months increasing from 74% to 93% after implementing a chronic disease management system.[304] Other overseas measures that have been shown to increase HCC surveillance rates include a national cancer surveillance programs [295, 302] and reminder

letters.[305, 306] In Australia, using an integrated hepatitis B nurse in community clinics who educated GPs, contacted patients, added in recall and reminder systems and organised the ultrasounds, increased the rate of having an ultrasound within the preceding 12 months from 7% to 56%. However, even with this intervention, 13% had an ultrasound less often than two yearly and 12% had no ultrasounds despite ultrasound requests having been ordered in 90% of patients at least every two years.[299] Within a tertiary centre in Australia, rates of surveillance increased with education of doctors and patients and a system redesign: from 0% to 64% having had four ultrasounds within the preceding two years, and 46% to 92% having an ultrasound within the preceding six months.[300]

2.1.5.6. Diagnosis of hepatocellular carcinoma

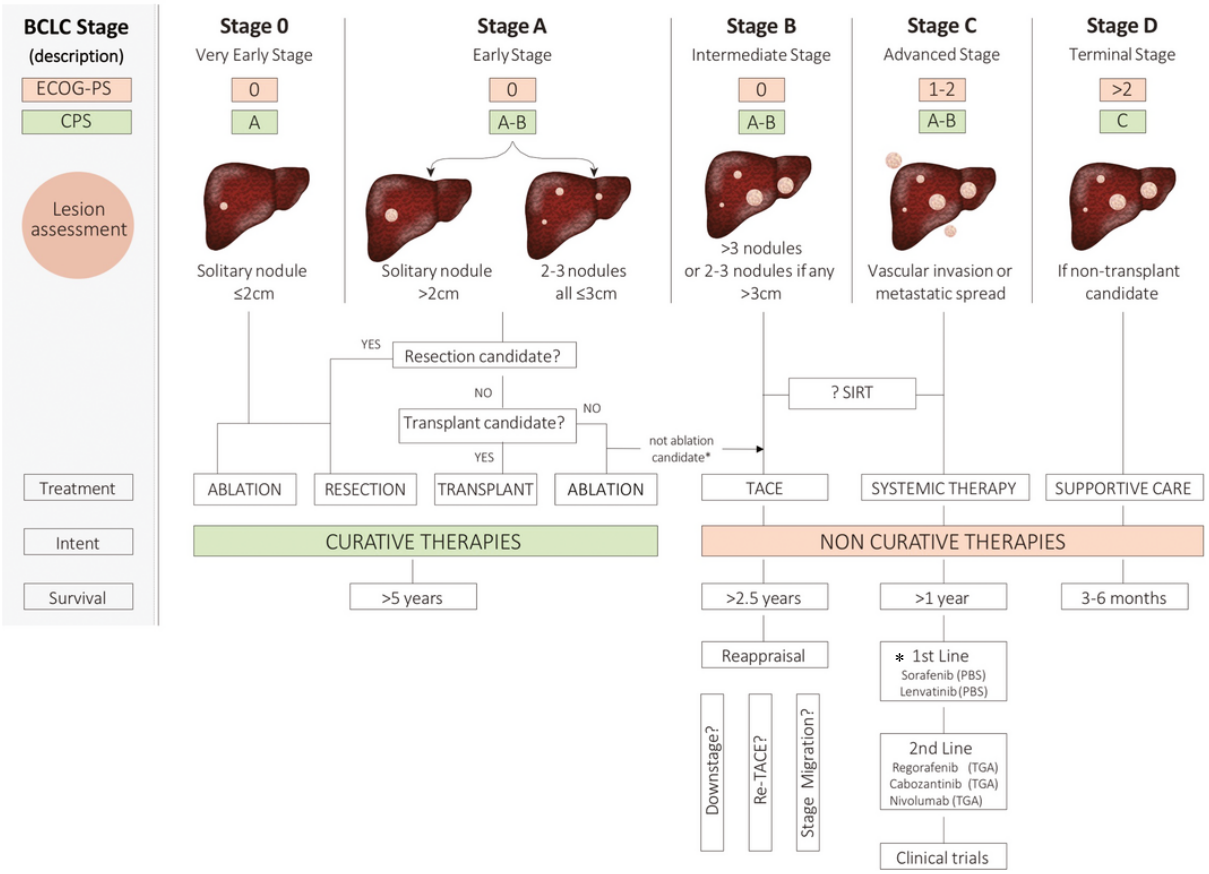
HCC is one of the only cancers that can be reliably diagnosed based on radiological criteria. In patients with cirrhosis, diagnosis of HCC can be made by contrast enhanced cross-sectional imaging; in non-cirrhotic patients with suspected HCC, a biopsy is required to confirm the diagnosis.[307] The typical imaging features of arterial phase hyperenhancement and washout on portal venous phases is due to altered vascular architecture within the tumour.[307] The imaging classification used is the Liver Imaging Reporting and Data System (LI-RADS) where the imaging characteristics are graded from LR-1 (definitely benign) to LR-5 (definitely HCC).[308] Cross sectional imaging also provides information about the stage of HCC.

2.1.5.7. Staging and treatment of hepatocellular carcinoma

Treatment of HCC is either curative or non-curative/palliative. The decision of which treatment to offer is based upon the stage of HCC, which considers multiple factors including tumour factors, underlying liver function and patient functional status factors. Tumour factors include size and number of HCC nodules, location within the liver and whether there is vascular invasion or metastatic spread. Underlying liver function guides treatment suitability, as, if there is decompensated liver disease, treatment options are more limited. Patient functional state refers to the persons level of activity that has been affected specifically by HCC. The most used staging system in Australia is the Barcelona Clinic Liver Cancer (BCLC) staging system. The BCLC staging system stages HCC from 0 (very early stage) then from A (early stage) to D (terminal stage) and has a suggested treatment option for each stage as well as median survival with each of these options. This is shown in Figure 2-6. Patients with earlier stage disease and without liver decompensation are more likely to be able to have curative therapy. Curative therapy includes resection, liver transplant and ablative therapies including microwave ablation

(MWA); radiofrequency ablation (RFA) and, now rarely used, percutaneous ethanol injection (PEI). Non curative therapy includes transarterial chemoembolisation (TACE); drug-eluting bead TACE (DEB-TACE); transarterial radiation therapy (TARE); stereotactic beam radiology (SBRT); systemic therapy and best supportive care.[11] First line systemic therapy is now combined Atezolizumab and Bevacizumab, listed on the PBS since November 2020.[45, 307]

Figure 2-6 Barcelona Clinic liver cancer staging system and treatment algorithm for hepatocellular carcinoma



CPS: Child–Pugh Score; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; PBS: Pharmaceutical Benefits Scheme; SIRT: selective internal radiation therapy; TACE: Transarterial chemoembolisation; TGA: Therapeutic Goods Administration. The BCLC staging system is the preferred system for classifying hepatocellular carcinoma; the stage is calculated from three clinical parameters: liver function, tumour characteristics, and functional status of the patient. Source: Hepatocellular Carcinoma Consensus Statement Working Group. Australian recommendations for the management of hepatocellular carcinoma: a consensus statement. Melbourne: Gastroenterological Society of Australia, 2020. *1st line therapy is now combination Atezolizumab and Bevacizumab.

2.1.5.8. Response to treatment of hepatocellular carcinoma

Response to treatment is measured based on the modified Response Evaluation Criteria in Solid Tumours (mRECIST) criteria.[309] This criteria grades the tumour radiologically:

complete response (CR) indicates no visible viable tumour, partial response (PR) indicates more than 30% reduction in the size of the tumours, stable disease indicates minimal change, and progressive disease (PD) indicates increase by 20% in the size of the tumours. This classification is important as the response correlates with outcomes and benefit of ongoing treatment.

To summarise, surveillance for HCC in those at risk is vital as it leads to earlier diagnosis and improved mortality. A large percentage of at-risk patients are not having appropriate surveillance, and quite a few patients diagnosed with HCC are unaware that they even have cirrhosis. It is important to determine the risk of HCC by assessing the degree of fibrosis as well as patient factors to ensure appropriate surveillance occurs. Treatment is based upon multiple factors: patients with more advanced liver disease or larger tumours are less likely to be able to have curative therapy. Patients who are not having surveillance are more likely to be diagnosed with later stage HCC and are thus less likely to be able to be offered curative therapy.

2.1.6. Management and Treatment of viral hepatitis

2.1.6.1. Treatment of chronic hepatitis B

As previously discussed, without treatment of CHB, there is a 15-25% chance of death due to this disease.[23] There are very efficacious treatments available, which significantly lower the chance of developing of fibrosis and also lower the risk of HCC by up to 75%.[23, 310] Treatment of CHB with antiviral therapy in Australia is also a cost-effective cancer prevention strategy.[311] Antiviral therapy for people living with CHB is not recommended in everyone: about 10-30% of people living with CHB require treatment.[1] Antiviral therapy for people living with CHB is usually considered in patients who have cirrhosis or who are in a phase where there is hepatic inflammation occurring, as these are the groups where treatment is most beneficial.[9] It is often also considered in people living with CHB with a family history of HCC.[23] Antiviral therapy in Australia is with entecavir, tenofovir or, less commonly, pegylated interferon, which are funded on the PBS.[45] The PBS states that these medications should only be used in patients with cirrhosis and a detectable viral load, or with HBeAg positive hepatitis or HBeAg negative hepatitis.[45] There is no PBS funding for the use of antiviral therapy in lowering HCC risk in patients with a family history of HCC or during pregnancy to lower vertical transmission risk without one of these other indications.[45]

Antiviral therapy is also considered, but not PBS funded, in patients who are immunosuppressed as these patients have risk of CHB flare with significant liver damage.[9]

2.1.6.2. Treatment of chronic hepatitis B in Australia

In Australia, the percentage of people living with CHB on antiviral therapy is far lower than the recommended targets set out in the Third National Hepatitis B Strategy.[1] This is due to low rates of diagnosis, linkage into care and thus subsequently treatment.[1] The biggest gaps in care in Australia are diagnosis and long-term follow-up or linkage into care.[13, 312] Treatment of CHB with antiviral therapy if efficacious: it has had a positive effect on CHB morbidity and mortality in Australia: from 2017 to 2019, the reduction in deaths due to CHB was 5.5%.[13] Treatment has also lowered rates of HCC due to CHB.[313] Treatment is also cost effective at lowering HCC risk in Australia.[311] The concern is that despite this decrease, CHB related mortality is likely to increase due to immigration and an aging population.[13]

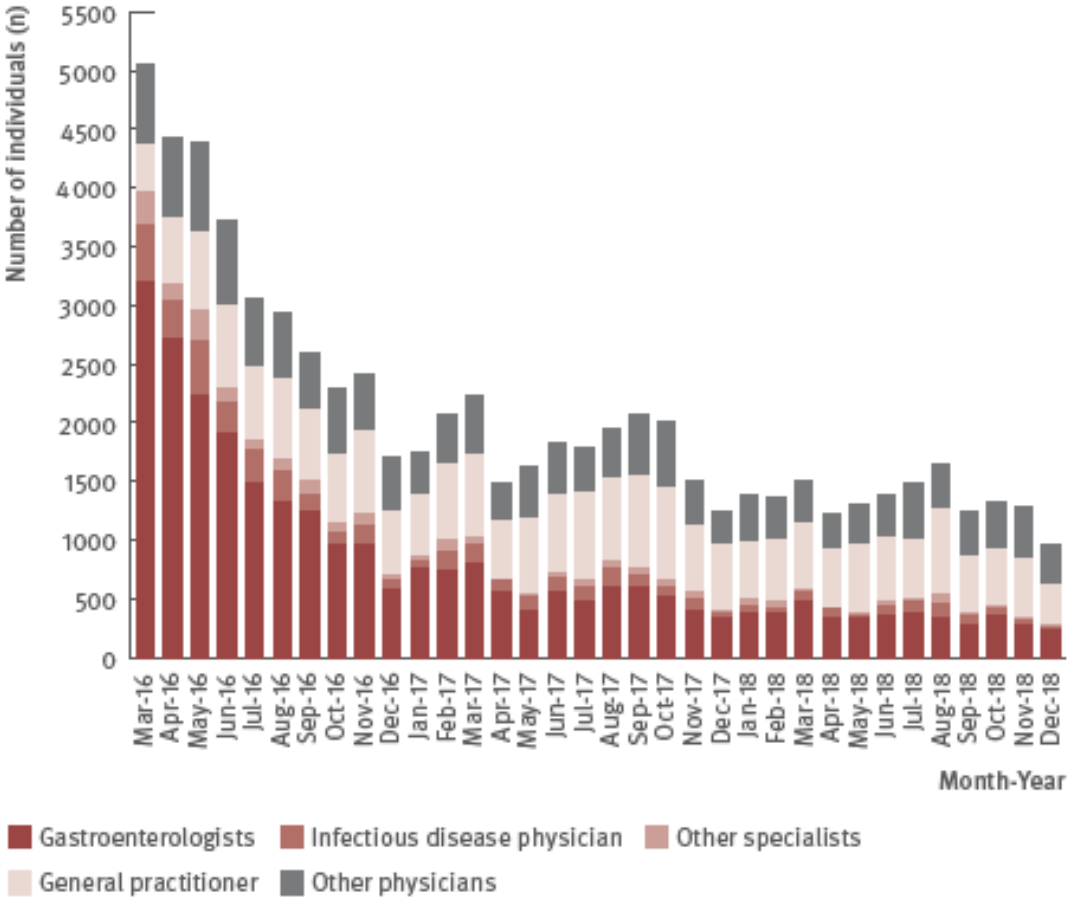
2.1.6.3. Treatment of chronic hepatitis C

Treatment of CHC can prevent the development of, and complications of cirrhosis, and can improve liver function in those with cirrhosis and decompensation. There have been significant advances in therapeutic options for patients infected with CHC, with the introduction of DAAs which offer very high chances of cure, with minimal side-effects with simple dosing regimens.[10] These DAAs rapidly reduce viral replication by affecting the polymerases or essential proteins (always a combination of 2 of NS5A, NS5B, NS3 inhibitors) required by the virus. DAAs are now considered standard of care for the treatment of CHC and became available on the PBS on the 1st of March 2016. These new therapies are oral regimens which are very efficacious: there is a 90-98% likelihood of SVR which represents long-term cure.[10] The choice of which DAAs to use and for how long depends on degree of fibrosis and whether the person has had previous CHC treatment, along with other factors such as renal function and patient preference for tablet number versus treatment length.[10] Treatment duration is between 8 to 24 weeks depending on the aforementioned factors.[10] There are no PBS limitations on who can receive treatment and Australia is unique in that these medications are easily accessible to patients, and all doctors, including gastroenterologists, infectious disease physicians, and GPs are authorised to prescribe DAAs to people living with CHC.[10] Historically, prior to March 2016, treatment for CHC was with interferon with ribavirin. his treatment had lower SVR rates and were much less tolerable with more severe side effects and poorer patient tolerability.[10]

2.1.6.4. Treatment of chronic hepatitis C in Australia

Treatment rates have significantly increased in Australia since the introduction of DAAs; from 2000-4000 patients per year (1-2% of those infected) to 74,704 patients from March 2016 to June 2019 (39.5% of those infected).[46] In March 2016, when DAAs became available on the PBS, the rates of CHC treatment were high but have since decreased despite a large number of patients still living with this disease.[19] The decline in non-GP specialist prescription was not offset by an increase in GP prescription rates although GP prescription rates have held relatively steady.[19] This is shown in Figure 2-7. There have been extensive education programs for GPs in Australia aimed at facilitating and thus increasing rates of treatment of CHC by GPs.[314]

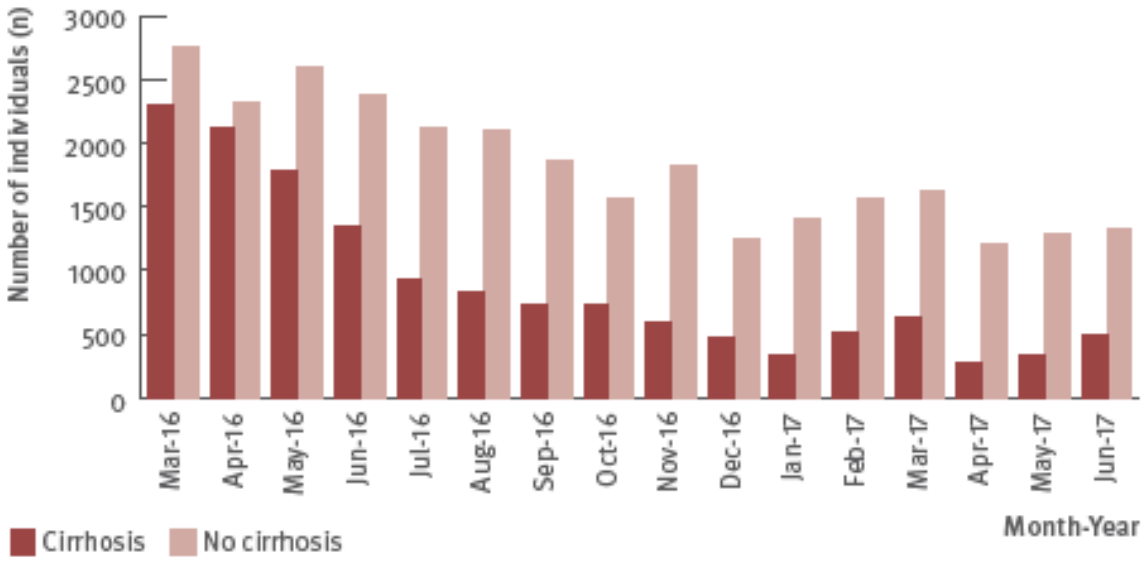
Figure 2-7 Estimated number of individuals initiating direct acting antiviral treatment, by prescriber type, 10% random sample of the pharmaceutical benefits scheme database, March 2016 to December 2018.



Reprinted from Institute, B.I.a.K., *Australia's progress towards hepatitis C elimination, Annual Report 2019.* Melbourne: Burnet Institute 2019, 2019.

Within Australia, DAA treatment rates per capita were lowest in regional and rural areas, areas with lower socioeconomic status, and in areas with higher populations born overseas.[315] Of those with cirrhosis, approximately 70% have received DAA therapy, however, the treatment rates for patients with cirrhosis due to CHC are also decreasing (Figure 2-8).[19] Patients with a high probability of advanced fibrosis or cirrhosis based on FibroScan® are more likely to have treatment [21, 316] highlighting the importance of accessibility to fibrosis assessment methods, although the easier access to Fibroscan® in tertiary centres may also confound this data.

Figure 2-8 Estimated number of individuals initiating direct acting antiviral treatment, 10% random sample of the pharmaceutical benefits scheme database, by cirrhosis status, March 2016 to June 2017



Reprinted from: Institute, B.I.a.K., *Australia's progress towards hepatitis C elimination, Annual Report 2019.* Melbourne: Burnet Institute 2019, 2019 with permission

Adherence with DAA therapy may have an impact on SVR. Of those who have had treatment of CHC with DAAs in Australia, only 70.5% have had testing for SVR.[46] Adherence rates with DAA therapy have been shown to be higher in patients who have detailed education regarding their treatment plan [317] and lower in patients with moderate to heavy alcohol use.[318] There are no studies looking at DAA adherence and socioeconomic status, however, patients from lower socioeconomic status have lower adherence rates for management of other medical conditions.[319-323] Impact of adherence on SVR rates has conflicting data: there is no clear definition for adherence and studies all report adherence rates differently. One study found that there was no difference in SVR rates between those who took 95% or more of tablets

and those who took less[324] with similar findings in another study.[318] Another study found lower SVR rates in less adherence patients,[317] however, this was analysed as intention to treat meaning that those who did not have testing for SVR were counted as DAA failure. This is not ideal as SVR rates are very high, so of those who did not have testing for SVR, a very high percentage will potentially have achieved SVR. One study of 1900 patients who were treated with DAAs found 2 patients had on treatment virological breakthrough (negative followed by a positive HCV PCR during treatment); both were suspected to be non- adherent with treatment.[325] Non- adherence with DAAs may also lead to DAA resistant CHC although this has not been proven definitively.[326] Thus, non-adherence may have an impact on SVR and other clinical outcomes, but the degree of non-adherence that has an effect is unclear.

DAA therapy already has had positive effects on morbidity and mortality for people living with CHC in Australia; there has been a decline in decompensated cirrhosis and liver-related mortality.[327] Prior to DAA therapy, rates of HCC diagnosis and all-cause mortality was increasing, now these rates have plateaued.[327]

There are clearly many people living with CHB and CHC in Australia who are still not accessing treatment despite the ease, minimal side effects and clear benefits. The next section will look at the cascade of care, then treatment models and highlight some of the areas that could be targeted to improve treatment rates.

2.1.7. Treatment Cascade for viral hepatitis

2.1.7.1. Models of care for disease management in Australia

GPs play a central role in health care management in Australia in disease prevention, management and referral onwards for non-GP specialist care when required. In Australia, access to medical care, outside of emergency care, generally requires a patient to see their GP for care or for a referral to another practitioner.[328] Medical care for people living with CHB and/or CHC can occur in different settings, with the two most common being in a GP clinic or hospital outpatient setting. This section will focus on the differences these as they are the two most common ways people living with CHB and/or CHC are managed in Australia.

GPs mostly practice locally in the community where there is easy access for patients in a familiar environment. GPs also manage all aspects of a person health, however, there are variable levels of interest and expertise in certain aspects such as CHB and CHC management.

For those patients who are referred onwards for management of CHB and/or CHC, they will usually see a non-GP specialist, or a hepatology nurse in a hospital outpatient setting. There are two main differences for patients who see a non-GP specialist compared to seeing a GP for management of their condition: firstly, the location of the appointment is different. Hospitals are more centralised so are often further away from a patient's residential address meaning longer distance to travel,[329-331] they're in an unfamiliar environment and parking may be difficult and expensive.[332, 333] Secondly, a non-GP specialist usually will manage one aspect of a person's disease compared to GP's who usually will manage all aspects of the patient's health care. There are many conditions where management by a non-GP specialist is vital, however, many conditions do not have improved outcomes when managed by a non-GP specialist compared to GP's, for example diabetes, cystic fibrosis and arthritis.[334] Waiting times to see a non-GP specialist can also be long: the 90th centile waiting time for appointments with a hospital based Gastroenterologist in Victoria has increased from 242 days in July to September 2019 to 343.8 days to July to September 2020, with one health service having a wait time of 1862 days.[335] Although there are clearly benefits to GP based care, some patients also benefit from seeing a non-GP specialist for management, for example, Australian guidelines recommend anyone with cirrhosis should be managed by a non-GP specialist for this condition.[11] Studies analysing differences in patient characteristics in community versus non-GP specialist centres have shown some consistent differences; people living with CHC managed in a community clinic are younger, more likely to be of lower socioeconomic status, more likely to have been incarcerated and more likely to have a history of substance abuse.[336, 337] People living with CHC also generally prefer to be managed in a community based setting.[338]

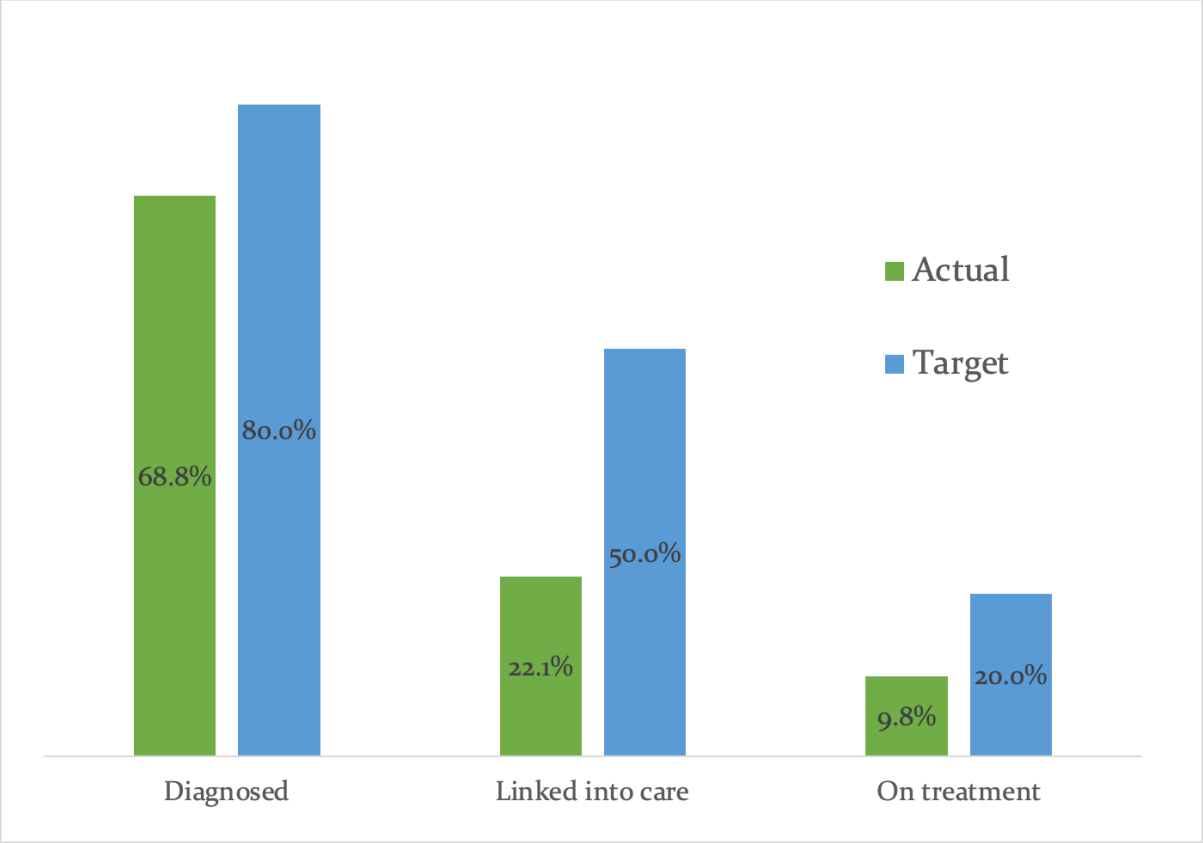
2.1.7.2. Cascade of care

There are multiple steps in the cascade of care for CHB and CHC from prevention to diagnosis and treatment. First, patients who are at risk of infection should have screening blood tests and confirmatory testing for diagnosis. The patient needs to be aware of their diagnosis and then linked into care. They should have a baseline assessment to determine the disease phase (CHB), degree of fibrosis and risk of HCC to determine the best management and treatment plan. For people living with CHB who are non-cirrhotic and not in a hepatitis phase, monitoring every six months with LFTs and every 12 months with a viral load is recommended. Patients at risk of HCC should have surveillance. Any patient with CHC should be considered for treatment with DAAs and have an assessment of treatment outcome with SVR. Ultimately,

the aim is to increase treatment rates to subsequently decrease CHB and CHC liver-related outcome rates in the long term. For this to happen, all the steps of the treatment cascade must occur.

Australia's goals to meet the WHO hepatitis B and C targets by 2030 are unlikely to be met if the current testing and treatment continues at its current rate. Rates of diagnosis, linkage into care and treatment for CHB is far below the 2022 targets (Figure 2-7).[13] The treatment target of 20% is based upon modelling for cost-effectiveness of antiviral therapy in Australia.[13] Other modelling data has demonstrated that by 2025 all people living with a *diagnosis* of CHC would have had treatment, however, the prevalence of CHC would only be 59% lower in 2030 than in 2015.[339] This indicates that increased testing for diagnosis of CHB and CHC needs to occur.

Figure 2-9 Percentage of people living with chronic hepatitis B diagnosed/linked into care/on treatment in 2019 compared to 2022 targets



Adapted from: Romero N, McCulloch K, Allard N, MacLachlan JH, Cowie BC. National Surveillance for Hepatitis B Indicators: Measuring the progress towards the targets of the National Hepatitis B Strategy – Annual Report 2019. Melbourne: WHO Collaborating Centre for Viral Hepatitis, The Doherty Institute; 2020.

2.1.7.2.1. Screening and confirmation of diagnosis

Since 2010, the rates of new diagnoses of CHB have been decreasing: modelling data has shown that Australia is unlikely to meet their target of 80% diagnosed by 2022.[13] Rates of diagnosis need to be improved and there are many studies that have looked at different ways to increase the screening rates. One review article analysed 27 different programs from different countries that aimed to improve testing rates for CHB. The programs that successfully increased the rates of testing mainly focused on community awareness and education using different strategies. The successful programs also ensured easy access to testing within familiar and community settings.[340] There have been various different strategies to improve rates of CHB diagnosis in Australia with specific regional programs and integrated CHB nurses. Robotin et al initiated a hepatitis B program in Sydney that aimed to increase diagnosis and treatment rates. Initially, education for communities and GPs was provided but this had very low uptake. They then introduced enhanced support for GPs, nurse educators and financial incentives to the GP clinic for testing, with significantly increased rates of testing.[14] Other successful programs have worked to improve rates of testing in Aboriginal communities using educational tools in Indigenous patient's first language.[17] Large scale community screening to diagnose CHB is also cost effective.[341]

Approximately 80% of people living with CHC in Australia have been diagnosed.[19] One area of concern however, is that, of PWID who are still currently using injectable drugs and thus at high risk of infection, only one in two had been tested for hepatitis C virus within the preceding 12 months.[19] This is an issue as almost half (48%) of people living with CHC and a history of IVDU report injecting drug use within the last 12 months.[21] Rates of confirmation of CHC infection are also low with PCR testing only occurring in 50%-75% of patients.[19, 342, 343] Studies have looked at ways to improve testing rates, including clinician reminders in high risk populations,[344] on site testing [344, 345] and rapid testing [346] all with beneficial effects on testing rates. Non-traditional testing sites have also been explored from needle and syringe exchange programs,[347] speciality addiction clinics,[348] mobile medical clinics,[349] community mental health programs[350] and pharmacies, all with beneficial results on testing and diagnosis rates.[351] Alternative testing methods such as dried blood spot samples,[352] self-testing or saliva testing[353] have also been shown to be accurate but have not yet been studied to determine whether these can increase testing rates for viral hepatitis.

What is likely needed is extensive Government support with a multi-pronged approach aiming at education for both patients and GPs and changes in testing methods to increase testing rates of CHB and CHC.

2.1.7.2.2. Linkage into care

Linkage into care is a vital part of optimised management. For people living with CHB, this means having lifelong regular LFTs and hepatitis B viral load testing, and, if required, HCC surveillance and antiviral therapy. This monitoring has been shown to be cost effective by prevention of cirrhosis with antiviral therapy and early diagnosis of HCC.[354] Rates of linkage into care for people living with CHB in Australia is far below what it should be. Linkage into care rates were calculated using Medicare records for the number of patients on treatment or with a hepatitis B viral load test within a given year. The percentage of patients linked into care varied between different regions in Australia, from 9.7% to 26.7%.[13] Rates of linkage into care in Australia has increased over time, from 11.8% in 2011 to 22.1% in 2019,[13] however, most of that increase was between 2011 and 2015. The number of people living with CHB in Australia is also increasing due to immigration, so linkage into care must also be increased to meet the 2022 targets.[13] Following the current trajectory, Australia will not meet its target of 50% of people living with CHB linked into care until 2053.[13] Studies have looked at reasons why patients are not linked into care. In a group of people living with CHB who qualified for HCC surveillance, failure to attend (FTA) medical appointments for CHB occurred in 76% of patients.[299] Of these, 25% had reasons documented for failing to attend such as pregnancy, other health issues or travel overseas.[299] Concerningly, 58.2% of those at risk of HCC were not having regular viral load testing (>14 months apart).[299] There is no Australian data looking at the percentage of people living with CHB who have had an assessment of fibrosis level and data regarding HCC surveillance rates only assessed single centres or patients diagnosed with HCC.

For people living with CHC, only approximately 50% were actively linked into care in Australia.[16] Methods to increase linkage into care include patient navigation systems to facilitate referrals from GPs. In one study in the pre-DAA era, patient navigation systems resulted in 60% of patients seeing a non-GP specialist and 34.2% having interferon treatment.[16] Other studies have shown similar results with linkage into care using patient navigation services.[355] Other methods that have been shown to improve linkage into care include counsellors who assisted with appointment scheduling and performed home

visits;[356] integrated care with hepatology nurses;[21, 357] providing CHC management via hepatology nursing and counselling and drug and alcohol centres;[358-362] and mobile clinics with FibroScan® for current PWID.[15] FibroScan® as a community tool has also been studied in drug and alcohol centres, opioid replacement clinics or as a mobile van. Multiple studies [363-367] have shown that the uptake and acceptability of FibroScan® is high but all these studies have been in current drug users and have fairly low numbers with either no comparison group or a comparison group of current drug users without CHC. None of these studies have looked at outcomes of long-term linkage in care or treatment or liver-related outcomes. Ultimately, linkage into care with either GPs, nurse practitioners or non-GP specialists is vital for assessment and treatment.

2.1.7.2.3. Methods of fibrosis assessment in the community as part of the treatment cascade

Methods for the assessment of fibrosis have already been discussed in section 2.1.4. Current Australian guidelines for fibrosis assessment for people living with CHC recommend using elastography with FibroScan®, or SWE or ARFI; and, if these aren't available, APRI.[10] FibroScan® as a tool in current PWID with CHC in a community setting has been shown to correlate with degrees of fibrosis on liver biopsies [367] and has been reported to be an acceptable part of care by patients who inject drugs.[363] There are no community based studies for fibrosis in people living with CHB. FibroScan® and other elastography methods as tools to determine risk of liver-related outcomes also have not been studied in a community setting of people living with CHB and/or CHC.

2.1.7.2.4. Treatment

Treatment rates for CHB are far lower than they should be in Australia. The current strategy has an aim of 20%,[1] however, modelling data suggests that in Australia in 2019, 30.3% of people living with CHB would qualify for treatment.[13, 46] Although treatment rates have increased over time very slowly, modelling data also suggests that current treatment rates are far too low to meet our treatment uptake goal: we are unlikely to meet the current 2030 treatment goal until 2046.[13] Methods to increase treatment rates in people living with CHB have been studied. Treatment rates increase with increased testing and community engagement, and a study by Robotin et al also found that with increased testing rates, treatment rates also increased.[14, 368] Access to treatment for patients has changed recently also, since 2015, GPs

with section 100 (S100) prescription training have been able to prescribe antiviral therapy, with 17.9% of patients on therapy receiving a script from their GP in 2017.[1]

There are multiple current models of care for CHC treatment in Australia, each with their own benefits and limitations. The multiple models of care are important as it maximises the ability of people living with CHC to access treatment. Hospital outpatient management has traditionally been the main source of management and is important as it can offer treatment assessment for all people living with CHC regardless of disease severity and comorbidities. Treatment by other practitioners in a community setting including GPs, hepatology nurses and visiting non-GP specialists is important as previous studies have shown increased rates of treatment in familiar environments as discussed below. There are other models of care for patients in custodial settings, patients who inject drugs and their injecting networks and people living in rural and remote settings. Aboriginal and Torres Strait Islander patients, migrant populations and patients with mental illness living with CHC are relatively under-served populations for a multitude of reasons, which is beyond the scope of this thesis.

Treatment uptake rates differ between different settings; one Australian study found that non-cirrhotic people living with CHC were more likely to receive DAA treatment when managed in a community GP clinic than those managed in a hospital setting. Patients were randomly allocated to have DAA treatment in a hospital outpatient setting or at their local GP clinic. This study found that 75% of patients commenced treatment when managed at their local GP clinic compared to 34% who were managed in the hospital setting. There was a higher percentage of patients who did not do the required pre-treatment liver assessment in the hospital outpatient cohort (36% compared to 13% in the GP clinic arm) and this cohort also had a higher percentage of patients who exited the study by being uncontactable or declining appointments.[369] Other studies have also shown increase in treatment uptake for CHC with interferon-based treatment when treatment was made available at GP clinics [370-373] with one study showing higher uptake in community setting compared to a liver transplant centre.[374] One study found that DAA treatment uptake was higher when pharmacists offered testing and treatment compared to those referred on to a local hospital outpatient clinic.[375] Patients also reported a positive emotional impact of having community based care for CHC.[338] There were also very similar SVR rates between hospital based and community based treatment in multiple studies.[369, 376-379] Telehealth has also been shown to have similar or higher SVR rates compared to a hospital-based outpatient setting with interferon-based treatment.[337, 380, 381] Cost effectiveness studies have also shown lower cost of DAA

treatment in a community rather than hospital based setting; this is likely due to increased retention in medical care in community settings.[382] Further cost effectiveness studies have found that outreach hepatology care in a community setting is far more cost effective than treatment within a hospital outpatient setting; community treatment also improves health outcomes with gains in quality adjusted life-years.[383]

For people living with CHC and cirrhosis, community treatment is less clear, and current Australian guidelines suggest that treatment for this group should be via non-GP specialists.[10] Despite this, some studies have shown safe and effective CHC treatment in patients with cirrhosis in a community setting. Treatment in community based drug addiction centres,[377] homeless sites [379] and GP clinics [378] all had very similar SVR rates to previous studies. The adequacy of monitoring for complications of cirrhosis in a community setting is less clear.

Part of DAA treatment is also ensuring that patients who have DAA therapy are tested for SVR. Rates of testing for SVR are variable: 88.9% in a hospital based setting compared to 60.9-89% in a community based setting.[369, 384-386] One study looking at factors associated with testing for SVR, when treated in a primary care setting, found that the only variable associated with higher rates of testing for SVR was having DAA treatment at the same clinic as where the patient usually has their opioid replacement therapy.[387] Another study found older age was positively associated with testing for SVR.[369] Options to increase SVR testing include checking HCV PCR at 4 weeks, where, if negative at that time, 91-98% of patients remain negative at 12 weeks.[388, 389] Other methods also include similar methods for diagnosis with clinical reminders, on site and rapid testing.

2.1.8. Socioeconomic implications for people living with viral hepatitis

Socioeconomic status can have a significant effect on patients' morbidity and mortality. Patients from a lower socioeconomic status have higher all-cause mortality.[390] Patients from lower socioeconomic status with cirrhosis from any cause also have a worse prognosis than those with cirrhosis from higher socioeconomic status [391] and are less likely to seek treatment.[315] People living with CHB are more likely to be of lower socioeconomic status than those without CHB.[392, 393] There are also higher rates of CHB in refugees in Australia (4-22%) compared to those born in Australia (less than 1%)[394] and these patients have also been shown to have poor understanding of the consequences of having CHB.[312, 395]

Patients from lower socioeconomic status also have increased rates of CHC; in Australia, the greatest CHC burden and lowest health service coverage is in lower socioeconomic areas.[396] People living with CHC are more likely to be unemployed and/or on a disability pension compared to patients without CHC [393, 397, 398]; people living with CHC are also likely to have lower education levels than those without CHC.[393, 397, 398] People living with CHC also have high rates (85%) of psychiatric diagnoses.[21] They are also more likely to have a history of substance abuse than those without CHC.[393, 397, 398] Patients with a history of substance abuse are also more likely to be from a lower socioeconomic status than those without a history of substance abuse.[399] People living with CHC from lower socioeconomic status also have a worse prognosis than those with CHC from higher socioeconomic status.[397]

2.1.9. Medical appointment attendance in people living with viral hepatitis

2.1.9.1. Medical appointment attendance rates

International data shows hospital outpatient attendance rates for people living with CHB and/or CHC can be variable; in Australia there is limited data published on attendance rates in outpatient settings in people living with CHB and/or CHC. International studies have shown that people living with CHB and/or CHC are less likely to attend outpatient appointments than those without CHB/CHC. Of a group of people living with HIV in Indonesia, those with dual infection CHB/CHC were far less likely to attend outpatient follow-up than those without dual infection.[322] Other overseas data also shows that people living with CHB and/or CHC have varying rates of attendance to outpatient clinics from 33% in the United States of America [400] to 10-60% in the United Kingdom.[330, 401] Outpatient attendance rates also vary between countries. One meta-analysis of patients with chronic diseases found an overall FTA rate of 23% worldwide, however, the FTA rate was only 13.2% in Oceania [402] of which Australia comprises 59.8%.[403] In Australia, there is some data on community-based care for people living with CHB and/or CHC, with fairly poor attendance rates. One Australian study of people living with CHC looked at attendance rates with a hepatology nurse in a community setting: only 74.4% attended the nurse appointment and of those attendees, only 67% attended a hospital outpatient follow-up appointment.[21] One other study looking at refugees in an Australian population found that only 35.4% attended all infectious diseases outpatient clinic appointments.[20] There are clearly differences between outpatient attendance rates in different countries and we cannot rely on international data.

2.1.9.2. Factors associated with hospital outpatient non-attendance

There are complex reasons for people living with CHB and/or CHC failing to attend outpatient appointments. There are individual characteristics, socioeconomic and structural reasons leading to FTA to outpatient appointments. Individual characteristics that are associated with non-attendance include male gender,[320, 321, 329] younger age [20, 320, 323, 329, 331, 401] and drug use.[330, 404] In one study, patients reported prioritizing drug use over medical appointments.[330] Socioeconomic factors associated with lower attendance rates include unemployment,[319] lower educational levels,[320-322] refugee status,[323] receiving welfare payments [320] and patients being concerned about the financial cost of attending outpatient appointments.[330] Structural reasons for lower attendance rates include living further away from the location of the outpatient clinic,[329, 330] perceived difficulty getting to the hospital,[331] having attended their GP or a private non-GP specialist for care,[405] or reporting feeling too busy or finding outpatients inconvenient.[405] The reasons for non-attendance are complex and has implications on health outcomes.

2.1.9.3. Implications of outpatient non-attendance

Non-attendance to medical appointments has negative effects on health. Patients with diabetes who do not attend hospital outpatient clinics have higher rates of hospitalisations, and those with a previous hospital admission who did not attend outpatients had a 60% greater risk of readmission compared to those with a previous admission who attended outpatients.[406] FTA to community-based clinics is also associated with higher rates of emergency presentations and hospital admissions. The same study also found patients who FTA community-based clinics were much less likely to have appropriate preventative cancer screening for colorectal, cervical and breast cancer screening than those who attended. Those who did not attend appointments in a community clinic also had poorer chronic disease control measures.[407] People living with CHC who fail to attend outpatients are also less likely to have treatment; of people living with CHC who attended at least one outpatient appointment but FTA to one or more appointments, they had a treatment rate of 27% compared to 67% in those who attended all their outpatient appointments.[319] Failing to attend outpatient appointments and other medical appointments has negative effects on health outcomes.

2.1.10.Screening programs and surveillance

Community screening programs are a vital part of community health care; they aim to diagnose conditions or identify risk factors for diseases in otherwise healthy patients. There are many screening programs in Australia, which all have significant community health benefits.

2.1.10.1. Screening versus Surveillance

The difference between screening and surveillance is important to distinguish. Screening is the active search for disease or risk factors, performed in average risk groups, to stratify into low and high-risk groups. This is often performed as mass screening of a whole community based on certain cut-offs such as age and gender. An example of a screening program includes the National Bowel Cancer Screening Program (NBCSP),[408] where asymptomatic patients are sent faecal occult blood (FOB) testing kits based only on age and gender. The results of these kits determine if they are at a low or high risk of bowel cancer and subsequent need for colonoscopy. Australia has two other population-based screening programs; BreastScreen Australia for breast cancer and the National Cervical Screening Program (NCSP) for cervical cancer.[408] The NBCSP and NCSP also decrease the incidence of cancer by diagnosing and treating the pre-cursers to cancer.[408] Surveillance is the systematic and ongoing follow-up of patients who are at increased risk of a disease, or those with a disease who are at risk of complications. For example, surveillance colonoscopies are performed in patients who have had polyps found during colonoscopy, as they have an increased risk of further polyps and subsequently bowel cancer.

2.1.10.2. Participation in screening programs

Participation rates vary significantly between different programs, populations and location with a host of other factors contributing. Patient location has different effects depending on the program, for example, inner regional and outer regional areas of Australia had the highest participation for BreastScreen and the NBCSP, however, for NCSP the highest rates of participation was in major cities and inner regional areas.[408] Socioeconomic status also has an effect with lowest participation in the most disadvantaged socioeconomic groups for all three screening programs.[408] Indigenous groups and non-English speaking background groups also have a lower participation rates for all programs.[408] The national rate of participation in the NBCSP in 2015-6 was overall 41% with a variation between patient location, with a participation range of 29-49%.[408] This low rate is probably also affected by the fact that some patients perform the FOB test through their GP rather than the screening

program.[408] There is also evidence that other screening programs affect participation in subsequent screening programs. The Australian "Analysis of cancer outcomes and screening behaviour for national screening programs" demonstrated improved screening in other programs in women who had a positive or high risk BreastScreen result, or who had had a high risk NCSP result.[408]

2.1.10.3. Retention in screening programs

Retention in screening programs is also an important issue with repeat testing at the recommended interval also being vital in prevention and early diagnosis. There is limited data on retention within the three Australian screening programs. Overseas data identified demographic, socioeconomic, psychological factors, medical history and cost all correlated with retention in screening programs.[409-411] One study from Ontario in 2013 demonstrated that reminder letters worked to improve rescreening rates with their equivalent NCSP with an adjusted odds ratio of 1.82.[412] Although even single episodes of participation in screening programs has benefits, repeated assessments are a vital part of care.

2.1.11.Summary

The previous section (2.1) has highlighted the relevance of CHB and CHC and risk of cirrhosis and HCC development as a major health issue in Australia. Early diagnosis and appropriate management of CHB and CHC can significantly reduce the risk of liver complications including future HCC development.[13, 23, 310, 313, 327] Fibrosis assessment has readily available tests available also: such as fibrosis assessment with FibroScan® which is cost effective and safe. Implementation of HCC surveillance strategies can also assist in the detection of HCC at an earlier and potentially curable stage. Surveillance of patients with cirrhosis and those with CHB who are at high risk of HCC is broadly accepted by the international community and reflected in Australian and International guidelines.[11] However, the high rates of HCC development outside of surveillance programs[18] is reflective of the challenges in accurately identifying this high-risk population and also ensuring appropriate HCC surveillance. Treatment also leads to improved outcomes: treatment of the underlying disease can prevent fibrosis progression and thus lower HCC risk. Diagnosis, linkage into care and treatment for people living with CHB and/or CHC is vital, however, the rates of these are far below what they should be to meet Australia's 2030 goals. To further clarify the extent of disease and where gaps in patient care occur, further knowledge is required.

A community management program was designed to determine the prevalence of cirrhosis in a community cohort of patients and determine adherence with medical management. The next section will discuss the rationale behind the development of this study, highlight the current knowledge gaps then present the broad aims of this thesis.

2.2. Rationale behind development of the CATCH study

In this section, the rationale behind the design of the CATCH study will be discussed.

2.2.1. Knowledge gaps and solutions to fill these gaps

Most of the previous research regarding the prevalence of cirrhosis, rates of adherence with medical management and risks of liver related outcomes in people living with CHB and CHC has been performed in specific populations, such as patients managed within a hospital outpatient setting, veterans, current PWID or aboriginal populations.[13-19] Larger studies that have assessed whole populations use linkage or Medicare data or assess only patients who have been diagnosed with the outcome of interest.[13-19] Studies performed overseas where patient characteristics and health systems differ to the Australian health care system are difficult to interpret. The overarching aim of this thesis is to examine in detail a community population of patients diagnosed with CHB and/or CHC in Australia, to determine outcomes and factors that can contribute to these outcomes rather than just patients within specific groups or outcomes of interest as mentioned above.

Previous research from the CATCH study, presented in Dr Bloom's thesis[7] demonstrated that community and hospital cohorts with CHC had similar prevalence of LSM ≥12.5kPa (16.5% vs 20.2% respectively). This important finding highlights the unexpectedly high proportion of patients with unrecognized, advanced liver disease/cirrhosis in the community. In comparison, people living with CHB from the community cohort had lower rates of LSM ≥11kPa compared to a hospital cohort (1.9% vs 7.5% respectively).[7, 12] An important caveat of this previous research is that a single measure of fibrosis assessment (LSM as assessed by FibroScan®) was used to determine the extent of fibrosis. The performance of a more comprehensive assessment using a combination of non-invasive tools and biomarkers in the community setting is unknown. In this thesis the *clinical criteria* of advanced fibrosis and cirrhosis was determined using an assessment comprising LSM and ultrasound findings. LSM cut-off points will be discussed in section 2.2.2.2 and ultrasound findings of cirrhosis in section 2.1.4.3.

2.2.1.1. Additional risk factors for morbidity and mortality

Current knowledge regarding the prevalence of cirrhosis in people living with CHB and/or CHC is based upon studies from the specific populations mentioned above or from overseas data. When CATCH was designed, it was assumed that patients with a high probability of cirrhosis were more likely to be referred onwards by GPs for hospital-based management rather

than retained in GP care, and thus rates of cirrhosis in a community cohort of patients may be lower. There is also a knowledge gap regarding the prevalence of people living with CHB who are in a phase of infection where antiviral therapy should be considered (hepatitis phase). Previous Australian studies have been based on specific populations or Medicare linkage and extrapolation of data, however there are limitations to this.[13-19] The main problem with linkage data is that patients who are having regular blood tests may be those who require close monitoring and thus the percentage in a hepatitis phase may be overestimated. Hospital based studies may also overestimate the percentage of patients in a hepatitis phase due to similar issues with referral bias, retention in care and closer monitoring of those at higher risk. The knowledge regarding the percentage of patients who require HCC surveillance also has similar limitations. Thus, determining the percentage of patients who have a high probability of cirrhosis, who are in a hepatitis phase (CHB) or require HCC surveillance within a community cohort is important, to clarify the risks for patients within Australia.

2.2.1.2. Patient linkage into care

Patient attendance to medical practitioners is vital to be able to provide appropriate medical management. In hospital outpatient settings, there are variable rates of attendance which vary significantly between disease and geographical location. Previous data has shown certain patient characteristics such as age and socioeconomic status, as well as geographical barriers can predict lower attendance rates.[20, 319, 321-323, 329, 331, 401] Lower attendance rates to medical appointments is also well established to correlate with poorer health outcomes, higher rates of emergency presentations and hospital admissions.[319, 406, 407] People living with CHB and/or CHC are more likely to be from a lower socioeconomic status than those without CHB and/or CHC [392, 393, 397, 398] and patients from lower socioeconomic status are less likely to attend outpatient appointments.[321, 322] People living with viral hepatitis also have other factors that may make them at higher risk of missing medical appointments, such as a history of substance abuse.[393, 397-399] Patients who are immigrants have higher rates of CHB than those born in Australia [394] and are more likely to be refugees [394] and/or have lower health literacy.[395] Thus, there is a higher chance that people living with CHB and/or CHC may have lower medical appointment attendance rates compared to those with other chronic diseases.

Adherence of people living with CHB and/or CHC to medical appointment attendance in Australia is unknown. We do not know rates of retention in care and where the current barriers to attendance are. Furthermore, it is unknown whether these are due to factors associated with

the health care system, factors associated with the patient, or a combination of both. Determining the rates of, and factors associated with medical appointment attendance will hopefully identify the barriers to attending medical appointment for people living with CHB and CHC and hopefully lead to future research focusing on improving retention in care.

2.2.1.3. Hepatocellular carcinoma surveillance rates

HCC surveillance has significant benefits for patients at risk of HCC. Patients who undergo appropriate HCC surveillance are more likely to have HCC diagnosed at an earlier stage compared to those not having surveillance.[18] Patients having HCC surveillance are also more likely to be treated with curative therapy [18] and have improved survival compared to those not having surveillance, even once corrected for lead time and lag time biases.[18] Despite this clear benefit of surveillance, only approximately 40% of patients diagnosed with HCC are in an appropriate surveillance program in Australia.[18] Previous studies that assessed HCC surveillance rates have been in hospital based settings or other specific subgroups of patients or have looked only at patients diagnosed with HCC. Determining the rates of appropriate surveillance and predictors of those who are less likely to have appropriate HCC surveillance is important as future focused interventions may lead to improved surveillance rates and thus improved outcomes for patients.

2.2.1.4. Treatment of viral hepatitis

Treatment rates for CHB and CHC are not high enough to meet Australia's 2030 goal. The treatment rates for CHC have been steadily decreasing, and treatment rates for CHB are far below targets. The current knowledge is based upon population-based linkage data studies and further information is required to be able to increase treatment rates. Determining patient characteristics that are associated with lower treatment rates in Australia will be helpful as future interventions can hopefully address these issues or subgroups of patients to optimise treatment rates.

Another important aspect of care for people living with CHC is ensuring that SVR has been achieved by testing viral PCR at 12 weeks post completion of therapy. DAA treatment has very high rates of cure and one could argue that focusing on improving SVR rates is a poor utilisation of health resources. Nonetheless, there is a risk of missing ongoing CHC infection which may have poor health outcomes for the individual person and, if they have ongoing high-risk behaviours, there is a risk of spreading CHC to other patients. Due to this, it is important for all patients who have DAA therapy for CHC to be testing for SVR. The rates of testing for

SVR is unknown outside of specific populations such as PWID, patients managed in a hospital setting or from extrapolation of Medicare data. Improved understanding of the rates and factors associated with testing for SVR will provide necessary information to allocate finite health care resources at the population who are most likely to benefit from targeted programs to increase rates of testing for SVR.

2.2.1.5. Liver-related outcomes

The risk and incidence of liver-related outcomes in people living with CHB and/or CHC is well established, however, this data is also from specific cohorts, large population-based linkage studies or only include patients who have been diagnosed with the specific liver-related outcomes of interest. Clarifying whether rates of liver-related outcomes within a community cohort of patients are similar to a hospital cohort will help determine patient management and health resource utilisation. The risks of liver-related outcomes may be similar, however, there is a complex interplay between disease factors and co-existing risk factors such as at-risk alcohol intake which may lead to differing risks. These disease factors include the prevalence of cirrhosis or percentage with risk factors for fibrosis development or HCC.

2.2.2. Rationale behind decisions made in this thesis

In this section, the rationale behind decisions made in the development of the CATCH study will be discussed. The reasons behind the choice of diseases and fibrosis assessment methods will be discussed.

2.1.1.1 Rationale of choosing viral hepatitis

CHB and CHC were chosen as the diseases to assess for multiple reasons. Firstly, CHB and CHC are clearly defined diseases. Secondly, LSM have defined cut-offs for CHB/CHC which could therefore serve as a measurement to determine those at risk of HCC and thus those who should undergo HCC surveillance as well identify patients with increased risk of liver-related events. Thirdly, there are additional measures that can estimate the degree of fibrosis and HCC risk. These measures include indirect biomarker algorithms such as APRI and FIB4 which have also be used to assess the likelihood of HCC and/or liver-related events. CHB and CHC also both have treatments available that improve outcomes as previously discussed. Thus, CHB and CHC are ideal diseases to assess in a new model of care.

Other causes of liver disease were considered for this study. NAFLD is the most prevalent liver disease in western communities, however accurately defining the disease without a liver biopsy remains a challenge. In addition, the significant association with obesity creates further complications, particularly as LSM can often be more difficult to obtain in patients with a larger skin to capsule distance. ALD was also considered, however, CHB and CHC were chosen over this as it was felt that recruitment could be more targeted with a clearly defined disease process that can be objectively measured. ALD can have a large variation with the amount of alcohol intake, and alcohol intake itself can increase LSM independent of fibrosis stage and often requires a subjective assessment of alcohol intake.[413] Other liver diseases such as autoimmune liver diseases have far lower prevalence, but also require long-term non-GP specialist management, as they require treatment and close follow-up. CHB and CHC were ultimately chosen given the above suitability criteria, with the potential to expand this type of program to other liver diseases in the future.

Data was also collected regarding the risks of other causes of liver disease, including BMI, cholesterol and alcohol intake. There is often overlap between liver diseases with high rates of alcohol use and obesity in people with viral hepatitis as discussed in section 2.1.3.2.

2.2.2.1. Rationale for presenting chronic hepatitis B and C separately

Although CHB and CHC were chosen as the diseases to be assessed, they have been presented separately in this thesis. They are different viruses with different disease characteristics and have differences in clinical progression, management and outcomes. Comparing CHB to CHC is beyond the scope of this thesis.

2.2.2.2. Rationale of choosing FibroScan® and the algorithms of indirect biomarkers

Assessment of liver fibrosis is not based on one test or variable: multiple factors are assessed in clinical practise. This is important as no test has 100% sensitivity or specificity and even the gold standard of liver biopsy is imperfect. In section 2.1.4.6 it was discussed that using a combination of fibrosis measures increased the sensitivity and specificity for predicting those at highest risk of advanced fibrosis. It was thus decided to use multiple methods of liver fibrosis assessment in this study.

Based on the high applicability and multiple validation studies, LSM as measured by FibroScan® was chosen to estimate the degree of fibrosis. Indirect biomarker algorithms and ultrasound findings of cirrhosis have also been assessed and presented. Liver biopsy has not

been performed routinely in this study as this is not part of standard medical care and has risks associated with it. Direct biomarkers were not performed as they are also not part of standard care and have costs associated with them, however, as discussed in the methods chapter, serum samples have been taken and frozen and testing of direct biomarkers is planned as future research. Algorithms of indirect biomarkers are easily calculated using patient characteristics and routine pathology tests; they have also been shown to correlate with the degree of fibrosis and liver-related outcomes as discussed in section 2.1.4.4. The following algorithms of indirect biomarkers were chosen: APRI, FIB4 and Forn's index, as they have a large evidence base behind them, for both estimating the degree of fibrosis, but also the risk of liver-related outcomes. They're also well-known and widely used in clinical practice. The newer 4AGP algorithm was also chosen as it was developed as part of another aspect of the CATCH study and this thesis aimed to determine whether 4AGP also correlated with liver outcomes. Although algorithms of indirect biomarkers are used very commonly in clinical practice, they're also commonly used in combination with other tests to predict the degree of liver fibrosis.

The use of elastography provides the opportunity to compare its performance to other modalities of estimating the degree of liver fibrosis such as the algorithms of indirect biomarkers. FibroScan® is reproducible, portable, well validated, and correlates well with liver-related outcomes. SWE was another option considered; studies have shown equal efficacy to FibroScan®, however, at the time of the study conception, ARFI and SWE had less evidence behind them and the study investigators were already extensively trained in the use of FibroScan®. MRE was not an option as this is not portable and the purpose of the study was to assess patients within a community setting. FibroScan® was thus determined the best method of elastography for this study.

Choice of LSM cut-off points was made based on the information discussed in section 2.1.4.2. The decision was made to use a cut-off point of 7kPa for F2 fibrosis in people living with CHB [148] and CHC.[150] Although there are different cut-off points for CHB study discussed, the lower LSM was chosen as ultimately, not missing cirrhosis is important. To determine those at high risk of cirrhosis, 11kPa was chosen for people living with CHB [148] and 12.5kpa was chosen for people living with CHC.[150] These are standard accepted cut-offs in international literature.[9]

To determine the patients with a high probability of cirrhosis, it was decided to use a combination of LSM and ultrasound findings. The reason for this decision, was that the positive

predictive value of LSM and ultrasound are high and adding in extra variables would have increased the false positive (FP) rates. Indirect biomarker algorithms are very useful in clinical practise but are potentially more easily affected by other diseases. To determine the risk of liver-related outcomes, FibroScan® and indirect biomarker algorithms will be assessed.

Although comparing the different methods of elastography would be ideal, this was not deemed practical due to time, cost and answering this question is not the aim of this study, thus one elastography method (FibroScan®) was used along with indirect biomarker algorithms in this thesis.

2.2.2.3. Clarification about similarities and differences between community and hospital cohorts of patients

Understanding patient characteristics is important for any disease as it can impact disease progression and have implications for management and monitoring. Understanding disease extent is also a vital part of patient management. Most of the previous research addressing viral hepatitis has included patients managed in a hospital outpatient setting, in patients who are currently injecting drugs or veterans. Some people living with CHB and/or CHC do not fit into any of these groups. Thus, it is unknown whether the current understanding of viral hepatitis can be applied to a boarder community of people living with CHB and/or CHC. Significant differences between the community and hospital patients may limit the ability to apply pre-existing knowledge to all people living with CHB and/or CHC. Alternatively, if there are minimal differences then perhaps generalisation of results to all patients with the disease can occur. Identification of differences will also help with application of previous and future research by accounting for these variables when interpreting data.

2.2.2.4. Predictors of elevated liver stiffness measurements – comparison to pre-existing literature

The variables associated with elevated LSM have been assessed as the community cohort of patients included in the CATCH study are different to previous studies. These variables are likely to be very similar to previous studies, but if there are differences, this may have implications for patient management and generalisation of previous data.

2.2.3. Research Hypotheses

2.2.3.1. Factors associated with morbidity and mortality at initial assessment

As mentioned in section 2.2.1, previous research from the CATCH study[7] demonstrated that community and hospital cohorts with CHC had similar prevalence of elevated LSM and people living with CHB from the community cohort had lower rates of elevated LSM compared to a hospital cohort. This data suggests that in contrast to people living with CHC, people living with CHB with advanced fibrosis/cirrhosis are more likely to be referred onwards for non-GP specialist management. Therefore, one might infer that patients in a hepatitis phase or requiring HCC surveillance are also referred onwards to non-GP specialist care.

The first two hypotheses are thus:

1. The prevalence of advanced fibrosis/cirrhosis using *clinical criteria* in the CHC community cohort will be similar to the hospital cohort
2. Compared to the CHB hospital cohort, the community cohort will have lower
   a. prevalence of advanced fibrosis/cirrhosis using *clinical criteria*,
   b. rates of eligibility of HCC surveillance
   c. percentage of patients eligible for antiviral therapy based on phase of disease

2.2.3.2. Adherence with medical appointment and management

Multiple factors have been identified as barriers to patient adherence with clinical care, including socioeconomic status. People of lower socioeconomic status are consistently less likely to attend outpatient clinics and adhere to medical care,[319-323] and people living with viral hepatitis managed in a community setting are likely to be from lower socioeconomic status.[336, 337] Therefore patients who were referred and/or attended non-GP specialist hospital-based care may be fundamentally different to the cohort who remained with the GPs for community-based management thereby highlighting a selection bias in the referral patterns of GPs.

The next hypothesis is thus:

3. The CHB and CHC community cohorts will have lower rates of adherence with medical appointments, HCC surveillance and antiviral treatment compared to the hospital cohorts

2.2.3.3. Incidence of liver-related outcomes

Given the previous research [7, 12] has shown that the rates of elevated LSM were similar between CHC community and hospital cohorts, and elevated LSM correlates with the likelihood of cirrhosis,[150] it would be expected that the incidence of liver-related outcomes will be similar between the CHC cohorts. In people living with CHB, the community cohort of patients had lower rates of elevated LSM compared to the hospital cohort [7] and are thus likely to have lower rates of cirrhosis. Therefore, it is likely that rates of liver-related outcomes will be lower in the community cohort than the hospital cohort in people living with CHB.

The hypotheses are thus:

4. Liver-related outcomes will be similar between the hospital and community CHC cohorts

5. The CHB hospital cohort of patients will have higher rates of liver-related outcomes during the study follow-up period when compared to the CHB community cohort.

2.2.4. Research Aims

There are three broad aims for this thesis:

1. Determine the percentage of patients with factors that are associated with morbidity and mortality at initial assessment
2. Determine the percentage of patients who adhere to medical appointments and management for CHB and CHC
3. Determine incidence of liver-related outcomes and factors associated with these outcomes.

These aims will be further clarified at the end of chapter 3 (section 3.4) with the specifics of how these will be answered.

Chapter 3. Methods

This chapter will discuss the methods behind the development of the CATCH study and then present the aims in more detail with the specifics of how these will be addressed.

3.1. CATCH Study Design

The CATCH study was designed in two parts; phase one was an observational cross-sectional study, phase two is an observational cohort study. Patient recruitment based on location, assessment and follow-up is shown in Figure 3-1.

3.1.1. Phase One: Observational cross-sectional study

The observational cross-sectional part of the CATCH study was designed to ascertain the baseline differences between a community cohort of people living with CHB and/or CHC and a current standard of care cohort (hospital cohort). These baseline characteristics include patient characteristics such as age, gender and medical history, LSM measured by FibroScan®, ultrasound findings of cirrhosis, need for HCC surveillance and, in people living with CHB, the percentage in a hepatitis phase.

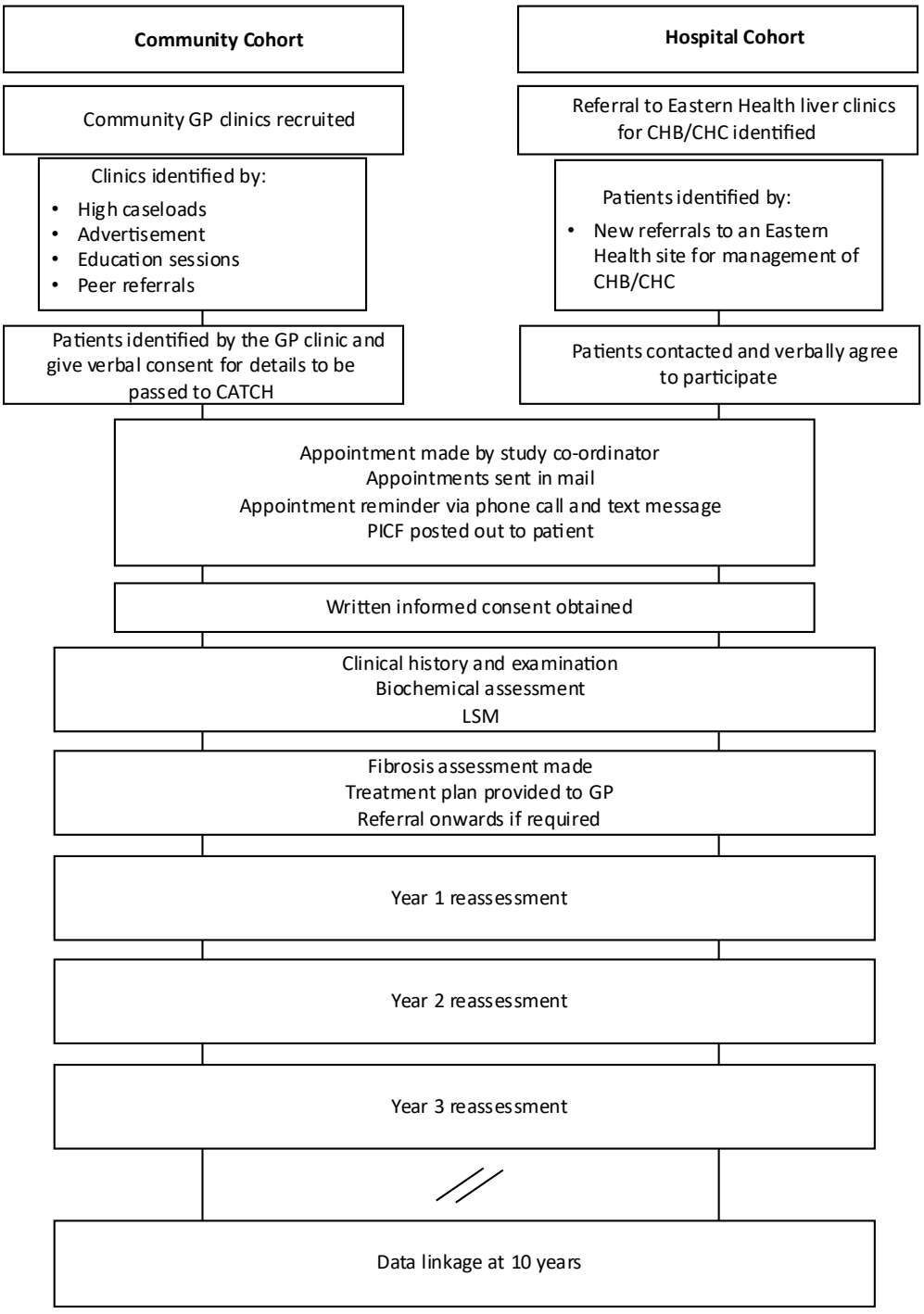
3.1.2. Phase Two: Observational Cohort study

The observational cohort phase of the study is a longitudinal study to determine relevant outcomes for patients including adherence with management and risk of HCC and other liver-related outcomes. Patients from the phase one study were offered yearly assessments to determine if changes to LSM or other non-invasive estimates of liver fibrosis over time correlate with clinical outcomes. At these visits, retention in non-GP specialist care, HCC surveillance, treatment and liver-related outcomes such as development of HCC were recorded. If patients did not attend follow-up or had no follow-up for more than one year, at the end of the study period, for this thesis, their medical records were reviewed to determine if any of these outcomes occurred.

As part of this second phase of the CATCH study, patients were also consented for data linkage to registries including:

- Australasian Association of Cancer Registries
- Department of Health hospital admissions and discharge data
- Australian Registry of Birth, Deaths and Marriages

Figure 3-1 Flow diagram of patient recruitment and follow-up



GP: general practitioner; CHB: chronic hepatitis B; CHC: chronic hepatitis C; CATCH: Community Approach targeting Cirrhosis and Hepatocellular carcinoma; PICF: patient information and consent form; LSM: liver stiffness measurement via FibroScan®

3.1.3. Study Patients and Recruitment

Between October 2014 and December 2016, patients were prospectively recruited through primary care practices within Melbourne in parallel with prospective recruitment of a hospital

cohort of patients referred for specialist care. Patients were consecutively recruited to minimise recruitment bias.

3.1.3.1. Inclusion and exclusion criteria

Inclusion criteria:

- Age over 18 years
- Evidence of CHB or CHC (infection for more than 6 months)

Exclusion criteria:

- Recent non-GP specialist for management of CHB/CHC in the last 18 months. This time frame was decided based on the need for 6 monthly review, when advanced fibrosis is present; 18 months was felt to clearly indicate a cessation of non-GP specialist management.
- Previous or current diagnosis of HCC (as these patients have a higher risk of recurrence and should already be undergoing follow-up).
- Individuals with implantable devices or who were pregnant were not recruited (as per FibroScan® manufacturing recommendations at the time of protocol design).

3.1.3.2. Community Cohort Recruitment

GP clinics were invited to take part in the CATCH study with voluntary participation and no financial incentives. GPs and the clinic received information about the project, along with inclusion and exclusion criteria and, for the participating clinics, patient information and advertisement material were provided along with patient referral paperwork.

Practices were recruited via the following methods:

- Practices with high caseloads of CHB and CHC. These centres were located by reviewing records of referrals for CHB and CHC to Eastern Health and identifying high referral centres
- Advertisement:
    - Government Medicare-locals services
    - Hepatitis Australia
    - Primary Health Networks (PHN)

- GP education sessions were offered through The Fellowship of the Royal Australian College of General Practitioners (FRAGP) with advertisement of the CATCH project
- Peer related referrals between sites, in centres who provided opioid replacement therapy and thus had higher rates of people living with CHC.

All participating sites also had to have sufficient space for the CATCH study non-GP specialist to assess patients.

3.1.3.3. Hospital Cohort Recruitment

The hospital control cohort patients were recruited from new referrals to Eastern Health liver clinics for management of CHB or CHC, from any GP in the Eastern Health catchment area. These patients were used as a hospital control group to examine for differences: to determine if patients referred onto a specialist hepatology management are different to those patients who remained under the care of their GP.

3.1.4. Informed consent

Patients who met the inclusion and exclusion criteria were offered participation in the study by their GP (community cohort) or at their first liver clinic review (hospital cohort). If they agreed, they gave verbal consent to their doctor for their information to be passed along to the CATCH study team. They were then contacted by the study coordinator and provided with a Patient Information and Consent Form (PICF) and were included in the study once written informed consent was obtained (appendix section 1).

3.1.5. Appointments

Patients were offered an appointment at either their local GP clinics or the hospital site they were recruited from. Given attendance rates are variable as discussed in chapter 2, several established methods were employed to maximise attendance rates. These methods included postal reminders and telephone and text message reminders within one day of the appointment.[405, 414, 415] The CATCH study sent patients their appointment details in the mail close to their appointment time, patients were also provided with phone call and text message reminders. They also received the PICF in the mail prior to their appointment although the written consent was taken at the time of the CATCH assessment.

3.1.6. Data collection and Database – Filemaker®

Patient data was collected in a purpose built Filemaker Pro® database. The database was designed to produce a patient specific report for each patient with the results and a management plan for the treating GP, as well as referral onwards for non-GP specialist management if required. Images of this database and a sample report are in appendix section 0.

3.1.7. Patient assessment

Patients underwent an initial assessment which included a detailed history, a complete clinical examination, biochemical tests and LSM using FibroScan® on the same day. These assessments were completed by one of two hepatologists appropriately trained in the use of FibroScan® with at least 500 examinations prior to commencing the CATCH study as per recommendations by Castera et. al.[416, 417] A plan was provided to the referring GP and, if required, a referral to a non-GP specialist was made for management. Table 3-1 shows the data that was collected at each time point.

Table 3-1 Data collected at baseline and repeated assessments

Data collected	Screening	Baseline	Reassessment
Sociodemographic Information Age, gender, postcode		X	
Medical history History of psychiatric diagnosis, cancer history, family history of HCC		X	
CHB/CHC infection characteristics Estimated duration of infection, mode of virus acquisition		X	
History of liver ultrasound within 12 months		X	X
Other substance use Alcohol intake, smoking pack-year history, cannabis use		X	X
Examination (BMI)		X	X
Biochemical Platelets, cholesterol, ALT, AST, GGT, albumin		X	X
Viral parameters CHB Viral load, e-antibody/antigen status		X	X
Viral parameters CHC Viral load, PCR, genotype		X	X
Co-infection (HIV testing)		X	
HCC markers (AFP)		X	X
LSM as measured by FibroScan®		X	X
If relevant, retention in non-GP specialist management			X
Antiviral therapy and outcome		X	X
*Diagnosis of HCC	X		X
*Development of liver-related outcome *Decompensation with ascites, encephalopathy, variceal bleeding	X		X
*Death due to liver disease			

*: primary outcome measures; HCC: hepatocellular carcinoma; CHB: chronic hepatitis B; CHC: chronic hepatitis C; BMI: body mass index; ALT: alanine aminotransferase; AST: aspartate transaminase; GGT: gamma-glutamyl transferase; PCR: polymerase chain reaction; HIV: human immunodeficiency virus; AFP: alfa fetoprotein; LSM: liver stiffness measurement; GP: general practitioner

3.1.7.1. Repeat Assessment

Patients were invited to have repeat assessments yearly, which included clinical history, examination, pathology and LSM. Of those that had antiviral therapy, post treatment LSM assessments were also offered. Patients were recalled using the following methods:

- Telephone calls
- Text message reminders
- Written correspondence via mail
- General practice recall systems using their practice management software
- Booking appointments with CATCH on the same day as, and just prior to, a GP appointment for the community cohort of patients
- Booking appointments with CATCH on the same day as, and just prior to, the non-GP specialist appointment for the hospital cohort of patients

This was done to maximise repeat attendance within CATCH. Data was also collected regarding reasons for not having repeat assessment within CATCH, for example being uncontactable.

3.1.7.2. FibroScan® assessment

FibroScan® assessment was carried out by two investigators. Both proceduralists completed a minimum 500 supervised procedures prior to commencement of the study). FibroScan 402® (Echosens, France) was used initially; however, following unrepairable mechanical issues, the device was changed to a FibroScan 430 mini®. These machines show excellent inter-equipment agreement for LSM results on the same patient on the same day by the same operator.[418] The initial machine used did not have CAP measurements so this data was not collected.

LSM assessment was obtained after fasting for a minimum of 2 hours, with either an M or XL probe as determined by skin capsule distance and manufacturer specification. The optimal position was determined using an ultrasound (KiaXin KX5600®) as well as the skin to capsule distance as the Fibroscan® machines used did not have the automatic suggested probe feature. A minimum of ten valid LSM readings were required with a success rate greater than 60% and an IQR:ms of less than 30% as per manufacturer guidelines.[417] Any results not meeting this standard accepted criteria were considered an invalid assessment and were excluded from analysis.

An LSM≥7kPa and ≥12.5kPa for the CHC group were used as the cut-off points for high likelihood of significant fibrosis and cirrhosis respectively, with LSM≥7kPa and ≥11kPa used as cut-off points for high likelihood of significant fibrosis and cirrhosis for people living with CHB. These cut-offs were chosen based on previous studies including a meta-analysis of LSM and the degree of fibrosis as discussed in section 2.1.4.[263, 419]

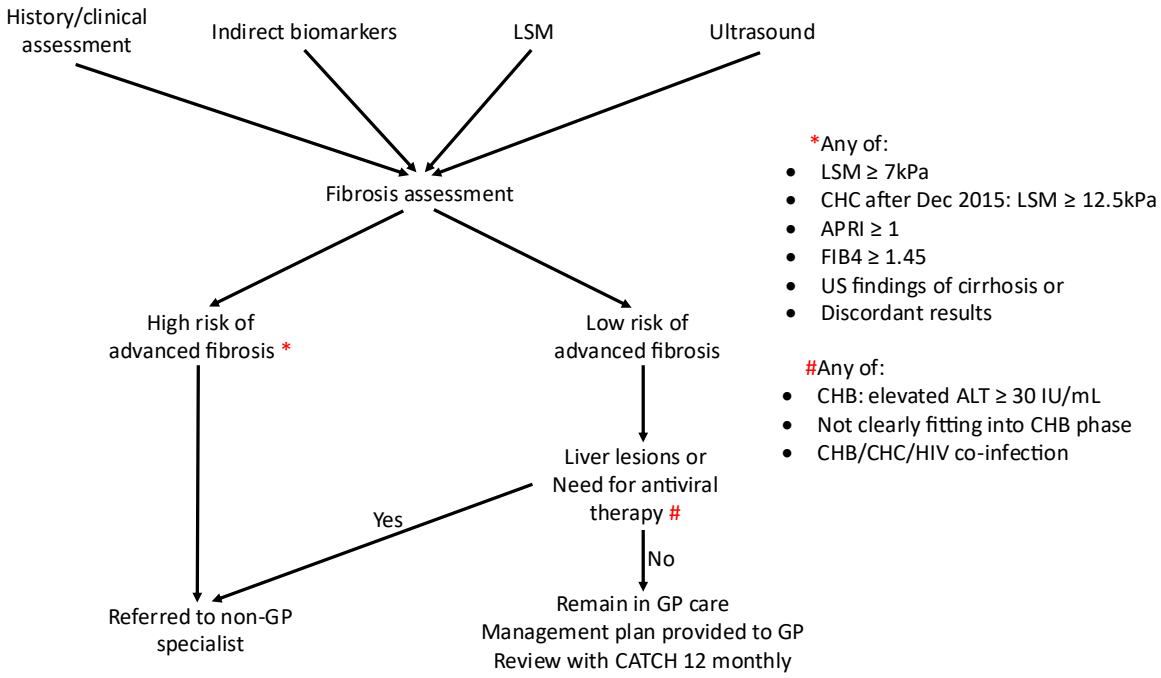
3.1.7.3. Algorithms of indirect biomarkers assessment

The algorithms of indirect biomarkers were also calculated for each patient; APRI and FIB4 were selected as these are included in the management guidelines for chronic viral hepatitis by the Australian Liver Association.[10] A score of 1 for APRI and 1.45 for FIB4 were used as cut-off points for probabilities of advanced fibrosis as discussed in section 2.1.4.[225, 420, 421] All patients also had Forn's index and 4AGP calculated although these results weren't included within the management protocol.

3.1.7.4. Treatment/management Plans

Following the study assessment, a patient specific management plan was completed (Figure 3-2). This plan was provided to the community cohorts patient's GP with the individualised HCC risk and individualised suggestions for monitoring (see appendix section 0 for an example). If necessary, patients were referred onwards for non-GP specialist management. Hospital patients were seen by a non-GP specialist in the outpatient department liver clinics for ongoing care.

Figure 3-2 Management algorithm for community cohort of patients



LSM: liver stiffness measurements as assessed by FibroScan®; kPa: kilopascals; CHC: chronic hepatitis C; APRI: aspartate transaminase to platelet ratio; FIB4: Mean fibrosis index based on four factors; US: ultrasound; CHB: chronic hepatitis B; ALT: alanine aminotransferase; IU/mL: international units per millilitre; HIV: human immunodeficiency virus; GP: general practitioner; CATCH: Community Approach Targeting Cirrhosis and Hepatocellular carcinoma

3.1.7.1. Patient referral for non-general practitioner specialist input

Patients in the community cohort were referred onwards to a Gastroenterology outpatient clinic if diagnosed with cirrhosis or other complications as appropriate. The availability of DAAs for the treatment of CHC including the option of community GP treatment changed the paradigm for referral. Referral to hospital directed treatment was based on LSM for people living with CHC infection. From December 2015 onwards those with an LSM less than 12.5Kpa remained with their GPs for treatment when it was announced that DAAs would be made available in the community from March 2016. Treatment plans were adapted to include suggested DAA therapy.

3.1.7.2. Patient non-general practitioner specialist attendance, hepatocellular carcinoma surveillance and liver and other health related outcomes data collection

At the end of the study, all patients had a record review. This was performed to determine if they were linked into non-GP specialist care for CHB and/or CHC, whether they had had an ultrasound within the preceding 12 months (if required), as well as treatment, treatment outcomes and liver-related outcome events. Other data was collected including incarceration, death due to non-liver-related causes and diagnosis of non-liver-related cancer. Record reviews were performed for the community cohort at the GP clinic patients were recruited from and, if they were referred onwards for non-GP specialist management, at the hospital they were referred to. Patients from the hospital cohort had their hospital medical records reviewed.

3.2. Statistical methods

Data cleaning, transposition and statistical analyses were performed using RStudio version 1.2.5 for Mac. The code for this, along with the results of the analyses are included in appendix section 3.

3.2.1. Data cleaning

Data was re-categorised for some of the variables. Past history was categorised into history of psychiatric illness as per the Diagnostic and Statistical Manual of Mental Disorders (DSM) version 5.[422] Alcohol use refers to those who drink alcohol at an at-risk level of more than 100g per week, following the Australian guidelines.[67] History of IVDU refers to those who reported IVDU as one of their risk factors for infection. Smoking history refer to a more than 15 pack-year cigarette tobacco smoking history as per previous studies showing this as the cut-off for higher risk of smoking related health complications.[77] Non-smoker refer to those who do not smoke cigarettes or those with less than a 15 pack-year smoking history. Cannabis use refers to a history (current or past) of cannabis use in any formulation. Ultrasound findings of cirrhosis include nodular liver surface and/or signs of portal hypertension such as dilated or altered direction of flow in the portal vein, recanalization of the umbilical vein, splenomegaly and/or visible varices. Ethnicity was categorised based upon participant reporting of their ethnicity using Australian Standard Classification of Cultural and Ethnic Groups (ASCCEG 2019).[423]

Patients postcode data was classified as per the Australian Bureau of Statistics (ABS) Socio-Economic Indexes for Australia (SEIFA) 2016;[424] this report looks at different areas of socio-economic advantage and disadvantage and the results indicate patient's ability to access material and social resources as well as their ability to participate in society. The Index of Relative Socio-economic Disadvantage looks at how many households there are with low income; patients with no qualifications; and patients in low skill occupations. The Index of Relative Socio-economic Disadvantage was used as the other Indexes consider other variables which can complicate the interpretation of results. For example, the Index of Relative Socio-economic Advantage and Disadvantage scores consider disadvantage as well as advantage, so, in areas with high advantage, the fact that there are disadvantaged groups within that area will be missed with this score. Another reason The Index of Relative Socio-economic Disadvantage was used was that the purpose of looking at this variable was to assess degrees of disadvantage. A lower score indicates more disadvantage and a higher score indicates a higher level of advantage; scores were also standardised to have a mean of 1000 and a standard deviation of 100 across all areas in Australia. Areas were also grouped into quintiles from lowest to highest disadvantage scores within Australia; the lowest 20% given a score of 1 and the highest 20% given a score of 5. The lower the score or quintile, the more disadvantage in that area.

3.2.2. Statistical analysis

Continuous data variable skewness was assessed to determine which statistical tests to use. The moment coefficient of skewness (g_1) is calculated using:

$$g_1 = \frac{m_3}{m_2^{3/2}}$$

$$\text{Where } m_3 = \sum(x - \bar{x})^3/n \text{ and } m_2 = \sum(x - \bar{x})^2/n$$

$\bar{x}$ is the mean and n is the same size.

These two equations are used to calculate the skewness for a whole population of data.[425] However, when you have a sample of a population, the next step is to calculate the sample skewness using the $g_1$results from the above equation and the below equation:

$$G_1 = g_1 \frac{\sqrt{n(n-1)}}{(n-2)}$$

Where G_1 indicates the skewness of the sample data and n is the number within the sample.[425] A positive G_1indicates the data is skewed to the right and a negative G_1indicates

left skewed data.[425] The cut-offs for degree of skewness are -1/1 indicating highly skewed or non-Gaussian distributed, -0.5/0.5 indicating moderately non-Gaussian distributed and anything between -0.5 and 0.5 indicates approximately Gaussian distributed data.[425] Results of skewness testing is in the appendix section 3.

Differences between categorical variables were analysed using Chi squared analyses. Ordinal data was analysed using chi-squared analyses as well as Goodman and Kruskal's gamma (γ).[426] For analyses with continuous outcome variables with Gaussian distribution, a Welsh's t-test was used for to examine differences between two groups [427] with mean and standard deviation (SD) reported. A t-value is also reported (in appendix 3) along with a p-value to assess for statistical significance. Effects sizes for these analyses were calculated with Cohen's D,[428] this indicates the standardised differences between two means, a result of 0.2 means a small effect size; 0.5 indicates a medium effect size and 0.8 indicates a large effect size. Cohen's D is calculated as follows:[428]

$$Cohen's\ D = (mean2 - mean1) / (Square\ root\ [(SD1^2 + SD2^2)/2])$$

Mean2 and mean1 and SD1 and SD2 are the means and standard deviations of groups 1 and 2 respectively.

For non-Gaussian distributed variables, transforming the data to a Gaussian distribution was not performed as interpreting transformed data is much more difficult from a clinical perspective. There are also appropriate statistical methods that take into account the skewed distribution of the data; Wilcoxon rank sum tests do that and were thus used [429] with results reported with median and IQR. A W value has also been calculated for this test (presented in appendix 3) along with a p-value to assess for statistical significance. Cliff d was used to determine effect size for this group.[430] Cliff d estimates the probability that an observation randomly selected from one group will be larger than the same from the other group; it does not make any assumptions about the distribution of data. The interpretation of Cliff d requires both the Cliff d result and the 95% confidence interval (CI); The Cliff d ranges from -1 to +1; a result of -/+1 indicates no overlap between the groups, a score of 0 indicates that the groups distributions overlap completely. Ideally the 95% CI should not cross zero. The Cliff d equation is:[430]

$$Delta = [\#(X_1 > X_2) - \#(X_1 X x_2)] / (n_1 X n_2)$$

X_1 and X_2 are scores within group 1 and group 2 and n_1 and n_2 are the sizes of the groups. The cardinal # symbol indicates counting: the test is repeated multiple times.

Survival curves were analysed using a Kaplan Meier log-rank test [431] and HRs were calculated using cox proportional HR.[432] Linear and logistic regressions were used to examine the effects of multiple variables and/or interactions between variables.[433] Statistical significance was assessed using p-values (2 side p value <0.05 being considered statistically significant) as well as W, t, $\chi 2$, and γ values and degrees of freedom, as appropriate, depending on the statistical method.

3.2.2.1. Receiver operator characteristic and optimal cut-off points

The ability of the tests to determine those with and those without the disease were assessed using receiver operator characteristic (ROC) and the AUROC analysis.

Optimal cut-off points for LSM and indirect biomarkers for predicting outcomes were calculated based on maximising the product of sensitivity and specificity and thus the accuracy area (AA), by using the numbers of true positives and negatives and false negatives and positives.[434-436] The calculation is as follows:

AA(c)=fracTP(c) X TN(c) X **[**TP(c) + FN(c)**]** X **[**FP(c) + TN(c)**]**

TP, TN, FN and FP are the numbers of True Positives, True Negatives, False Negatives and False Positives, respectively.

All the statistical test results are in appendix section 3.

3.2.3. Correlations

To determine which variables to use for multivariate analyses, Pearson Product-Moment Correlation was performed for variables suspected to be highly correlated. When there is a high correlation coefficient (*r*) then the variables are highly correlated and both variables should not be used in a multivariate analysis as they can cancel out each other's effect within the analysis.[437] Generally, a cut-off of r=0.3 is used.[437]

Age and duration of virus infection were moderately correlated (r=0.47); AST and ALT were highly correlated (r=0.86) and LSM and all the indirect biomarkers were highly correlated (APRI, FIB4, Forn's index, 4AGP, r>0.5 for all). The implications for these results mean that age and years of infection; ALT and AST; LSM and the indirect biomarker algorithms cannot be used within the same regression analyses due to multicollinearity. There were also strong correlations between some of the categorical variables: age and smoking (0.44) and at-risk alcohol intake and history of IVDU (0.49). These results are shown in appendix section 3.

It was decided that for regression analyses where age and years of infection were both significant in the univariate analysis to use age in the multivariate analysis. The reason for this is because years of infection adds in a recall bias, and age is a definite result. We also found that patients were sometimes unsure about when they acquired their infection and so often reported their 'best guess' although this data was not formally collected. ALT was used in the multivariate analysis when AST and ALT were both significant in the univariate analysis as some of the patient's AST results were not available due to haemolysis or the pathology lab not performing this as part of routine LFTs and missing the AST request on the pathology result slip.

3.2.4. Sample size calculation

Given the lack of previous data within a community cohort of people living with CHB and/or CHC, sample size calculation was unable to be performed with any degree of certainty at the inception of this study.

Sample size was calculated using The Power and Sample Size Calculation Program Version 3.0.[438, 439]

The following assumptions were made:

1. The prevalence of cirrhosis is 5% in people living with CHB [440]
2. The prevalence of cirrhosis is 10% in people living with CHC [441]

The sample size calculation estimated that 553 community people living with CHC were required to estimate the prevalence of cirrhosis within the community and determine a difference between the community and the hospital cohort for a precision of 2.5%. For the people living with CHB, 297 patients were required to determine the differences between the cohorts. These results, however, should be interpreted with extreme caution.

3.3. Ethics

The CATCH study was approved as per the Declaration of Helsinki, through the local ethics committee human research application via Eastern Health Human Research Ethics Committee (ECRU, E38-1314, appendix section 0).

3.4. Methodology for assessment of aims

To assess the aims listed in section 2.2.4 the following specific factors have been assessed within each of the broader aims. Each of these aims have been assessed and compared between the hospital and community cohorts.

3.4.1. Factors associated with morbidity and mortality at initial assessment

This was done by assessing the following:

- The severity of liver fibrosis as assessed by:
    - LSM using FibroScan® and
    - Indirect biomarker algorithms including APRI, FIB4, Forn's index and 4AGP and
    - Factors associated with elevated LSM including:
        - Patient factors such as age, gender, dual infection with CHC, history of at-risk alcohol use and BMI and
        - Pathology results including platelets, ALT, AST, GGT, albumin, cholesterol, AFP and, in people with CHB hepatitis B viral load and
    - Ultrasound findings of cirrhosis as defined in section 2.1.4.3
- In people living with CHB, the percentage who:
    - Require HCC surveillance and
    - Are in a phase of HBV that warrants treatment
- Risk factors for fibrosis development, HCC and/or non-liver-related morbidity and mortality as assessed by:
    - The percentage of patients with a history of IVDU, psychiatric diagnosis, at-risk alcohol use, cannabis use, cigarette smoking history and
    - The socioeconomic status of patients

To determine the phase of disease for people living with CHB, two cut-off points for ALT were assessed. In the laboratories used for the CATCH study, the accepted ALT cut-off was 30 international units per litre (IU/L). As discussed in section 2.1.1.6, the upper limit of normal should be lower than this at 19 IU/L for women and 30 IU/L for men.[40-42] This section will thus assess both of these cut-off points for women (19 and 30 IU/L) and 30 IU/mL for men. As mentioned earlier in this chapter, patients were offered reassessment yearly; their phase at the last assessment with CATCH was also assessed to determine movement between phases over time. Patients were excluded from this part of the analysis if they didn't have repeat

assessments or complete pathology results available to determine the disease phase. If they were commenced on treatment, the last phase prior to commencing treatment was assessed.

This section will also focus on the phases where antiviral therapy should be considered, namely the hepatitis phases. The reason for this is that antiviral therapy is usually lifelong and although commencement of antiviral therapy is not always based on results from a single time point, patients in a treatment may need more regular monitoring if antiviral therapy is not commenced. Patients with HBeAg negative disease with high viral load (>2000 IU/mL) but with a normal ALT have also been included in this group as they are at risk of developing ALT flare within 12 months in approximately one third of cases and thus require closer monitoring.[38, 39] To determine the percentage of patients in a hepatitis phase, an ALT cut-off of 19 IU/L for women and 30 IU/mL for men has been used. There was also a group of patients who had HBeAg negative infection (eAg negative and viral load of less than 2000 IU/mL) but have an elevated ALT. These results have been reported but are not included percentage of patients in a hepatitis phase as typically do not require antiviral therapy for CHB. Those who had HBeAg negative infection with elevated ALT who were at higher risk of having current complications will have been picked up in the group that have elevated LSM or dual infection with CHC.

To determine the prevalence of factors associated with morbidity and mortality in the CHB community and hospital cohorts, those with a high probability of cirrhosis, in a hepatitis phase, who required HCC surveillance or had dual infection with CHC or HIV were included. The phase of disease includes only the phase at baseline to capture the percentage of patients with factors that have an impact at one timepoint. To determine the primary contributing factor, the factors were allocated to patients in the following order:

(1) High probability of cirrhosis,
(2) Hepatitis phase
(3) HCC surveillance recommended
(4) Dual infection with CHC or HIV

This order was chosen as it was deemed to be likely the highest risk order with higher liver-related outcomes in people living with CHB and cirrhosis. CHB in a hepatitis phase can occasionally be a high-risk condition with rapid fibrosis development. Those requiring HCC surveillance who are not cirrhotic have a low risk of HCC. Dual infection with CHC or HIV

were not included within the analysis that determined the primary contributing factor as the numbers were too low for meaningful statistical tests.

To determine the primary indication for HCC surveillance in the CHB community and hospital cohorts, each patient had a single indication made based on the following order:

(1) High probability of cirrhosis based on LSM/ultrasound
(2) Age/gender/ethnicity criteria
(3) Family history HCC

The reason these were categorised in this order was based on HCC incidence as discussed in section 2.1.5.2.

3.4.2. Adherence with medical appointment and management

This has been performed by establishing:

- In all patients:
    - Percentage retained in medical care by assessing repeat attendance rates within CATCH and reasons for non-attendance
    - Percentage who commenced treatment (CHC) and outcomes of treatment including SVR testing and SVR results
- In patients who are at higher risk of liver-related outcomes based on disease phase, need for HCC surveillance or with a high probability of cirrhosis:
    - Percentage retained in non-GP specialist care
    - Percentage who had appropriate HCC surveillance
    - Percentage who commenced treatment
- Factors associated with adherence with the above measures

Although ultrasounds should be performed every 6 months in patients who are at risk of HCC, a decision was made to use a cut-off of 12 months. The reason behind this decision was to allow for reporting/recall bias and to allow some leeway. As discussed in chapter 2, many patients do not strictly adhere to the 6 months so allowing for 12 months will capture the patients who will generally be adhering to HCC surveillance. When referring to ultrasound in the results sections, it is referring to an abdominal ultrasound that includes examination of the liver.

In this section assessing factors associated with treatment for the CHC community and hospital cohorts, patients were excluded if it was unknown if they had treatment and in those who cleared CHC without treatment. It was felt that those where treatment status was unknown should not be included (as in an intention to treat analysis) as a lot of these patients moved between clinics or interstate and may well have had treatment. If patients self-cleared CHC then they don't require treatment and thus should not be included in the analysis looking at predictors of treatment. It is also assumed that if treatment was started, unless it was documented otherwise, that the treatment course was finished. In the sections assessing whether testing for SVR was performed, those who were lost to follow-up or where SVR was not yet due were excluded due to similar reasons above. In the analysis regarding predictors of DAA failure, those without SVR results were excluded. This was chosen as there are very high cure rates, so it is likely that more than 90% of those who didn't have testing for SVR were cured, however, they were excluded as this can't be assumed. The analysis regarding predictors of DAA failure is based on the first treatment course outcome although cure rates for second line therapy will be presented.

To determine the indication for treatment for the CHB community and hospital cohorts, each patient had a single indication made based on the following order:

1) High probability of cirrhosis based on LSM/ultrasound
2) In a hepatitis phase

This order was chosen based on degree of benefit from treatment as discussed in section 2.1.6.

3.4.3. Incidence of liver-related outcomes

This has been performed by determining:

- Incidence of liver-related outcomes as defined by:
    - Hepatocellular carcinoma
    - Liver decompensation (ascites, hepatic encephalopathy, variceal bleeding)
    - Death due to liver disease
    - A composite end point of the above liver-related outcomes
- Factors associated with liver-related outcomes

- The performance of non-invasive tools including LSM, APRI, FIB4, Forn's index and 4AGP in estimating the risk of developing a composite of liver-related outcome as assessed by:
    - AUROC
    - Kaplan Meier survival curves
    - Cox-proportional HR
- The optimal cut-off points to predict a composite of liver-related outcomes

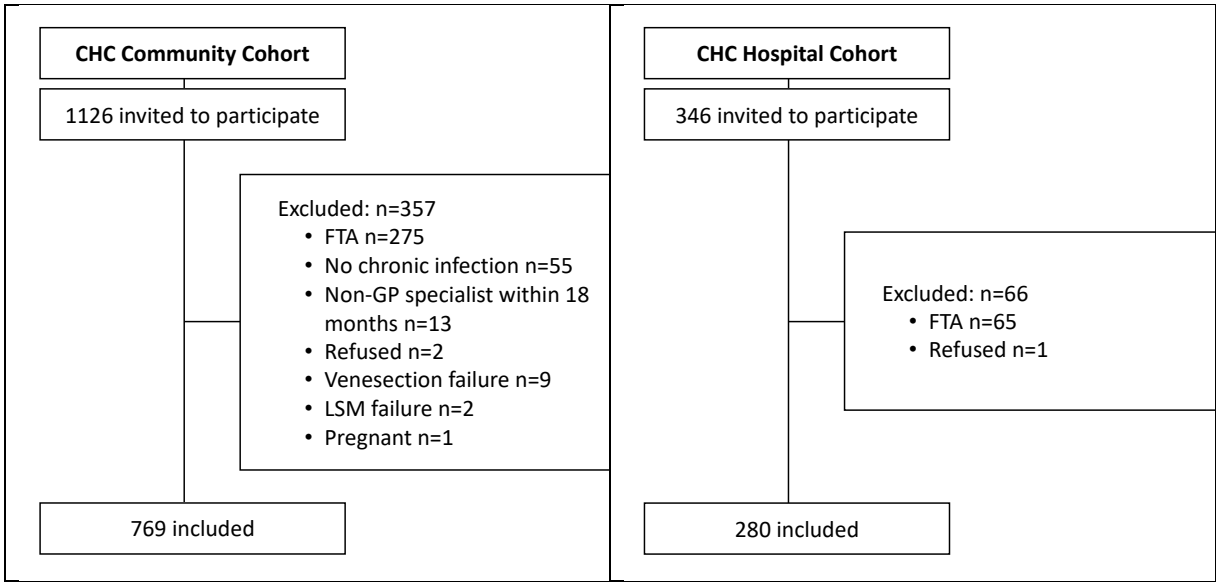
Chapter 4. Results: Chronic Hepatitis C

This chapter aims to determine the prevalence of factors associated with increased risk of morbidity and mortality, determine adherence with management and assess risk of liver-related outcomes, in people living with CHC. The factors associated with increased risk of morbidity and mortality include patients with (1) a high probability of cirrhosis based on LSM and ultrasound findings, and (2) risk factors for liver fibrosis development and non-liver causes of morbidity and mortality. These include history of IVDU, psychiatric diagnoses, at-risk alcohol use, cannabis use, cigarette smoking history and socioeconomic status. Adherence includes (1) retention in CATCH, (2) retention in non-GP specialist care in patients where this is required, (3) HCC surveillance and (4) antiviral therapy. Liver-related outcomes include (1) diagnosis of HCC, (2) decompensation (ascites, encephalopathy, variceal bleeding) or (3) death due to liver disease. Predictors of all of these will be assessed, and, to provide greater context in answering these questions, the study cohort (community cohort) will be compared to a current standard of care cohort (hospital cohort).

4.1. Patient recruitment results

Between October 2014 and March 2017, 1049 people living with CHC were recruited: 769 from the community cohort and 280 from the hospital cohort. Community cohort was over-sampled because this was the focus of the study with the hospital cohort as a comparator cohort. The patients from the community cohort were recruited from 18 GP clinics around Melbourne, Australia, of which 11 were opiate replacement therapy prescribing clinics. The patients from the hospital cohort were recruited from Eastern Health liver and hepatitis outpatient clinics in Melbourne, Australia. A further 423 patients were excluded due to FTA, failure to meet inclusion criteria or refusal or inability to obtain LSM or biochemical assessment (Figure 4-1). There was a higher FTA rate in the community cohort (24.2%) compared to hospital cohort (18.8%, $p = .03$).

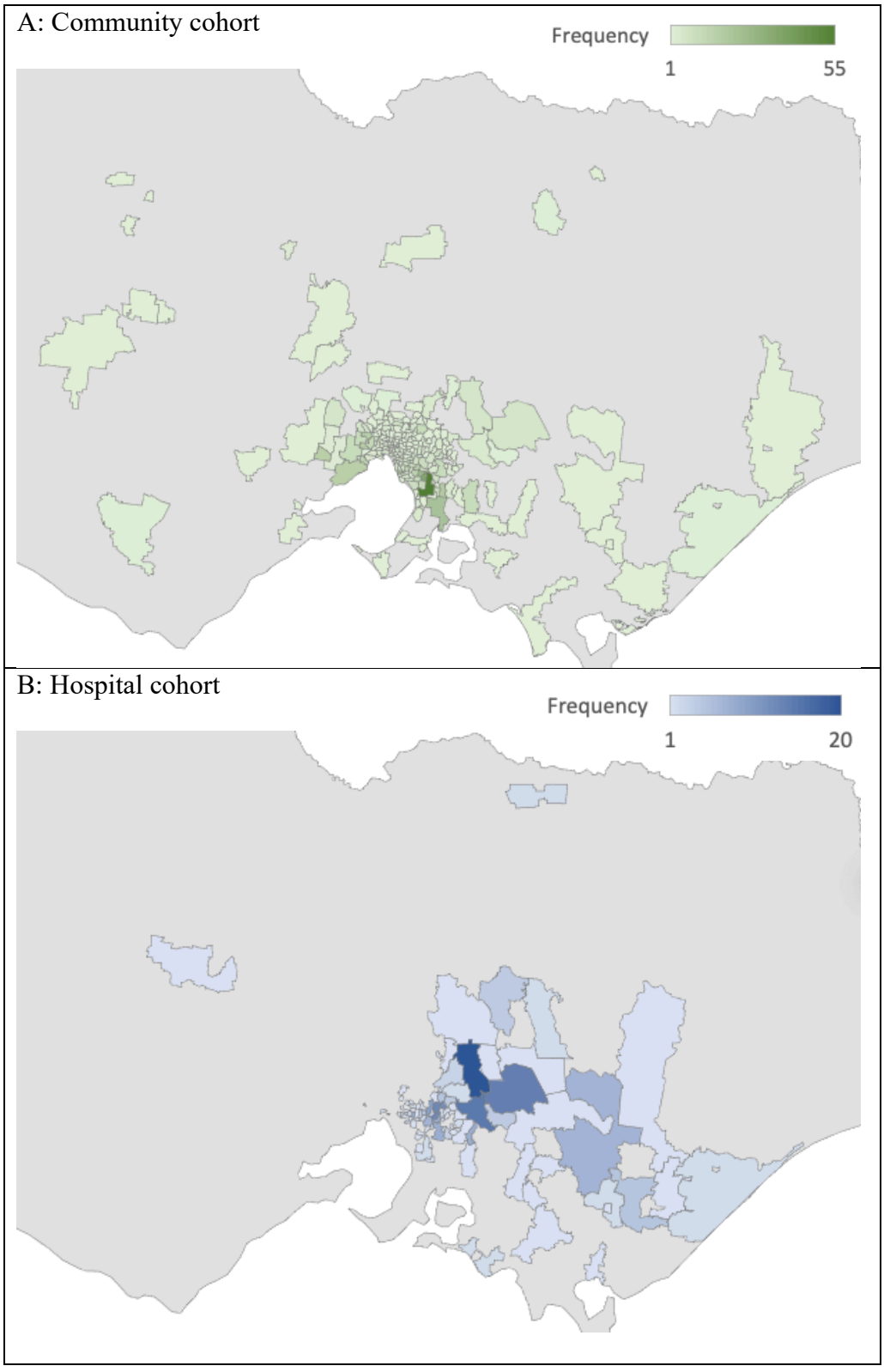
Figure 4-1 Flow chart of study recruitment



CHC: chronic hepatitis C; FTA: failed to attend; GP: general practitioner; LSM: liver stiffness measurement

Figure 4-2 demonstrates the patients' geographical location by postcode. The geographical distribution of the community cohort (Figure 4-2 A) was more widely distributed across Victoria compared to the hospital cohort (Figure 4-2 B) principally as a consequence of the differences in number of recruitment sites between the two groups; the hospital cohort was recruited from Eastern Health sites which services patients who live in the eastern suburbs of Melbourne whereas the community cohort was recruited from multiple primary health care setting across Victoria.

Figure 4-2 Geographical distribution of patients by postcode in community and hospital cohorts. Victoria, Australia



4.2. Factors associated with morbidity and mortality at initial assessment

As discussed in chapter 2, most of the morbidity and mortality attributed to CHC is related to the degree of liver fibrosis and ultimately cirrhosis. Therefore, identifying patients who have a high probability of cirrhosis is an important part of risk stratification. This section aims to determine the prevalence of those with a high probability of cirrhosis based on LSM ≥12.5kPa and ultrasound findings of cirrhosis as well as indirect biomarker algorithms including APRI; FIB4; Forn's index and 4AGP.

Several factors are also known to influence the progression of fibrosis and themselves may add to the morbidity and mortality of CHC. Patients with CHC may also have higher rates of other factors that play a role in morbidity and mortality from non-liver related causes. The impact of these factors has been variably reported in the literature and are therefore examined in our study to determine if any differences exist between the two cohorts. This section thus also aims to determine factors associated with LSM ≥12.5kPa and the prevalence of other factors associated with morbidity and mortality. These factors include age, years of infection, gender, history of dual infection with CHB, family history of HCC, at-risk alcohol intake and BMI, pathology results, namely platelets; ALT; AST; GGT; albumin; total cholesterol; and AFP. All of these will be compared between the cohorts.

4.2.1. Results

4.2.1.1. Baseline characteristics

Table 4-1 shows the baseline variables and differences between the community and hospital cohort of patients. The community CHC cohort was younger than the hospital cohort with a moderate effect size meaning a moderate sized difference ($p < .001$, Cohen's $D = 0.43$), and had a shorter estimated duration of infection also with moderate sized difference ($p < .001$, Cohen's $D = 0.45$) compared to the hospital cohort. IVDU was more commonly reported as a risk factor for infection in the community cohort compared to the hospital cohort ($p < .001$) as were rates of psychiatric history diagnoses ($p = .008$). There were lower rates of at-risk alcohol intake in the community cohort ($p = .04$). Other patient factors including gender, rates of dual infection with CHB, cigarette smoking, and cannabis use were similar between the cohorts ($p>.05$ for all).

Table 4-1 Baseline characteristics and variables in community and hospital cohorts. Univariate analysis.

Variable	Community n=769	Hospital n=280	p-value
Age (years, mean, SD)	**43.1 (9.5)**	**47.3 (10.5)**	**<.001**
Years of infection (years, mean, SD)	**14.6 (8.7)**	**18.6 (10.2)**	**<.001**
Dual Infection CHB, n (%)	15 (1.9)	2 (0.7)	.2
Gender, n (female, %)	225 (29.2)	95 (33.9)	.1
Cigarette smoking, n (%)	303 (43.3%)	113 (49.6)	.1
Cannabis use, n (%)	503 (67.2)	166 (61.7)	.1
Alcohol, n (%)	324 (42.1)	138 (49.2)	.04
History of IVDU, n (%)	**719 (93.4)**	**216 (77.1)**	**<.001**
History of psychiatric diagnosis, n (%)	**359 (46.7)**	**105 (37.5)**	**.008**
Personal history of cancer, n (%)	15 (2.0%)	10 (3.6%)	.1
Family history of HCC, n (%)	21 (2.7)	10 (3.6)	.5
BMI (kg/m^2, median, IQR)	25.2 (6.6)	26.0 (6.5)	.06

Bold: significant ($p < .05$); SD: standard deviation; CHB: chronic hepatitis B virus infection; cigarette smoking: > 15 pack-year history; alcohol: > 100g/week; IQR: interquartile range; IVDU: intravenous drug use as a risk factor for viral hepatitis; HCC: hepatocellular carcinoma; BMI: body mass index; kg: kilograms; m: metres

To examine the relationship between cohorts and socioeconomic status, patient postcode was linked to socioeconomic status using ABS data. There were significant differences in the distribution between the hospital and community cohorts ($p < .001$, Table 4-2) with the community cohort having greater socioeconomic disadvantage (i.e. the community cohort was more disadvantaged). There were very few patients within the 'high' socioeconomic disadvantage quintile.

Table 4-2 Socioeconomic disadvantage quintile in community and hospital cohorts

	Socioeconomic disadvantage quintile %				
Cohort	Very high	High	Moderate	Low	Very low
Community	26.9	9.9	20.9	17.7	24.4
Hospital	13.4	2.5	22.8	39.9	21.4
Total	23.3	8.0	21.4	23.6	23.6

Each cell represents the percentage of patients from the Cohort (row) belonging to the Socioeconomic disadvantage quintile (column). Very high: very high level of disadvantage, meaning most disadvantaged

Given there may be differences in rates of smoking, history of psychiatric diagnosis, IVDU, cannabis use and at-risk alcohol intake between areas of different socioeconomic status, these factors were also assessed. Analyses showed no differences between socioeconomic disadvantage quintiles, in either the community or hospital cohorts ($p > .5$ for all).

Examination of the pathology results (Table 4-3) showed total cholesterol was slightly lower in the community cohort, although the small effect size suggests a negligible difference clinically (p = .001, Cohen D = 0.23). AFP results were also different, although also with a small effect size (p < .001, Cliff Delta = 0.23 [0.2-0.3]). The other pathology results (platelets, AST, ALT, GGT, Albumin) were all similar between the cohorts (p > .05 for all).

Table 4-3 Baseline pathology results in the community and hospital cohorts

Variable	Community n=769	Hospital n=280	p-value
Platelets (x10^9/L, mean, SD)	226.9 (70.8)	220.5 (78.7)	.2
AST (U/L, median, IQR)	46 (44)	47 (47)	.6
ALT (U/L, median, IQR)	57 (63)	59 (80.3)	.2
GGT (U/L, median, IQR)	52 (69)	57.5 (78.3)	.09
Albumin (g/L, mean, SD)	39.2 (3.6)	39.0 (3.5)	.2
Cholesterol (mmol/L, mean, SD)	**4.2 (1.0)**	**4.5 (1.1)**	**.001**
AFP (ug/L, median, IQR)	**3 (2)**	**3 (3)**	**<.001**

Bold: significant (p < .05); SD: standard deviation; IQR: interquartile range; AST: aspartate aminotransferase; U/L: units per litre; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; g/L: grams per litre; mmol/L: millimoles per litre; AFP: alpha fetoprotein; ug/L: micrograms per litre.

Given known interactions of age, history of IVDU, history of psychiatric diagnoses, at-risk alcohol use and socioeconomic status, these factors were assessed with a binomial logistic regression analysis to determine which factors independently remained different between the cohorts. Duration of infection was not included in this model due to multicollinearity of this variable with age. Those from the community cohort were younger, had higher rates of IVDU and history of psychiatric diagnosis than the hospital cohort (Table 4-4). Those from the community cohort also had higher levels of socioeconomic disadvantage (lower socioeconomic disadvantage quintiles) and lower rates of at-risk alcohol use in this regression analysis.

Table 4-4 Regression results for age, socioeconomic disadvantage quintile, history of intravenous drug use or psychiatric history: community versus hospital cohort

Predictors	Significance	Odds ratio	95% CI
Age	< .001	0.97	(0.95, 0.98)
Socioeconomic disadvantage quintile	< .001	0.79	(0.71, 0.88)
IVDU	< .001	3.86	(2.53, 5.90)
Psychiatric diagnosis history	.03	1.41	(1.04, 1.90)
Alcohol	.02	0.70	(0.52, 0.94)

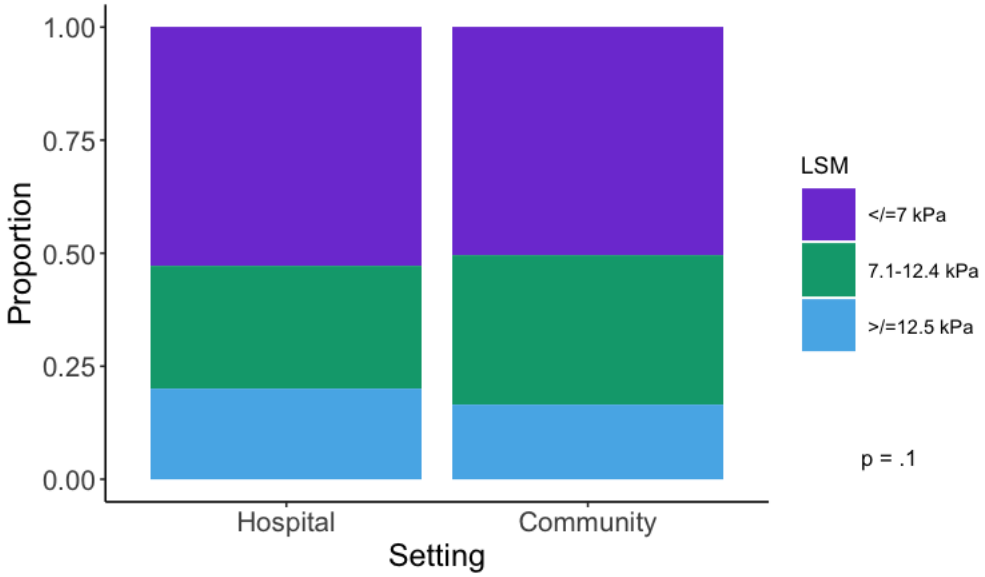
Statistical test: binary logistic regression. CI: confidence interval IVDU: intravenous drug use as a risk factor for viral hepatitis; Alcohol: > 100g/week

To summarise, those from the community cohort had higher rates of factors associated with morbidity and mortality, higher rates of IVDU, psychiatric diagnoses and higher degrees of socioeconomic disadvantage than the hospital cohort. The community cohort was also younger. The pathology results were very similar between the community and hospital cohort and although AFP and cholesterol were slightly lower in the community cohort, the difference was negligible.

4.2.1.2. Severity of liver disease as assessed by liver stiffness measurements and indirect biomarker algorithms

LSM and indirect biomarker algorithms were very similar between the two cohorts. Rates of LSM ≥12.5kPa and ≥7.1kPa were no different between the community and hospital cohorts (p = .15, Figure 4-3). There were no significant differences in LSM between the community and hospital cohorts when assessed using LSM as a continuous variable (p = .4, Table 4-5). Indirect biomarker algorithms were also very similar between the community and hospital cohorts. Forn's index was lower in the community cohort than the hospital cohort although the small effect size suggests the difference was negligible clinically (p < .005, Cohens D = 0.23). 4AGP was also slightly lower in the community cohort than the hospital cohort although also with a very small effect size (p = .03, Cliff Delta = 0.11 [0.18-0.03]).

Figure 4-3 Baseline liver stiffness measurements in community and hospital cohorts



LSM: liver stiffness measurements; kPa: kilopascals

Table 4-5 Baseline liver stiffness measurements and indirect biomarker algorithms in community and hospital cohorts. Univariate analysis

LSM and algorithms of indirect fibrosis markers	Community n=769	Hospital n=280	p-value
LSM (median, IQR)	6.9 (5.1)	6.8 (5.4)	.4
APRI (median, IQR)	0.6 (0.7)	0.6 (0.9)	1
FIB4 (median, IQR)	1.2 (1.0)	1.3 (1.1)	.2
Forn's index (mean, SD)	**7.1 (1.8)**	**7.5 (1.8)**	**<.001**
4AGP (median, IQR)	**-5.0 (2.5)**	**-4.5 (2.8)**	**.03**

Bold: significant ($p < .05$); LSM: liver stiffness measurements; IQR: interquartile range; APRI: AST to platelet ratio index; FIB4: Mean fibrosis index based on four factors; SD: standard deviation.

To summarise, LSM and indirect biomarker algorithms were very similar between the cohorts: although Forn's index and 4AGP were slightly lower in the community cohort, the effect size was very small meaning the differences were negligible.

4.2.1.3. Baseline associations with elevated liver stiffness measurements

There was 16.6% (n=128) of the community cohort and 20.0% (n=56) of the hospital cohort who had an LSM ≥12.5kPa. Variables associated with LSM ≥12.5kPa were assessed (Table 4-6). In both cohorts, increasing age and years of infection and at-risk alcohol intake were associated with LSM ≥12.5kPa. Female gender had lower rates of LSM ≥12.5kPa in the hospital cohort but not in the community cohort. Smoking history was associated with LSM ≥12.5kPa in the hospital cohort but not the community cohort. Increasing BMI, AST, ALT, GGT and AFP were also associated with LSM ≥12.5kPa in both cohorts, as was lower albumin and total cholesterol.

Table 4-6 Odds ratio with 95% confidence interval for liver stiffness measurements ≥12.5kPa in community and hospital cohorts. Univariate analysis

	Odds ratio (95% CI)	
Variable	**Community Cohort**	**Hospital Cohort**
Age	**1.07 (1.04-1.09)**	**1.09 (1.05-1.13)**
Years of infection	**1.05 (1.03-1.08)**	**1.06 (1.02-1.09)**
Gender (female)	0.7 (0.45-1.09)	**0.36 (0.17-0.74)**
Dual Infection with CHB	0.88 (0.41-1.85)	2.01 (0.50-8.11)
Cigarette smoking	1.44 (0.96-2.15)	**2.84 (1.39-5.78)**
Cannabis use	0.68 (0.45-1.01)	0.8 (0.44-1.46)
Alcohol	**2.06 (1.40-3.03)**	**4.33 (1.89-9.92)**
History of IVDU	0.54 (0.28-1.05)	0.61 (0.32-1.17)
History of psychiatric diagnosis	0.77 (0.53-1.14)	0.54 (0.28-1.04)
BMI	**1.11 (1.08-1.15)**	**1.09 (1.02-1.15)**
Platelets	**0.98 (0.98-0.99)**	**0.98 (0.97-0.98)**
AST	**1.02 (1.01-1.02)**	**1.02 (1.01-1.03)**
ALT	**1.007 (1.004-1.009)**	**1.006 (1.002-1.01)**
GGT	**1.006 (1.004-1.008)**	**1.007 (1.004-1.01)**
Albumin	**0.80 (0.75-0.84)**	**0.72 (0.65-0.80)**
Cholesterol	**0.63 (0.51-0.77)**	**0.52 (0.38-0.73)**
AFP	**1.29 (1.21-1.38)**	**1.23 (1.14-1.34)**

Bold: significant ($p < .05$, confidence interval does not cross 1); CI: confidence interval. CHB: chronic hepatitis B virus infection; IVDU: intravenous drug use as a risk factor for viral hepatitis; BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; AFP: alpha fetoprotein; cigarette smoking: > 15 pack-years; alcohol: > 100g/week

Comparison of socioeconomic disadvantage quintiles and LSM of </≥12.5kPa was performed which showed no differences in the distribution in the community cohort ($p = .2$). There was a trend towards a difference in the socioeconomic disadvantage score distribution and LSM </≥12.5kPa in the hospital cohort ($p = .05$; Table 4-7) with an overall trend of those with an LSM ≥12.5kPa having higher levels of socioeconomic disadvantage.

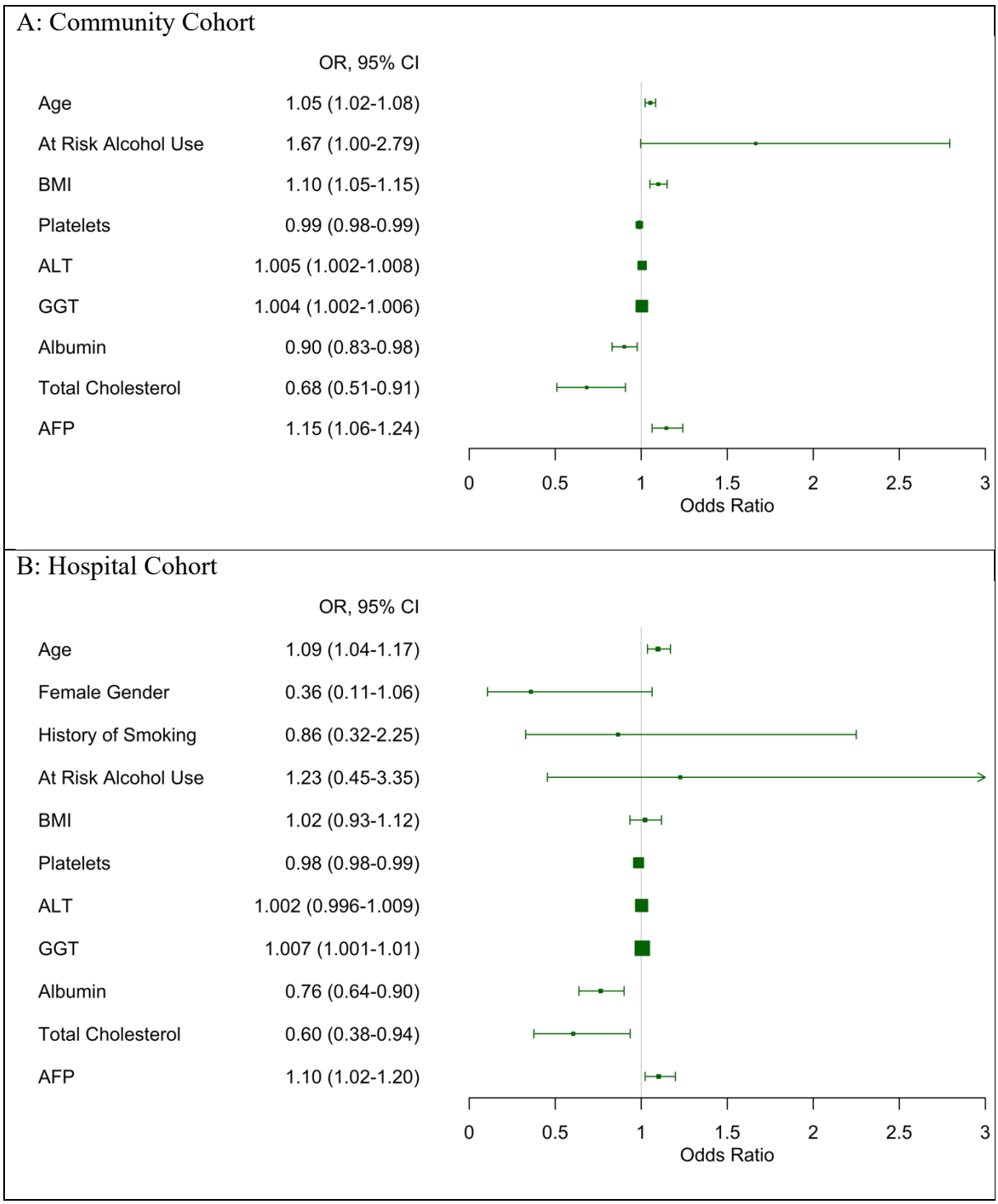
Table 4-7 Socioeconomic status and liver stiffness measurements </≥12.5kPa in the hospital cohort

	Socioeconomic disadvantage quintile %				
LSM	**Very high**	**High**	**Moderate**	**Low**	**Very low**
<12.5kPa	11.3	2.7	24.0	38.0	24.0
≥12.5kPa	21.8	1.8	18.2	47.3	10.9
Total	13.4	2.5	22.8	39.9	21.4

Each cell represents the percentage of patients from the LSM cut-off (row) belonging to the Socioeconomic disadvantage quintile (column). Very high: very high level of disadvantage, meaning most disadvantaged; LSM: liver stiffness measurement

To determine which factors were independently associated with LSM ≥12.5kPa and whether these differed between cohorts, two binary logistic regressions were performed, one with the community cohort and one with the hospital cohort. The community cohort examined LSM ≥12.5kPa and age, at-risk alcohol intake and BMI and the pathology results (platelets, ALT, GGT, albumin, total cholesterol, AFP) in the community cohort ($p < .001$, Figure 4-4 A). All these variables remained statistically significant except at-risk alcohol intake where there was a trend towards significance. The hospital cohort binary multiple logistic regression examined the same predictors of LSM ≥12.5kPa (i.e. age, gender, smoking, at-risk alcohol intake and BMI and the pathology results, $p < .001$, Figure 4-4 B). This showed that there were higher rates of LSM ≥12.5kPa with increasing age, male gender, increasing GGT and AFP and decreasing albumin, platelets and cholesterol. Smoking, at-risk alcohol intake, BMI, and ALT did not remain statistically significant.

Figure 4-4 Baseline variables: predictors of liver stiffness measurements ≥12.5kPa, multivariate analysis, odds ratio with 95% confidence intervals, in community and hospital cohorts



Statistical test: binomial logistic regression; OR: odds ratio; CI: confidence interval; history of smoking: cigarettes, > 15 pack-year history; Alcohol: > 100g/week; BMI: body mass index; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; AFP: alpha fetoprotein.

Lastly, ultrasound findings of cirrhosis (as discussed in section 2.1.4) and LSM ≥12.5kPa were assessed in both cohorts (Table 4-8). Of those who had an ultrasound, the rates of imaging

features of cirrhosis were similar between the cohorts with 20.6% of the community and 16.0% of the hospital cohorts (p = .2). Combining LSM ≥12.5kPa and ultrasound findings consistent with cirrhosis produces 18.3% (n=141, 128 + 13) of the community cohort and 23.6% (n=66, 56 + 10) of the hospital cohort who had a high probability of cirrhosis: there were no differences between the cohorts (p = .06).

Table 4-8 Percentage of patients with ultrasound findings of cirrhosis by liver stiffness measurement and cohort

Cohort	LSM (kPa), n	US performed, n (%)	US findings of cirrhosis, n (%)
Community	≥12.5, **128**	94 (73.4)	58 (61.7)
	<12.5, 641	251 (39.2)	**13 (5.2)**
Hospital	≥12.5, **56**	50 (89.3)	28 (56.0)
	<12.5, 224	187 (83.5)	**10 (5.3)**

Bold: values used to calculate the number with high probability of cirrhosis using both ultrasound and LSM data; LSM: liver stiffness measurements; kPa: kilopascals; US: ultrasound

4.2.2. Summary

The main finding of this section of the study was that the community and hospital cohorts had similar prevalence of patients with a high probability of cirrhosis, with similar results to previous studies suggesting that up to 20% of people living with CHC have cirrhosis.[44] Section 4.2.1.3 has also shown very similar predictors of elevated LSM as previous studies with increasing age, male gender, alcohol and higher BMI.[155, 259, 416, 441-446] There was also a trend towards higher degrees of socioeconomic disadvantage being associated with elevated LSM in the hospital cohort but not in the community cohort.

The other main finding of this section was that the rates of factors associated with morbidity and mortality were higher in the community cohort than the hospital cohort. The community cohort had higher rates of having a history IVDU or psychiatric diagnosis and they also had higher levels of socioeconomic disadvantage. The community cohort was also younger and had higher FTA rates in initial assessment.

4.3. Adherence with medical appointments and management

In the design of any new model of care, consideration must be made regarding retention within the program but also adherence with appropriate medical management. All people living with CHC or who have cirrhosis need regular monitoring and management. This section will

thus present data on all of the CHC community and hospital cohorts as well as those who had a high probability of cirrhosis, as they have difference management requirements. First, retention rates within CATCH will be assessed for all patients. Those with a higher risk of liver-related outcomes are those with a high probability of cirrhosis based on LSM ≥12.5kPa and ultrasound findings of cirrhosis. This group will be assessed with a focus on the specific management requirements that these patients should undergo. This includes retention in non-GP specialist care and HCC surveillance. Treatment rates for all patients as well as those with a high probability of cirrhosis will also be analysed. Predictors of adherence for all these aspects will also be assessed, including incarceration during the study follow-up period, as incarceration can lead to interrupted medical care and thus may have influenced attendance, HCC surveillance and treatment rates.

4.3.1. Results

Follow-up was for a mean of 3.5 +/- 0.6 years; indicating 3,631 patient years. There was no difference in follow-up time between the community and hospital cohorts ($p > .5$). During the study period, 80 patients were incarcerated, with a trend towards higher rates in the community cohort: 8.6% of the community cohort were incarcerated compared to 5.0% of the hospital cohort ($p = .053$).

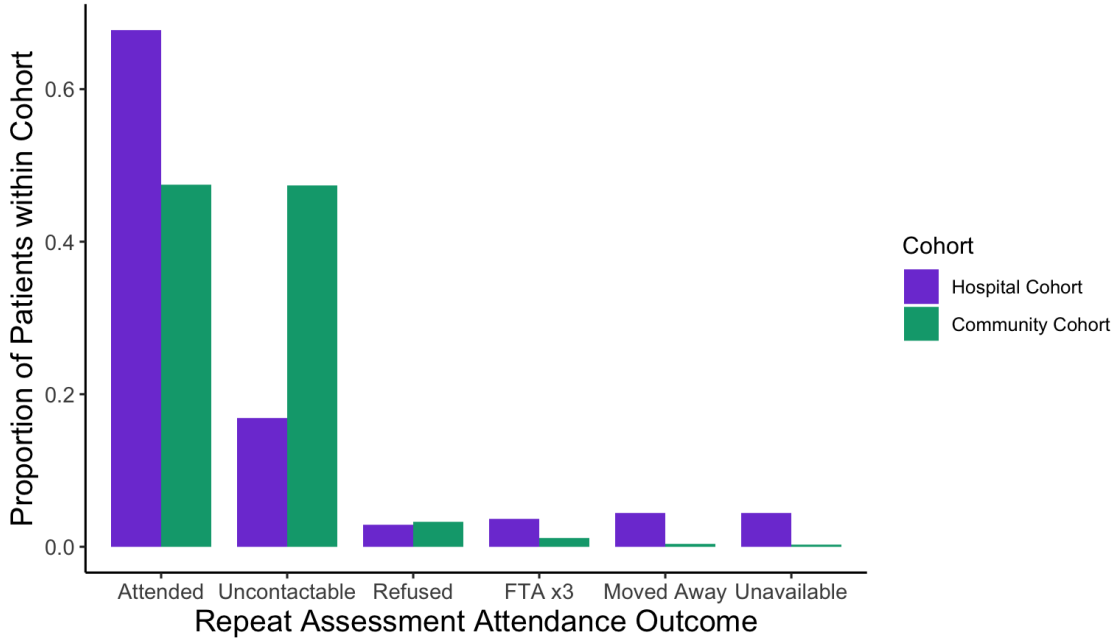
4.3.1.1. Repeat attendance rates within the study

As discussed in chapter 3, after recruitment, each patient was offered yearly reassessment within CATCH. This data looks at whether patients attended at least one repeat appointment and, of those who only attended the baseline assessment with no repeat assessments, the reasons for not attending. These reasons include being uncontactable using multiple methods including phone calls, text messaged, mailed letters and messages left for patients at their GP clinic. Other reasons include the patient having moved too far away, refusing repeat appointments, failing to attend on 3 occasions and being unavailable for multiple offered dates of review. This data will hopefully be able to provide further information regarding reasons why patients do not attend repeat medical appointments and patient factors associated with non-attendance. When using the term 'attendance' here, it is referring to at least one attendance *after* the initial assessment.

Of the 1049 people living with CHC, 52.9% attended a repeat assessment with CATCH. There was a lower attendance rates in the community than the hospital cohort (46.9% versus 66.1%, $p < .001$) and higher rates of being uncontactable in the community cohort (46.8%

versus 16.4% respectively, $p < .001$). Other reasons for non-attendance were refusing a repeat appointment (3.2%); accepting an appointment then failing to attend more than 3 times (1.8%); moving away (1.5%); followed by being unavailable on multiple occasions (1.4%). This is shown in Figure 4-5.

Figure 4-5 Repeat attendance to the study appointments and reasons for not attending in community and hospital cohorts



FTAx3: failed to attend appointments after accepting appointment booking

To determine factors associated with repeat attendance within CATCH, patients' characteristics were analysed including age, gender, at-risk alcohol intake, history of IVDU or psychiatric diagnosis, smoking history, dual infection with CHB, cannabis use and socioeconomic disadvantage quintiles (Table 4-9). Incarceration during the study follow-up period was also assessed as well as LSM and indirect biomarker algorithms. In the community cohort, those who attended were moderately older (Cohen's D = 0.30), had lower rates of at-risk alcohol use and lower rates of incarceration. The attendance rates were no different between genders, in patients with or without a history of a psychiatric diagnosis, IVDU, smoking history, dual infection with CHB or cannabis use ($p > .05$ for all). There was also no difference in attendance rates between socioeconomic disadvantage quintiles ($p = .4$). Those who attended had higher LSM, FIB4 and Forn's index although all with very small effect sizes meaning negligible differences (reported in appendix 3). APRI and 4AGP were no different between those who attended and those who did not ($p > .05$ for both).

Table 4-9 Repeat attendance rates within the study in the community cohort. Univariate analysis

Variable	Attended n=361	Did not attend n=408	p-value
Age (years, mean, SD)	**44.5 (10.0)**	**41.9 (8.9)**	**< .001**
Gender, n (female, %)	114 (31.6)	111 (27.2)	.1
Dual Infection CHB, n (%)	8 (2.2)	7 (1.8)	.6
Cigarette smoking, n (%)	151 (41.8)	152 (37.3)	.2
Cannabis use, n (%)	19 (5.3)	47 (11.5)	.6
Alcohol, n (%)	**137 (38.0)**	**187 (45.8)**	**.03**
History of IVDU, n (%)	333 (92.2)	386 (94.6)	.2
History of psychiatric diagnosis, n (%)	162 (44.9)	197 (48.3)	.3
Incarceration, n (%)	**19 (5.3)**	**47 (11.5)**	**.002**
LSM (median, IQR)	**7.9 (5.5)**	**6.7 (4.1)**	**.007**
APRI (median, IQR)	0.6 (0.7)	0.6 (0.7)	.1
FIB4 (median, IQR)	**1.2 (01.0)**	**1.1 (1.0)**	**.02**
Forn's index (mean, SD)	**7.1 (1.7)**	**6.9 (1.8)**	**.04**
4AGP (median, IQR)	-5.2 (2.5)	-5.4 (2.5)	.6

Bold: significant ($p < .05$); SD: standard deviation; CHB: chronic hepatitis B virus infection; cigarette smoking: > 15 pack-year history; alcohol: > 100g/week, IQR: interquartile range; IVDU: intravenous drug use as a risk factor for viral hepatitis; HCC: hepatocellular carcinoma; BMI: body mass index; kg: kilograms; m: metres

The above analyses were repeated with the hospital cohort (Table 4-10). Those who attended were also moderately older (Cohen's D = 0.41), had lower rates of incarceration and there was a trend towards higher rates of cigarette smoking. Attendance rates were no different between genders, in patients with or without a history of a psychiatric diagnosis, IVDU, at-risk alcohol intake, dual infection with CHB or cannabis use. There was also no difference in attendance rates between socioeconomic disadvantage quintiles ($p = .5$). Those who attended had higher APRI, FIB4, 4AGP and Forn's index, however, all had very negligible differences (effect sizes are reported in appendix 3). LSM was no different between those who attended and those who did not ($p > .05$).

Table 4-10 Repeat attendance rates within the study in the hospital cohort. Univariate analysis

Variable	Attended n=185	Did not attend n=95	p-value
Age (years, mean, SD)	**48.7 (9.9)**	**44.5 (11.1)**	**.002**
Gender, n (female, %)	65 (35.1)	30 (31.6)	.6
Dual Infection CHB, n (%)	1 (0.5)	1 (1.1)	*
Cigarette smoking, n (%)	82 (44.3)	31 (32.6)	.059
Cannabis use, n (%)	112 (62.2)	54 (60.7)	.8
Alcohol, n (%)	88 (47.6)	50 (52.6)	.4
History of IVDU, n (%)	142 (76.8)	74 (77.9)	.8
History of psychiatric diagnosis, n (%)	67 (36.2)	38 (40.0)	.5
Incarceration, n (%)	**4 (2.2)**	**10 (10.5)**	**.002**
LSM (median, IQR)	7.1 (5.0)	6.5 (4.3)	.08
APRI (median, IQR)	**0.6 (1.0)**	**0.5 (0.7)**	**.04**
FIB4 (median, IQR)	**1.3 (1.1)**	**1.1 (1.0)**	**.008**
Forn's index (mean, SD)	**7.7 (1.6)**	**7.1 (2.0)**	**.01**
4AGP (median, IQR)	**-4.8 (3.2)**	**-5.5 (2.3)**	**.01**

Bold: significant ($p < .05$); *: too few numbers for meaningful statistical tests; SD: standard deviation; CHB: chronic hepatitis B virus infection; cigarette smoking: > 15 pack-year history; alcohol: > 100g/week; IQR: interquartile range; IVDU: intravenous drug use as a risk factor for viral hepatitis; HCC: hepatocellular carcinoma; BMI: body mass index; kg: kilograms; m: metres

To determine which variable(s) were independently associated with repeat attendance within CATCH, a binomial logistic regression was performed using cohort, age, incarceration, at-risk alcohol use and cigarette smoking history ($p < .001$, Table 4-11). LSM and indirect biomarker algorithms were not used in this model as their differences were very minimal. There were higher rates of repeat attendance in those who were older, from the hospital cohort, in those who were not incarcerated during the study period and in those who did not drink alcohol at at-risk levels.

Table 4-11 Regression results for factors associated with repeat attendance within the study

Predictors	Significance	Odds ratio	95% CI
Community Cohort	**< .001**	**0.48**	**(0.35, 0.65)**
Age	**< .001**	**1.03**	**(1.02, 1.05)**
Alcohol	**.009**	**0.7**	**(0.54, 0.91)**
Smoking	.8	1.04	(0.78, 1.38)
Incarceration	**< .001**	**0.43**	**(0.26, 0.72)**

Bold: significant ($p < .05$); CI: confidence interval; alcohol: > 100g/week

To summarise, higher rates of repeat attendance within CATCH was seen in the hospital cohort, in those of older age and in those who were not incarcerated. There were very minimal

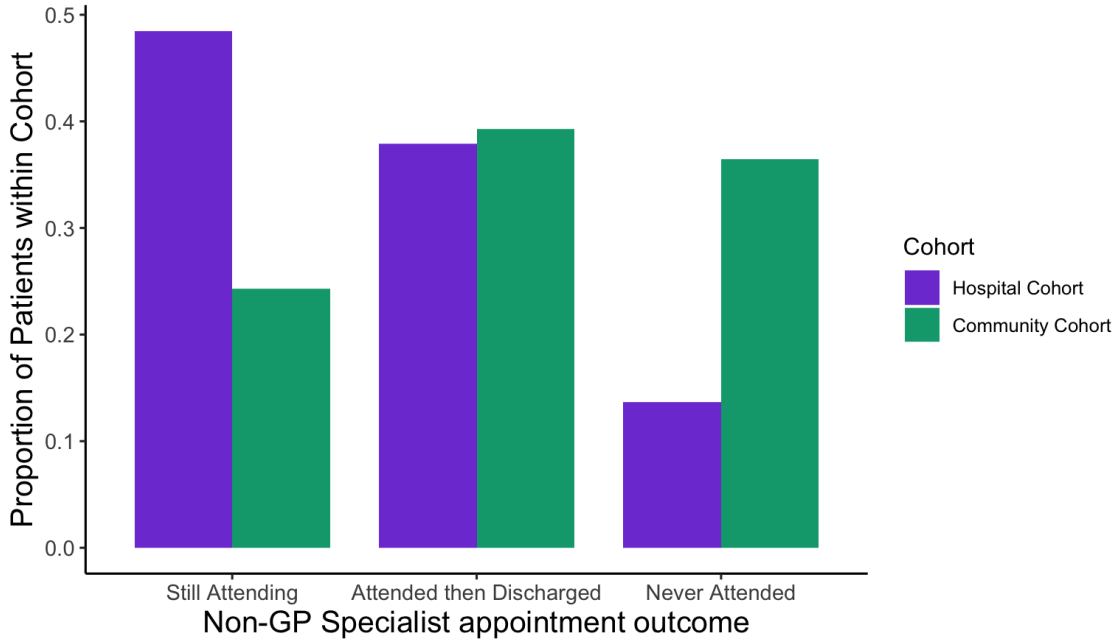
differences in attendance rates based on LSM or indirect biomarker algorithms. The most common reason for non-attendance was being uncontactable with much higher rates of this in the community cohort.

4.3.1.2. Retention in non-general practitioner specialist management

As discussed in chapter 3, some of the community cohort of patients were referred onwards by CATCH for non-GP specialist management due to high probability of advanced fibrosis, dual infection or discordant results. All the hospital cohort of patients had an appointment made with a non-GP specialist. This section will focus on patients with high probability of cirrhosis based on LSM ≥ 12.5kPa and/or ultrasound findings of cirrhosis as these are the patients that most benefit from long-term non-GP specialist management for appropriate monitoring such as HCC surveillance. Of those who are no longer attending, unfortunately it is unclear whether they were lost to follow-up due to being uncontactable or having multiple FTAs or whether they were discharged due to no longer requiring management by non-GP specialists. This section will also assess factors associated with retention in non-GP specialist care.

There were 141 patients in the community cohort (18.3%) with high probability of cirrhosis based on LSM ≥12.5kPa and/or ultrasound findings consistent with cirrhosis; 140 of these were referred onwards for non-GP specialist management care. One patient was not referred onwards as they had an LSM of 12.6kPa in the setting of large amounts of recent alcohol intake; repeated LSM testing after one month of abstinence showed a significant decrease in LSM to 7.6kPa. This leaves 140 community cohort patients included in the following analysis. Of these 140 patients, only 24.3% are retained in care with the non-GP specialist; 36.4% never attended and 39.3% attended at least one appointment but are no longer attending. This is shown in Figure 4-6.

Figure 4-6 Retention in non-general practitioner specialist care in those with a high probability of cirrhosis



GP: general practitioner

There were 66 patients in the hospital cohort (23.6%) with high probability of cirrhosis based on LSM ≥12.5kPa and/or ultrasound findings consistent with cirrhosis, all these patients had non-GP specialist appointments booked. Of these 66 patients with a high probability of cirrhosis, 48.5% are retained in care with the non-GP specialist, 13.6% never attended and 37.9% attended at least one appointment but are no longer attending. This is also shown in Figure 4-6.

There were much lower rates of retention in non-GP specialist care in the community cohort than the hospital cohort in those with a high probability of cirrhosis (24.2% versus 48.5%, $p < .001$).

To determine factors associated with retention in care, patient factors including age, gender, history of psychiatric diagnosis or IVDU, smoking history, at-risk alcohol intake, incarceration during the study period, cannabis use and socioeconomic disadvantage quintiles were assessed in both cohorts. First, in the community cohort, increasing age was associated with retention in non-GP specialist care (mean age of 51.9 years (+/- 10.1) versus 46.5 years (+/- 8.6) in those not retained in care, $p = .007$). There were higher retention rates in those who smoked cigarettes (28.1% retained in care compared to 13.3% in non-smokers, $p = .04$). There were no differences

in gender, psychiatric history, at-risk alcohol intake, cannabis use, history of IVDU, incarceration or socioeconomic disadvantage quintiles ($p > .05$ for all).

Second, in the hospital cohort, none of age, gender, smoking history, psychiatric history, cannabis use, history of IVDU or socioeconomic disadvantage quintiles influenced retention in non-GP specialist care. Interestingly, at-risk alcohol intake appeared to have a positive effect on retention in care: 59.1% of those drinking alcohol at at-risk levels were retained in non-GP specialist care compared to 27.3% of those not drinking ($p = .01$). Incarceration was unable to be analysed in a statistically reliable way due to low numbers.

To summarise, retention rates in both cohorts within both CATCH and non-GP specialist attendance rates was variable. The hospital cohort was more adherent cohort with higher repeat attendance rates within CATCH and higher retention rates in non-GP specialist care. Increasing age was also associated with higher rates of retention in non-GP specialist care in the community cohort.

4.3.1.3. Hepatocellular carcinoma surveillance

This section will assess HCC surveillance rates in patients where HCC surveillance is recommended, that is those with a high probability of cirrhosis based on LSM ≥ 12.5kPa and/or ultrasound findings of cirrhosis. At baseline, data was recorded regarding whether an ultrasound was performed within the preceding 12 months. At time of last follow-up, data was recorded again regarding whether an ultrasound was performed in the preceding 12 months. This section will also assess factors associated with HCC surveillance.

There were 140 community cohort patients and 66 hospital cohort patients who high a high probability of cirrhosis based on the above-mentioned criteria and who were thus included in the following analyses. At baseline, the community cohort had much lower rates of ultrasound within the preceding 12 months compared to the hospital cohort at 10.8% compared to 45.5% ($p < .001$). In either cohort, there were no differences in age, gender, history of psychiatric diagnosis, IVDU, at-risk alcohol intake, cannabis use or socioeconomic disadvantage quintile in those with and those without an ultrasound at baseline.

At time of last follow-up, some patients were lost to follow-up where it is unknown if they had had an ultrasound within the preceding 12 months. These patients are excluded from the following analysis (lost to follow-up: community n=54, hospital n=37) leaving 87 patients in

the community cohort and 29 in the hospital cohort included in the following analyses[1]. These patients are excluded as some had moved interstate or between non-GP specialists so potentially some may have had ultrasound surveillance. When comparing the cohorts, there was again a much higher rate of ultrasound at last follow in the hospital cohort than the community cohort (82.8% versus 34.5%, $p < .001$). An intention to treat analysis was also performed with the results in appendix 3.

To determine factors associated with having had an ultrasound at time of last follow-up, patient factors including age, gender, history of psychiatric diagnosis or IVDU, smoking history, at-risk alcohol intake, incarceration during the study period, cannabis use and socioeconomic disadvantage quintiles were assessed in both cohorts. First, in the community cohort, those who had an ultrasound were older with a moderate difference (mean age 52.5 years +/-9.1 compared to 48.3 years +/- 8.9 years, $p = .04$, Cohen's $D = 0.47$). There were no differences in gender, history of psychiatric diagnosis, IVDU, at-risk alcohol intake, cannabis use or socioeconomic disadvantage quintile on HCC surveillance rates at follow-up in the community cohort. Those who were retained in non-GP specialist management care had higher rates of ultrasound at 83.3% compared to 16.7% in those who were no longer seeing non-GP specialists ($p < .001$). Those who had an ultrasound at baseline were also more likely to have had an ultrasound at time of last follow-up (71.4% versus 30.4% in those who had not had an ultrasound at baseline, $p = .03$). Incarceration during the study period had no effect on ultrasound rates at follow-up.

In the hospital cohort, the above analyses were repeated. There were no differences in age, gender, history of psychiatric diagnosis, IVDU, at-risk alcohol intake, cannabis use or socioeconomic disadvantage quintile on HCC surveillance rates at time of last follow-up, although some of these groups had quite low numbers. Those who were retained in non-GP specialist management care had higher rates of ultrasound at follow-up with all (100%, n=21) having had an ultrasound compared to 37.5% in those who were no longer seeing non-GP

[1] A higher percentage of patients had information regarding ultrasound data in the community cohort than the hospital cohort. This is because the community cohort patients had a record review performed at the GP clinic where they were recruited to determine if/where they were being managed. The hospital cohort who were lost to follow-up did not have a record review at their GP clinic unless their GP clinic was taking part in the CATCH study.

specialists (p < .001). Baseline ultrasound had no effect on repeat ultrasound in the hospital cohort. None of the patients included in this part of the analysis were incarcerated.

To determine whether cohort or retention in non-GP specialist care were independently associated with having had an ultrasound at follow-up, a binary logistic regression was performed (p = .005, Table 4-12). This showed that both those retained in non-GP specialist care and those from the hospital cohort had higher rates of ultrasound being performed within 12 months of last follow-up.

Table 4-12 Regression analysis for predictors of ultrasound at follow-up in those with a high probability of cirrhosis

Predictors	Significance	Odds ratio	95% CI
Community Cohort	.005	.012	(0.03, 0.52)
Retention in non-GP specialist care	< .001	63.82	(17.83, 228.4)

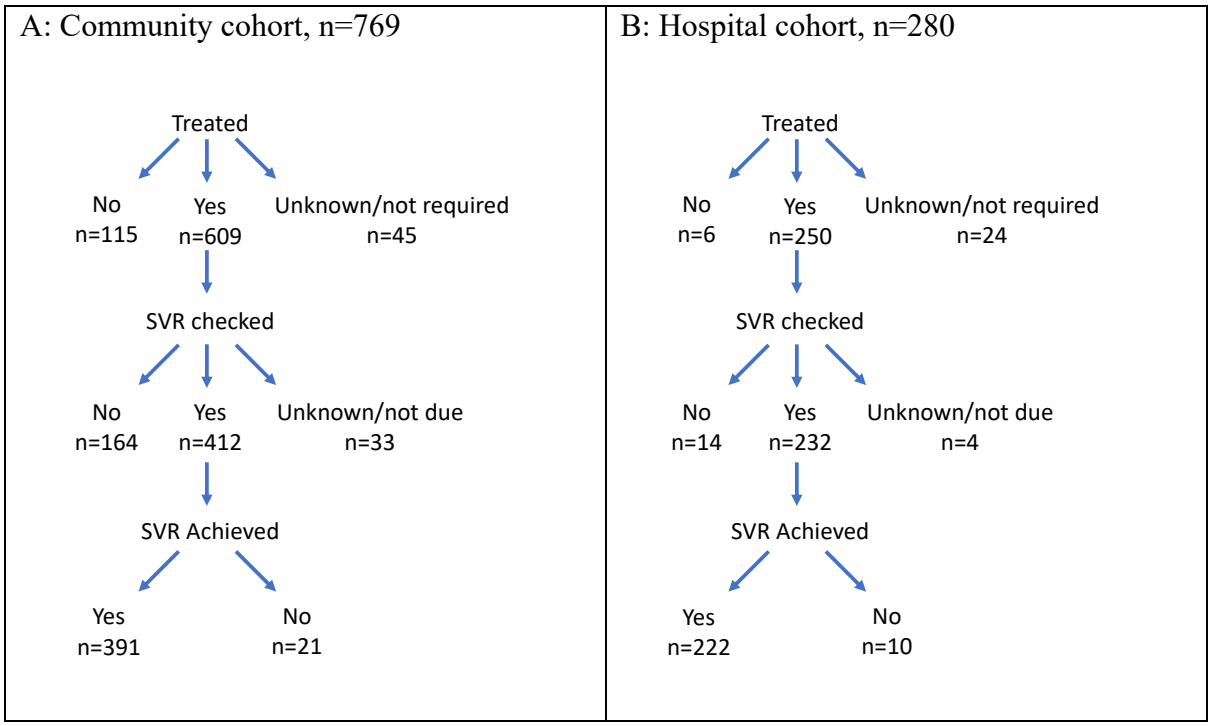
CI: confidence interval; GP: general practitioner

At baseline, very few patients who had a high probability of cirrhosis had had an ultrasound within the preceding 12 months. At last time of follow-up, the rates had increased in both cohorts, however, the community cohort consistently had lower rates and those who were retained in non-GP specialist care had higher rates.

4.3.1.4. Direct acting antiviral treatment

This section will assess rates of treatment; predictors of treatment; rates of checking for SVR; predictors of checking for SVR and SVR rates. Figure 4-7 shows the patients numbers that will be used in each section of analyses.

Figure 4-7 Flow chart of direct acting antiviral treatment for people living with chronic hepatitis C with numbers at each stage in the community and hospital cohorts



SVR: sustained virological response

4.3.1.4.1. Treatment summary

Of the 769 CHC community cohort patients, 79.2% had treatment. There was 15.0% who did not have treatment, 5.3% where treatment status was unknown and 0.5% where treatment was not required. Of the 280 patients from the hospital cohort, 89.3% had treatment. There was 2.1% who did not have treatment, 8.2% where treatment status was unknown and 0.4% where treatment was not required. One patient from each cohort had pegylated interferon and ribavirin treatment for genotype 2 CHC prior to the availability of DAAs for this genotype in Australia, the rest were all treated with DAAs. Those from the community cohort had much lower rates of treatment than those in the hospital cohort (84.1% versus 97.7%, $p < .001$).

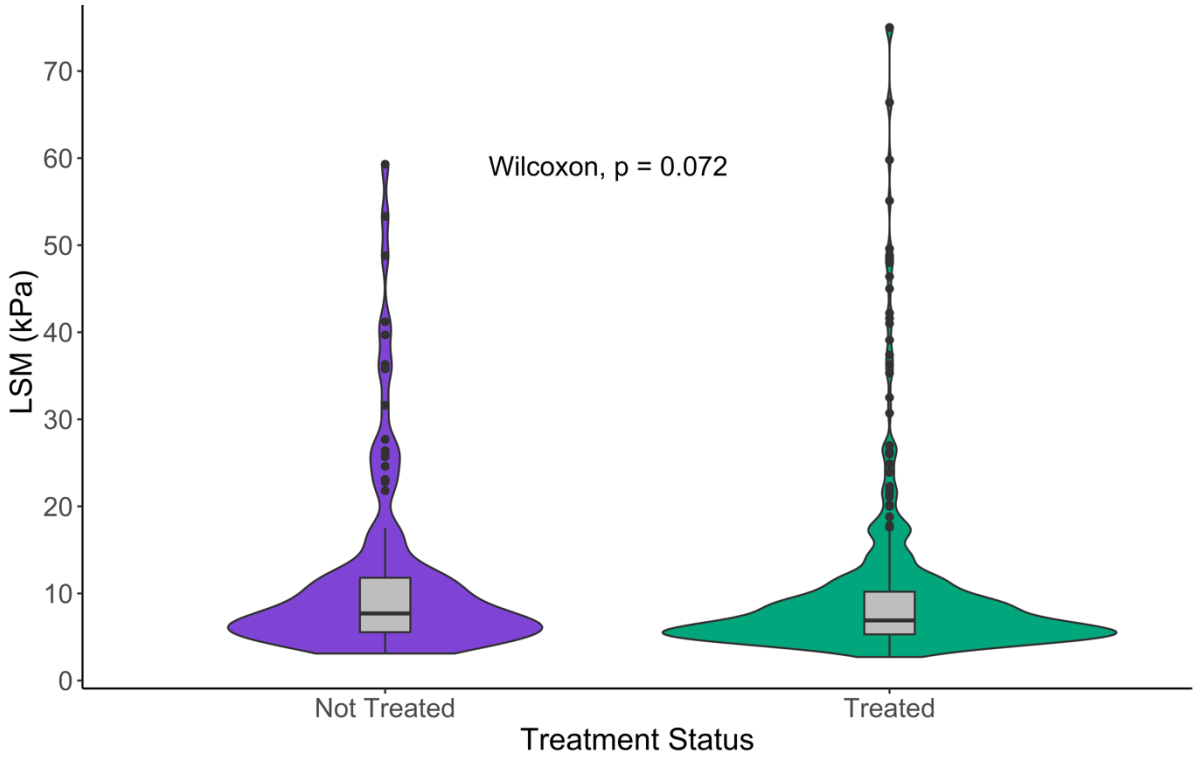
The time to treatment after baseline assessment with CATCH was longer in the community cohort with a median time of 33.6 weeks +/- 57.2 compared to 20.8 weeks +/- 48.5 with a medium effect size ($p = .004$, Cliff Delta = 0.29 [0.22 – 0.37]). In case there was a bias with recruitment timing within CATCH, time to treatment from the date that DAA's became available in Australia was also assessed. This also showed longer time to treatment in the community cohort (Median 29.2 weeks +/- 30.3 versus 24.9 weeks +/- 29.4, $p = .006$, Cliff Delta = 0.30 [0.22 – 0.38]).

4.3.1.4.2. Factors associated with treatment

This section only focuses on patients who either had or did not have treatment; patients where treatment was unknown or not required were excluded. To determine factors associated with treatment, patients who had treatment were compared with patients who did not have treatment. Predictors of treatment were assessed, including age, gender, history of IVDU or psychiatric diagnosis, at-risk alcohol intake, smoking, cannabis use, incarceration, socioeconomic disadvantage quintiles as well as LSM and indirect biomarker algorithms. In the community cohort, there were lower rates of treatment in those who drank alcohol at at-risk levels (80.4% compared to 86.7% in those not drinking alcohol at at-risk levels, $p < .02$. There were no differences in treatment rates between genders, history of IVDU or psychiatric diagnoses, smoking, cannabis use, or incarceration ($p > .5$ for all). Comparison of socioeconomic disadvantage quintiles was performed with no differences found ($p > .5$). There were no differences in age, Forn's index, LSM, APRI, FIB4 or 4AGP between those treated and those not treated ($p > .05$ for all, Figure 4-8). The prevalence of LSM ≥12.5kPa was also similar between those treated and those not treated.

In the group of patients with a high probability of cirrhosis in the community cohort (n=140), there were 9 patients where treatment status was either unknown (n=8) or not required (n=1). Of the remaining 131 patients, of whom 79.4% (n=104) had treatment, retention in non-GP specialist care was associated with higher rates of treatment at 97.0% compared to 73.5% in those who were lost to follow-up ($p = .004$). Nothing of the other above tested predictors of treatment were predictors in this group of patients with a high probability of cirrhosis from the community cohort.

Figure 4-8 Liver stiffness measurements in those treated versus those not treated in the community cohort



LSM: liver stiffness measurements; kPa: kilopascals

Predictors of treatment within the hospital cohort was unable to be assessed as there were not enough patients who did not have treatment for any meaningful statistical tests to be performed. Of the 66 patients with a high probability of cirrhosis, 89.4% (n=59) had treatment with the remaining having an unknown treatment status.

4.3.1.4.3. Treating Physician Type

Of those who had treatment from the community cohort, 64.9% were treated by GP's and the remaining treated by non-GP specialists. In the hospital cohort, the majority were treated by non-GP specialists (96.0%) with very few being treated by GP's (4%). Overall, GPs treated 47.1% of all patients.

4.3.1.4.4. Treatment outcomes: testing for sustained virological response

This section focuses on patients who had treatment and where testing for SVR status was either performed or not performed. To determine factors associated with testing for SVR, the same analyses performed above regarding predictors of treatment were performed. In the community cohort, of the patients who had treated, 2.6% had not yet reached the date for SVR and in 2.8% it was unknown if they had had testing for SVR, leaving 576 patients included in the following analysis.

Of these 576 community cohort patients, 71.5% had testing for SVR. There were higher rates of testing for SVR in those who were older with moderate effect size (mean age 44.7 years +/- 10.0 versus 40.8 years +/- 8.3, $p < .001$, Cohen's D = 0.42). There were higher rates of testing for SVR in those who were treated by non-GP specialists than those treated by GPs (83.8% versus 65.2%, $p < .001$). There were no differences in gender, history of IVDU or psychiatric diagnoses, at-risk alcohol intake, smoking, cannabis use, incarceration or socioeconomic disadvantage quintiles ($p > .05$ for all). Higher LSM and FIB4, Forn's index and 4AGP were also associated with higher rates of testing for SVR, with no differences in APRI (Table 4-13). In the 140 patients with a high probability of cirrhosis in the community cohort, there were 104 who had treatment, 5 of whom SVR status was either unknown (n=2) or not reached (n=3). Of the remaining 99 patients, retention in non-GP specialist care was associated with higher rates of testing for SVR (100% versus 78.3%, $p = .006$).

Table 4-13 Liver stiffness measurement and indirect biomarker algorithms and testing for sustained virological response in the community cohort

LSM and algorithms of indirect fibrosis markers	Tested n=412	Not tested n=164	p-value
LSM (median, IQR)	**7.6 (5.8)**	**6.3 (3.5)**	**< .001**
APRI (median, IQR)	0.64 (0.74)	0.57 (0.52)	.07
FIB4 (median, IQR)	**1.23 (1.07)**	**1.08 (0.76)**	**.001**
Forn's index (mean, SD)	**7.25 (1.73)**	**6.71 (1.60)**	**< .001**
4AGP (median, IQR)	**-5.20 (2.57)**	**-5.60 (2.17)**	**.01**

Bold: significant ($p < .05$); LSM: liver stiffness measurements; IQR: interquartile range; APRI: AST to platelet ratio index; FIB4: Mean fibrosis index based on four factors; SD: standard deviation.

In the community cohort, to determine interactions between age, treating prescriber type and LSM on whether testing for SVR was performed, a binary logistic regression was performed ($p < .001$, Table 4-14). Only increasing age and treating prescriber type remained significant

with higher testing for SVR rates in those treated by non-GP specialists and those who were older.

Table 4-14 Regression analysis: predictors of testing for sustained virological response in the community cohort

Predictors	Significance	Odds ratio	95% CI
Treating prescriber type: non-GP specialist	**< .001**	**2.7**	**(1.62, 4.48)**
LSM	.5	0.99	(0.97, 1.02)
Age	**< .001**	**1.04**	**(1.02, 1.06)**

Bold: significant (p < .05); CI: confidence interval; LSM: liver stiffness measurements; GP: general practitioner

In the hospital cohort, of the patients who had treatment, in 1.2%, it was unknown if they had testing for SVR and 0.4% were not yet due for SVR, leaving 246 patients included in the following analysis. Of these patients, 94.3% had testing for SVR. The predictors of testing for SVR were unable to be analysed in a statistically meaningful way due to very low numbers of those who did not have testing for SVR.

Those from the hospital cohort were much more likely to have testing for SVR than those from the community cohort (94.3% versus 71.5%, p < .001). To determine if this was due to a cohort effect or treating prescriber type difference, a binary logistic regression was performed (p < .001, Table 4-15). There were higher rates of testing for SVR in both those whose treating prescriber type was a non-GP specialist and in those from the hospital cohort.

Table 4-15 Regression analysis: predictors of testing for sustained virological response in the community and hospital cohorts

Predictors	Significance	Odds ratio	95% CI
Treating prescriber type: non-GP specialist	< .001	2.59	(1.7, 3.94)
Cohort: community	< .001	0.28	(0.15, 0.53)

CI: confidence interval; GP: general practitioner

4.3.1.4.5. Treatment outcomes: sustained virological response versus direct acting antiviral failure

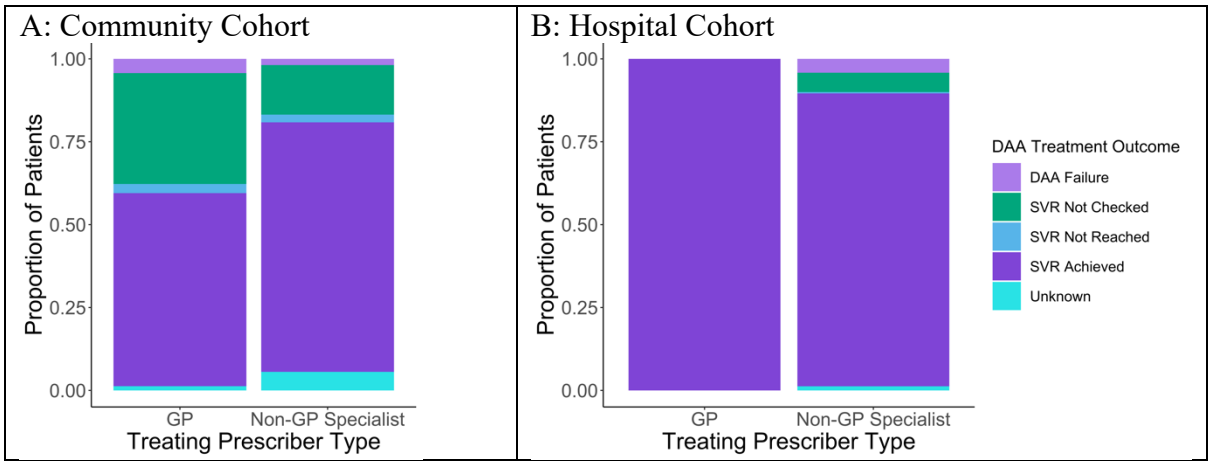
To determine the factors associated with DAA failure versus SVR, only those who were treated and with SVR results available were analysed. For this analysis, the outcome of the first treatment course is analysed. The same predictors used above were analysed again, along with interrupted or shortened DAA course.

In the community cohort, there was 5.1% who had DAA failure with the first course of treatment. Of those who had DAA failure, 5 patients achieved SVR with second line therapy. There were 3 patients who had an interrupted course of DAAs for more than one week, all achieved SVR. There were 21 who had a shortened course of DAA therapy with higher rates of DAA failure in those with a shortened course (41.4% achieved SVR compared to 97.2% who completed the course, $p < .001$). There were no differences in age, gender, history of IVDU or psychiatric diagnoses, smoking, cannabis use, at-risk alcohol intake, incarceration or socioeconomic disadvantage quintiles on SVR rates. There were lower rates of DAA failure in those treated by non-GP specialists 2.4% compared to 6.9% in those treated by GP's ($p = .04$). However, a binomial logistic regression assessing the effect of treating prescriber type and shortened course of DAA therapy showed that only shortened course had an effect with an odds ratio of 37.0 (95% CI: 12.3 - 111.34). There were minimal differences between LSM and indirect biomarker algorithms in those who had DAA failure and those who achieved SVR.

In the hospital cohort, there were 4.3% (n=10) who had DAA failure with the first course of treatment. Of those that had DAA failure, 7 achieved SVR with second line therapy. There were 2 patients who had an interrupted course of DAAs for more than one week, all achieved SVR. There were 5 who had a shortened course of DAA therapy; all achieved SVR. The predictors of SVR were unable to be analysed in a statistically meaningful way due to very low numbers of those with DAA failure.

There was no difference in DAA failure rates between the community and hospital cohorts ($p > .5$, Figure 4-9).

Figure 4-9 Treatment outcome by treating prescriber type, community and hospital cohorts



GP: general practitioner; SVR: sustained virological response; DAA: direct acting antiviral

In summary, the community cohort had lower rates of treatment, had treatment later and had lower rates of testing for SVR. Those treated by non-GP specialists also had higher rates of testing for SVR. DAA failure was associated with a shortened course of therapy, which was seen more commonly in the community cohort.

4.3.2. Summary

This section has shown that the community cohort is overall a less adherent cohort with higher rates of gaps in care identified: lower repeat attendance rates within CATCH, lower retention rates in non-GP specialist care in those with cirrhosis, lower HCC surveillance rates at baseline and at follow-up, lower treatment rates and lower rates of testing for SVR. However, of those with highest risk of complications (LSM ≥12.5kPa and/or ultrasound findings consistent with cirrhosis), a significant percentage attended at least one outpatient appointment and HCC surveillance rates increased in both cohorts from baseline to follow-up. Also, for this group, retention in non-GP specialist care was associated with higher HCC surveillance, treatment and testing for SVR rates. Time to treatment was longer in the community cohort which is likely multifactorial with differences in the patient cohort, prescriber experience and initial community pharmacy DAA access.

4.4. Incidence of liver-related outcomes

Given people living with CHC are at risk of cirrhosis and thus liver-related outcomes, these will be assessed to further determine the risk of these in a community cohort of patients. The

liver outcomes presented include diagnosis of HCC, liver decompensation (ascites, hepatic encephalopathy or variceal bleeding) and death due to complications of liver disease. Lastly, a composite of liver-related outcomes will be presented. Due to the relatively brief follow-up, there is a low incidence of some of the liver-related outcomes, consequently, this section has also combined all the liver-related outcomes including HCC, liver decompensation and death due to liver disease to allow for increased statistical efficiency.

The risk of a composite of liver-related outcomes will be assessed using ROC, Kaplan Meier survival curves, Cox proportional HRs and by calculating the optimal cut-off points. Kaplan Meier survival curve analysis and Cox proportional HRs will use the time to the first liver-related outcome with censoring from the latest date of either last follow-up or record review. To further clarify the risks of liver-related outcomes, these outcomes have been compared between the cohorts as well as factors associated with a composite of liver-related outcomes.

4.4.1. Results

4.4.1.1. Hepatocellular carcinoma

In the follow-up period, eight patients were diagnosed with HCC, all of whom had a high probability of cirrhosis based on LSM ≥12.5kPa or ultrasound findings of cirrhosis. There was a lower rate of HCC diagnosis in the community cohort (n=3) compared to the hospital cohort (n=5, p = .02). Two of the community cohort patients were diagnosed within 6 weeks of recruitment into CATCH. In the patients with a high probability of cirrhosis, the incidence of HCC was 2.1% (or 0.7% if those diagnosed within 6 weeks of recruitment were excluded) in the community cohort and 7.6% in the hospital cohort. Given the mean follow-up time was 3.5 years, this indicates a 2.2% annual incidence in the hospital cohort and 0.6% (or 0.2% if those diagnosed within 6 weeks of recruitment were excluded) annual incidence in the community cohort, in those with a high probability of cirrhosis.

The majority (7 out of 8; 87.5%) were at a potentially curable stage at diagnosis (BCLC 0 or A) with the last patient, from the hospital cohort, in BCLC B stage at diagnosis. The characteristics of these eight patients who developed HCC are shown in Table 4-16 including treatment received and mRECIST treatment responses.

Table 4-16 Stage of hepatocellular carcinoma at diagnosis, treatment, modified response evaluation criteria in solid tumours outcomes and overall outcomes

Patient	Cohort	BCLC stage	Treatment(s)	Latest mRECIST response	Latest Outcome	Time to diagnosis (weeks) from CATCH recruitment
1	Hospital	BCLC0	RFA	CR	Well	174
2	Hospital	BCLC0	Resection	CR	Well	160
3	Community	BCLCA	RFA	PD	Death	5.4. Death at 62 weeks
4	Community	BCLCA	Resection	CR	Well	34
5	Community	BCLCA	MWA	CR	Being worked up for liver transplant	3
6	Hospital	BCLCA	RFA, DEB-TACE, Sorafenib, Lenvatinib	PD	Palliative	82
7	Hospital	BCLCA	RFA, PEI	PD	Referred for consideration of liver transplant	35
8	Hospital	BCLCB	DEB-TACE x4	CR	Well	74

BCLC: Barcelona clinic liver cancer staging; mRECIST: modified response evaluation criteria in solid tumours; CR: complete response; PD: progressive disease; RFA: radiofrequency ablation; MWA: microwave ablation; PEI: percutaneous ethanol injection; DEB-TACE: – drug-eluting bead transarterial chemoembolisation

4.4.1.2. Liver decompensation

There were 24 people living with CHC who were diagnosed with liver decompensation during the follow-up period. There was only one person who was diagnosed with decompensation who had a normal appearing ultrasound and LSM <12.5kPa, they were from the hospital cohort. There were no differences in decompensation rates between the community (n=17, 2.2% of the cohort) or hospital cohorts (n=7, 2.5% of the cohort, $p > .05$). In the community cohort of patients with high probability of cirrhosis, the rates of diagnosis of decompensation were 12.1%, with an annual incidence of 3.4%. In the hospital cohort of patients with a high probability of cirrhosis, the rates of diagnosis of decompensation were 9.1%, with an annual incidence of 2.6%.

4.4.1.3. Death due to liver disease

There were seven people living with CHC who died due to their liver disease, with one in the hospital cohort and six from the community cohort. All who died due to liver disease had a high probability of cirrhosis based on LSM and ultrasound findings. The hospital and community cohort cannot be compared statistically due to the low numbers. Of those with cirrhosis, there was a 1.5% incidence in the hospital cohort and 4.3% incidence in the community cohort.

4.4.1.4. Composite of liver-related outcomes

There were 29 patients who had any of the above liver-related outcomes: 2.5% (n=19) of the community cohort and 3.6% (n=10) of the hospital cohort. There were no differences in liver outcome event rates between the hospital and community cohorts ($p > .05$). In the patients with a high probability of cirrhosis, the incidence of a liver-related outcome was 13.5% in the community cohort and 13.6% in the hospital cohort, with a 3.9% annual incidence in both the community and hospital cohorts. All of those in the community with a liver-related outcome had a high probability of cirrhosis and 9 out of 10 from the hospital cohort had a high probability of cirrhosis.

Predictors of liver-related outcomes were first assessed in the community cohort (Table 4-17). These results should be interpreted with caution due to low numbers. Those who had a liver-related outcome were older with a large effect size meaning there was a significant difference (Cohen's D = 0.71). Estimated duration of infection had no effect. Patients who had a liver-related outcome were less likely to have a history of cannabis use; less likely to have a history of IVDU; more likely to have at-risk alcohol use and more likely to have a personal

history of cancer. Dual infection with CHB, gender, cigarette smoking, history of psychiatric diagnosis and family history of HCC had no effect on liver-related outcomes ($p > .05$ for all). Those with a liver-related outcome were also more likely to have a higher BMI. Rates of liver-related outcomes were compared between socioeconomic disadvantage quintiles with no significant differences in liver outcome events between the quintiles ($p = .5$).

Table 4-17 Predictors of a composite of liver-related outcomes in the community and hospital cohorts. Univariate analysis

	Community Cohort			Hospital Cohort		
Liver-related outcome:	**Yes n=19**	**No n=750**	**p value**	**Yes n=10**	**No n=270**	**p value**
Age (years, mean, SD)	**49.7 (6.4)**	**42.9 (9.5)**	**<.001**	**54.8 (8.7)**	**47.0 (10.4)**	**.02**
Years of infection (years, mean, SD)	17.7 (10.3)	14.5 (8.6)	.2	20.5 (13.9)	18.5 (10.0)	.7
Dual Infection CHB, n (%)	0 (0)	15 (2.0)	.5	0 (0)	2 (0.7)	*
Gender, n (female, %)	4 (21.1)	221 (29.5)	.4	4 (40.0)	91 (33.7)	.7
Cigarette smoking, n (%)	9 (47.3)	294 (39.2)	.5	4 (40.0)	109 (40.3)	.9
Cannabis use, n (%)	**7 (38.9)**	**496 (67.9)**	**.009**	**3 (30.0)**	**163 (62.9)**	**.04**
Alcohol, n (%)	**13 (68.4)**	**311 (41.4)**	**.02**	7 (70.0)	131 (48.5)	.2
History of IVDU, n (%)	**15 (78.9)**	**704 (93.9)**	**.009**	**5 (50.0)**	**211 (78.1)**	**.04**
History of psychiatric diagnosis, n (%)	5 (26.3)	14 (47.2)	.07	4 (40.0)	101 (37.4)	.9
Personal history of cancer, n (%)	**2 (10.5)**	**13 (1.7)**	**.006**	0 (0)	10 (3.7)	*
Family history of HCC, n (%)	(1) 5.2	20 (2.7)	.5	0 (0)	10 (3.7)	*
BMI (kg/m2, median, IQR)	**29 (10.5)**	**25 (6.5)**	**.01**	28.2 (4.3)	26.0 (6.5)	.4

Bold: significant ($p < .05$); *: too few patients for meaningful statistical tests; SD: standard deviation; CHB: chronic hepatitis B virus infection; cigarette smoking: >15 pack-year history; alcohol: > 100g/week; IQR: interquartile range; IVDU: intravenous drug use as a risk factor for viral hepatitis; HCC: hepatocellular carcinoma; BMI: body mass index; kg: kilograms; m: metres

To determine which of the above significant factors remained independently associated with liver-related outcome events in the community cohort, a binomial logistic regression was performed (p = .004, Table 4-18). Those who had a liver outcome event were older, had higher rates of at-risk alcohol intake and higher BMI.

Table 4-18 Regression results for liver-related outcomes in the community cohort

Predictors	Significance	Odds ratio	95% CI
Age	**.03**	**1.06**	**(1.01, 1.12)**
Cannabis use	.052	0.37	(0.13. 1.02)
Alcohol	**.01**	**3.79**	**(1.23, 11.7)**
IVDU	.1	0.32	(0.09, 1.17)
Personal history of cancer	.5	1.98	(0.32, 12.21)
BMI	**.01**	**1.11**	**(1.03, 1.19)**

Bold: significant (p < .05); statistical test: binary logistic regression; CI: confidence interval; alcohol: > 100g/week; IVDU: intravenous drug use as a risk factor for viral hepatitis; BMI: body mass index.

Predictors of liver-related events were analysed in the hospital cohort (Table 4-17). These results should also be interpreted with caution due to low numbers. Those who had a liver-related outcome were older with a large difference (Cohen's D = 0.75), but estimated duration of infection had no effect. Patients who had a liver-related outcome were less likely to have a history of cannabis use and less likely to have a history of IVDU. Dual infection with CHB, gender, cigarette smoking, at-risk alcohol intake, history of psychiatric diagnosis, personal history of cancer or family history of HCC and BMI had no effect on liver-related outcomes. Rates of liver-related outcomes were also compared between socioeconomic disadvantage quintiles with no significant differences liver outcome events between the quintiles (p = .3).

To determine which of the above significant factors remained significantly associated with liver-related outcome events in the hospital cohort, a binomial logistic regression was performed (p < .001, Table 4-19). Only increasing age remained a significant predictor of a composite of liver-related outcomes.

Table 4-19 Regression results for liver-related outcomes in the hospital cohort

Predictors	Significance	Odds ratio	95% CI
Age	**.049**	**1.08**	**(1.00, 1.17)**
Cannabis use	.1	0.31	(0.14, 2.23)
IVDU	.4	0.55	(0.07, 1.35)

Bold: significant (p < .05); statistical test: binary logistic regression; CI: confidence interval; IVDU: intravenous drug use as a risk factor for viral hepatitis

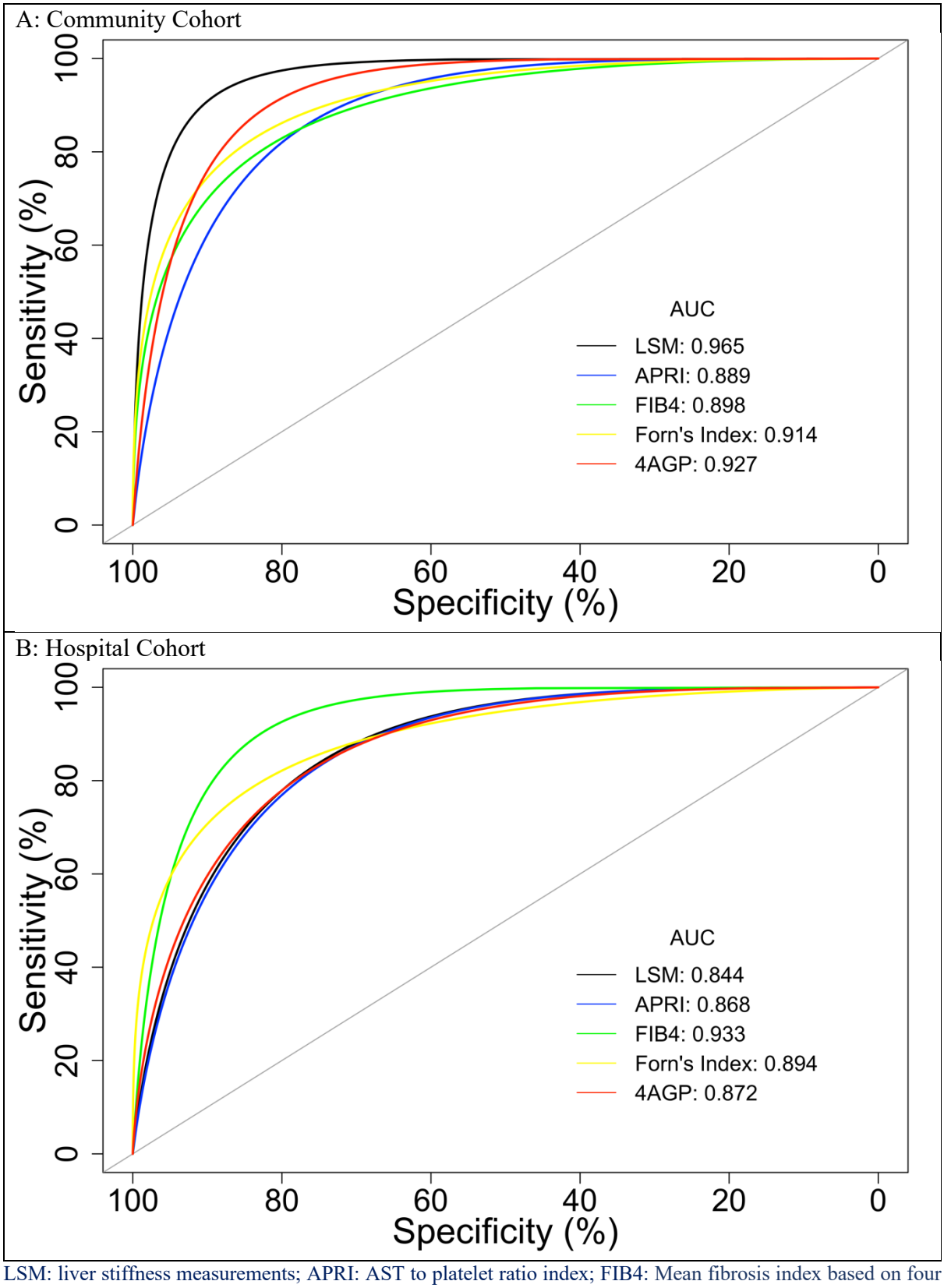
To summarise, liver-related outcome rates were similar between the cohorts with similar incidence of liver decompensation, death due to liver disease and a composite of liver-related outcomes. One main difference, however, was that the hospital cohort had higher rates of HCC diagnosis with very low rates in the community cohort, at 0.6% annual incidence in those with a high probability of cirrhosis. Predictors of liver outcome events in the community cohort included increasing age, at-risk alcohol use and BMI; in the hospital cohort, only age was a predictor.

4.4.1.5. Liver stiffness measurements and indirect biomarker algorithms and risk of a composite of liver-related outcomes

4.4.1.5.1. Receiver operator curves

To examine the relationship between LSM and indirect biomarker algorithms and the composite of liver-related outcomes, ROC and AUROC were analysed. In the community cohort, all LSM and indirect biomarker algorithms were able to accurately predict liver-related outcomes when assessed using ROC. LSM had the highest AUROC meaning it was best able to differentiate between patients who developed a liver-related outcome and those who did not. This was followed by 4AGP, Forn's index, FIB4 then APRI. This is shown in Figure 4-10 A. In the hospital cohort, FIB4 was best able to differentiate between those who developed a liver-related outcome and those who did not. This was followed by Forn's index, 4AGP, APRI then LSM. There are low numbers of liver-related outcomes in the hospital cohort so this data should be interpreted with caution. This is shown in Figure 4-10 B.

Figure 4-10 Receiver operator curves for liver stiffness measurements and indirect biomarker algorithms in predicting a composite of liver-related outcomes in community and hospital cohorts

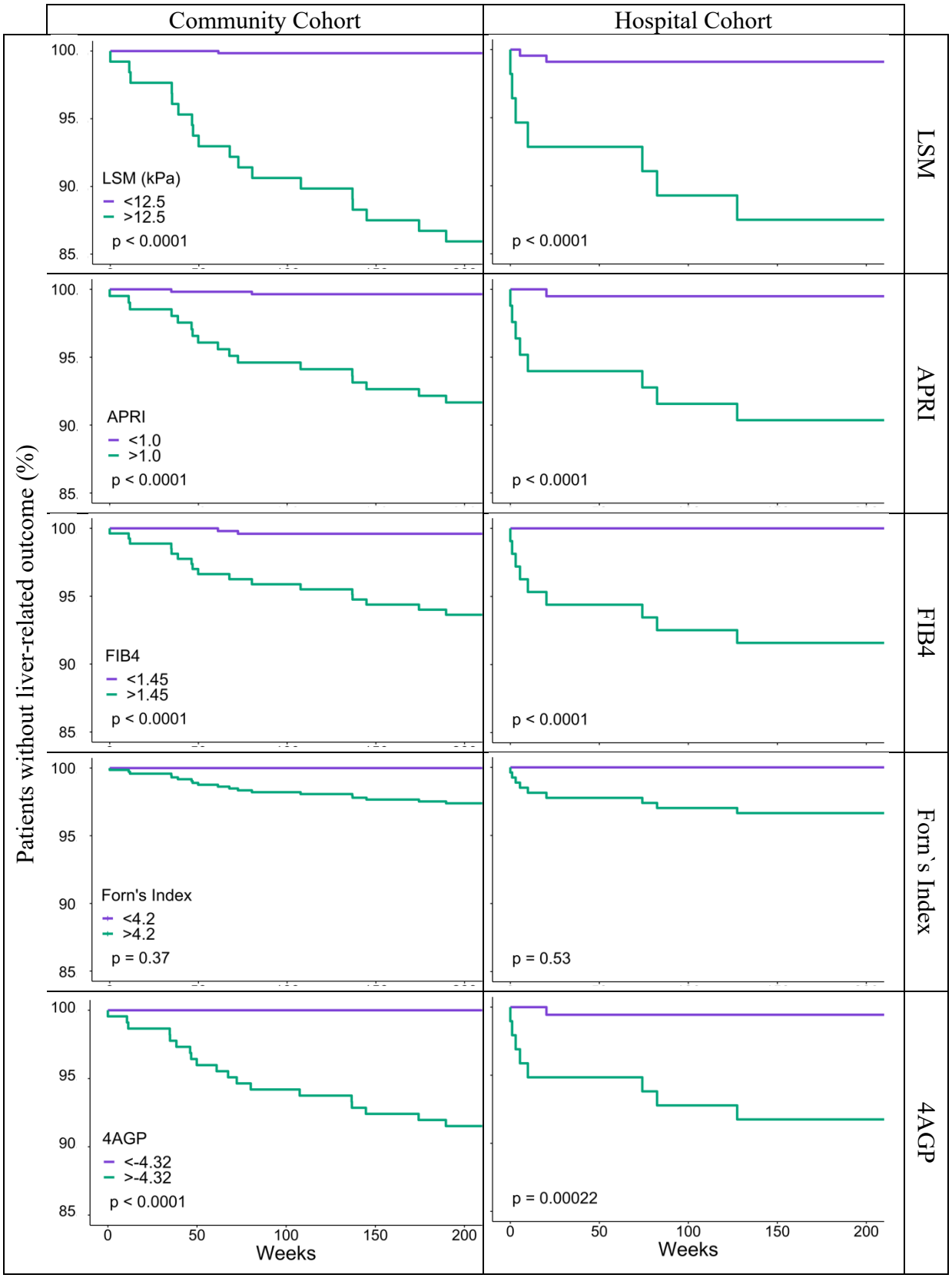


LSM: liver stiffness measurements; APRI: AST to platelet ratio index; FIB4: Mean fibrosis index based on four factors

4.4.1.5.2. Kaplan-Meier survival curves

Kaplan Meier survival curves with log rank testing found significant differences in rates of a composite of liver-related outcomes in those with LSM </≥12.5kPa, APRI </≥1, FIB4 </≥1.42 and 4AGP </≥-4.32. Forn's index with the accepted cut-off of 4.2 did not show any differences in those who developed a liver-related outcome and those who did not, in either cohort. This is shown in Figure 4-11.

Figure 4-11 Kaplan-Meier Curves for liver-related outcomes and liver stiffness measurements in the community cohort and hospital cohorts



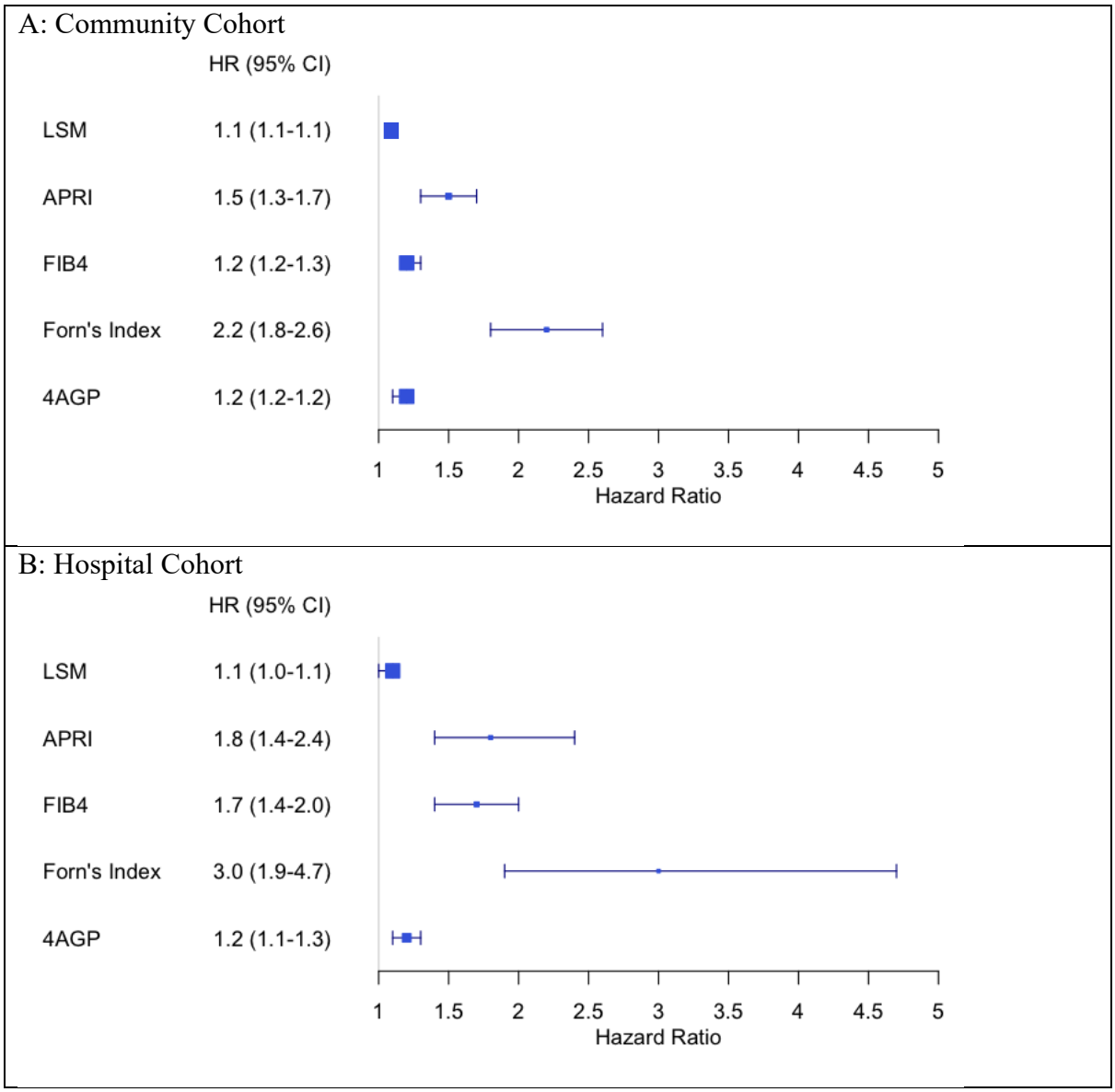
LSM: liver stiffness measurements; APRI: AST to platelet ratio index; FIB4: Mean fibrosis index based on four factors

4.4.1.5.3. Cox Proportional Hazard Ratios

Cox proportional HRs were calculated for each of LSM, APRI, FIB4, Forn's index and 4AGP using these as continuous rather than categorical variables.

Cox proportional HRs were calculated as a univariate model, for the community and the hospital cohorts (Figure 4-12 A and B respectively). In the community cohort, LSM had a HR of 1.1, meaning that for each 1-unit kPa increase, the risk of a liver-related outcome increased by 1.1. LSM was less reliable in the hospital cohort with a HR 95% CI that crossed over 1 meaning that it was not associated with increased or decreased risk of liver-related outcome events in a cox proportional HR analysis. Forn's index had the highest HR in both the community and hospital cohorts meaning that when used as a continuous variable, Forn's index was able to predict those who were more likely to have a liver-related outcome. APRI, FIB4 and 4AGP all had a HR above 1, meaning that they were all associated with increased risk of liver-related events, in both cohorts. Multivariate cox proportional HRs could not be performed due to high multicollinearity between all these variables as discussed in chapter 3.

Figure 4-12 Cox Proportional Hazard Ratios for liver-related outcomes in community and hospital cohort. Univariate analysis.



Hazard Ratio: HR; Confidence Interval: CI; LSM: liver stiffness measurements; APRI: AST to platelet ratio index; FIB4: Mean fibrosis index based on four factors

4.4.1.5.4. Optimal cut-off points of tests for predicting a composite of liver-related outcomes

Optimal cut-off points for liver-related outcomes in LSM and the indirect biomarker algorithms were calculated. In the community cohort, an LSM of 22.8kPa was the optimal cut-off point with a high sensitivity and specificity. APRI had both lower sensitivity and specificity

than LSM. FIB4 had a higher specificity but a lower sensitivity, and Forn's index and 4AGP both had slightly lower sensitivity and specificity than LSM. This is shown in Table 4-20.

Table 4-20 Calculated optimal cut-off points for liver-related outcomes and liver stiffness measurements and indirect biomarker algorithms in the community cohort

Test	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	FP (n)	FN (n)
LSM (kPa)	22.8	94.7	95.3	34.0	99.9	35	1
APRI	1.03	89.5	75.7	8.6	99.6	181	2
FIB4	5.66	73.7	97.7	45.2	99.3	17	5
Forn's index	8.87	84.2	88.3	15.5	99.5	87	3
4AGP	-2.81	84.2	88.8	16.2	99.5	83	3

PPV: positive predictive value; NPV: negative predictive value; FP: false positives; FN: false negatives; LSM: liver stiffness measurements; APRI: AST to platelet ratio index; FIB4: Mean fibrosis index based on four factors

In the hospital cohort, calculated optimal cut-off points for LSM and 4AGP both had the lowest sensitivity but highest specificity out of these variables. These optimal cut-off points should, however, be interpreted with caution due to low numbers of liver-related outcomes. This data is shown in Table 4-21.

Table 4-21 Calculated optimal cut-off points for liver-related outcomes and liver stiffness measurements and indirect biomarker algorithms in the hospital cohort

Test	Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	FP (n)	FN (n)
LSM (kPa)	21.0	70.0	91.9	24.1	98.8	22	3
APRI	1.04	90.0	73.0	11.0	99.5	73	1
FIB4	3.19	90.0	88.5	22.5	99.6	31	1
Forn's index	9.35	90.0	87.6	21.4	99.6	33	1
4AGP	-0.09	70.0	94.7	33.3	98.8	14	3

PPV: positive predictive value; NPV: negative predictive value; FP: false positives; FN: false negatives; LSM: liver stiffness measurements; APRI: AST to platelet ratio index; FIB4: Mean fibrosis index based on four factors

These optimal cut-off points were not used for the above analyses, rather the standard accepted cut-off points were used as discussed in section 2.1.4. The reason for this is that optimal cut-off points may be dataset dependant and using these within the same dataset can increase the risk of type 1 error.[447] It is thus recommended against using calculated optimal cut-off points within the same dataset for other analyses.[447]

4.4.1.5.5. Summary

In summary, LSM appeared superior to the indirect biomarker algorithms in determining those at greatest risk of a liver-related outcomes when assessed using ROC in the community cohort. However, when assessed using ROC in the hospital cohort and, in both cohorts, when time to event was considered, LSM was inferior to the other variables. When used as a categorical variable with a cut-off of 4.2, Forn's index appeared to poorly predict liver-related outcomes, however, when used as a continuous variable, it had the highest HR out of all LSM and indirect biomarker algorithms, although with a wide CI. APRI, FIB4 and 4AGP were all able to predict the risk of liver-related events regardless of method used to assess this in both cohorts, all with variable levels of accuracy depending on the method used.

Optimal cut-off points for LSM were similar between the community and hospital cohorts at 22.8kPa and 21.0kPa respectively. The optimal cut-off point for APRI was similar to previous studies. FIB4 had an optimal higher cut-off point than previous studies as did Forn's index and 4AGP. The hospital and community cohort optimal cut-off points were similar for LSM and APRI, but FIB4, Forn's index and 4AGP optimal cut-off points were all higher in the hospital cohort.

4.5. Chapter Discussion

Data from the CATCH study has shown a high prevalence of CHC community cohort patients with a high probability of cirrhosis and thus a high risk of complications without treatment. There was also high prevalence of patients who had factors associated with morbidity and mortality, with higher rates of IVDU, history of psychiatric diagnoses, at-risk alcohol intake and socioeconomic disadvantage in the community cohort than the hospital cohort.

The community cohort was also a less adherent cohort than the hospital cohort. Although the community cohort had lower rates of adherence with medical appointment attendance, HCC surveillance, treatment and checking for treatment outcomes, the rates were still moderately high, especially in those with a high probability of cirrhosis. The rates of HCC surveillance also increased after patients were recruited into CATCH indicating that CATCH had a positive effect on HCC surveillance rates. Retention in non-GP care for those with a high probability of cirrhosis also had a positive effect on HCC surveillance and treatment rates. The

implications for this, are that to increase HCC surveillance rates, we either need to improve retention in non-GP specialist management or change the way that HCC surveillance is performed.

The incidence of liver-related outcomes were very similar between the cohorts, however, importantly, the community cohort had lower rates of HCC diagnosis. This raises the possibility that these patients are either not being diagnosed or the rates are lower. Given the lower rates of retention in non-GP specialist care and lower HCC surveillance rates in the community cohort, it is more likely that these patients are not being diagnosed with HCC. Future linkage data studies will be able to address this further.

Another very important finding in these results is that a community management program for people living with CHC can predict liver-related outcomes with high sensitivity and specificity for different tests, each with benefits and limitations. Community management for CHC has not been studied previously and these results suggest that a program such as CATCH may be able to determine the risk of liver-related events for people living with CHC in a community setting. However, the best test to determine risk of liver-related events when used in a community management program was not clear. LSM was the best when assessed in the community cohort using ROC, however, it performed the worst when assessed the same way in the hospital cohort. When time was considered using Kaplan Meier survival curves, all of LSM and indirect biomarkers, except Forn's index, were able to differentiate between those who developed a liver-related outcome and those who did not. However, when the same variables were assessed using cox proportional HRs as continuous variables, Forn's index had the highest HR. The optimal cut-off point for a composite of liver-related outcomes for Forn's was higher than the 4.2 of the original study, raising the possibility that if Forn's index was used as a categorical variable to delineate patients into high and low risk of developing a liver-related outcome, then perhaps another cut-off should be used. This data showed that 8.87 and 9.35 were the optimal cut-off points in the community and hospital cohort respectively: these findings warrant validation studies with a different group of patients from a community cohort to determine whether these cut-off points are superior for determining risk. This is also the first study to assess 4AGP as a test for predicting the risk of liver-related outcomes in any setting: it performed slightly better than LSM when assessed using HRs but was possibly not as accurate as the other indirect biomarkers. Other studies are required to further determine if there is one test that is superior to other tests.

Overall, these results highlight a need for a program like this to be available to improve patient care. They also highlight significant gaps in patient care, especially in a community cohort of patient and suggest that future research is required. General limitations of the CATCH study will be discussed in more detail in the discussion chapter as these limitations are very similar between the CHB and CHC. Ultimately, the CATCH study will perform Births, Deaths and Marriage, and cancer registry linkage data at 10 years.

Chapter 5. Results: Chronic Hepatitis B

This chapter aims to determine the prevalence of factors associated with increased risk of morbidity and mortality, determine adherence with management and assess risk of liver-related outcomes, in people living with CHB. The factors associated with increased risk of morbidity and mortality include (1) high probability of cirrhosis based on LSM and ultrasound findings, (2) prevalence of factors that are associated with fibrosis development and morbidity and mortality; (3) the percentage of patients in a phase where antiviral therapy should be considered (hepatitis phase) and (4) the percentage of patients where HCC surveillance is beneficial. Adherence will be assessed via (1) retention in CATCH, (2) retention in non-GP specialist care where this is required, (3) appropriate HCC surveillance and (4) antiviral therapy. Liver related outcomes will also be assessed.

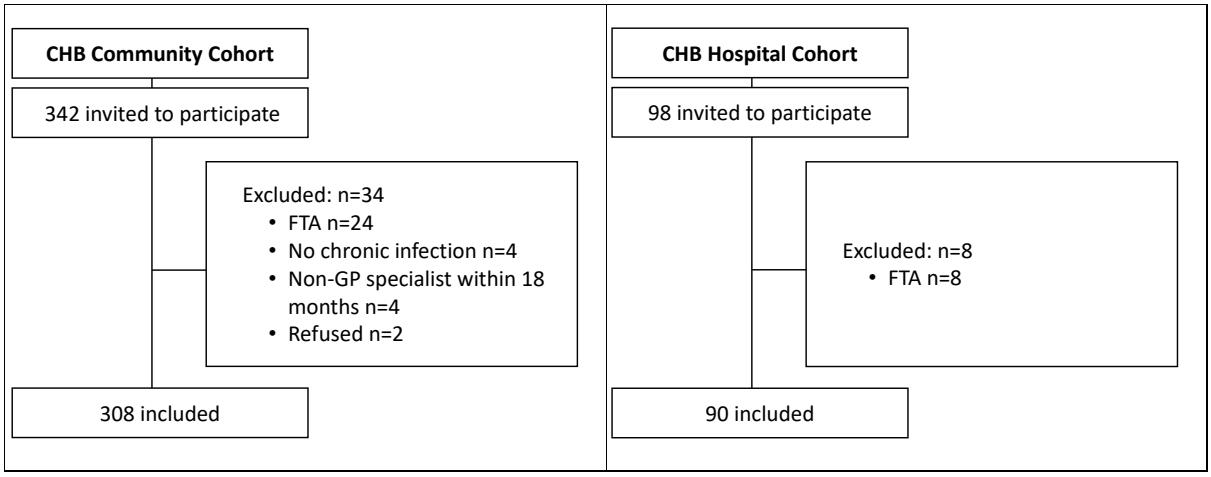
For this chapter assessing people living with CHB, an LSM cut-off of 11kPa has been used to detect those who are at a high probability of having cirrhosis. Factors associated with an elevated LSM have used a cut-off of 7kPa due to low numbers of patients with LSM≥11kPa; thus, the analysis for this single section determines factors associated with a high probability of advanced fibrosis rather than high probability of cirrhosis.

To provide greater context, the community cohort (study cohort) will be compared to a hospital cohort of patients (current standard of care).

5.1. Patient Recruitment results

Between October 2014 and March 2017, 398 people living with CHB were recruited: 308 from the community cohort and 90 from the hospital cohort. There were 20 GP clinics around Melbourne, Australia involved with the CHB community cohort, eight of which were opiate replacement therapy prescribing clinics. The hospital cohort of patients were recruited from Eastern Health liver and hepatitis outpatient clinics. There were 42 patients who were excluded due to FTA, failure to meet inclusion criteria or refusal to participate (Figure 5-1). There was no difference in FTA rates between the two cohorts ($p = .8$).

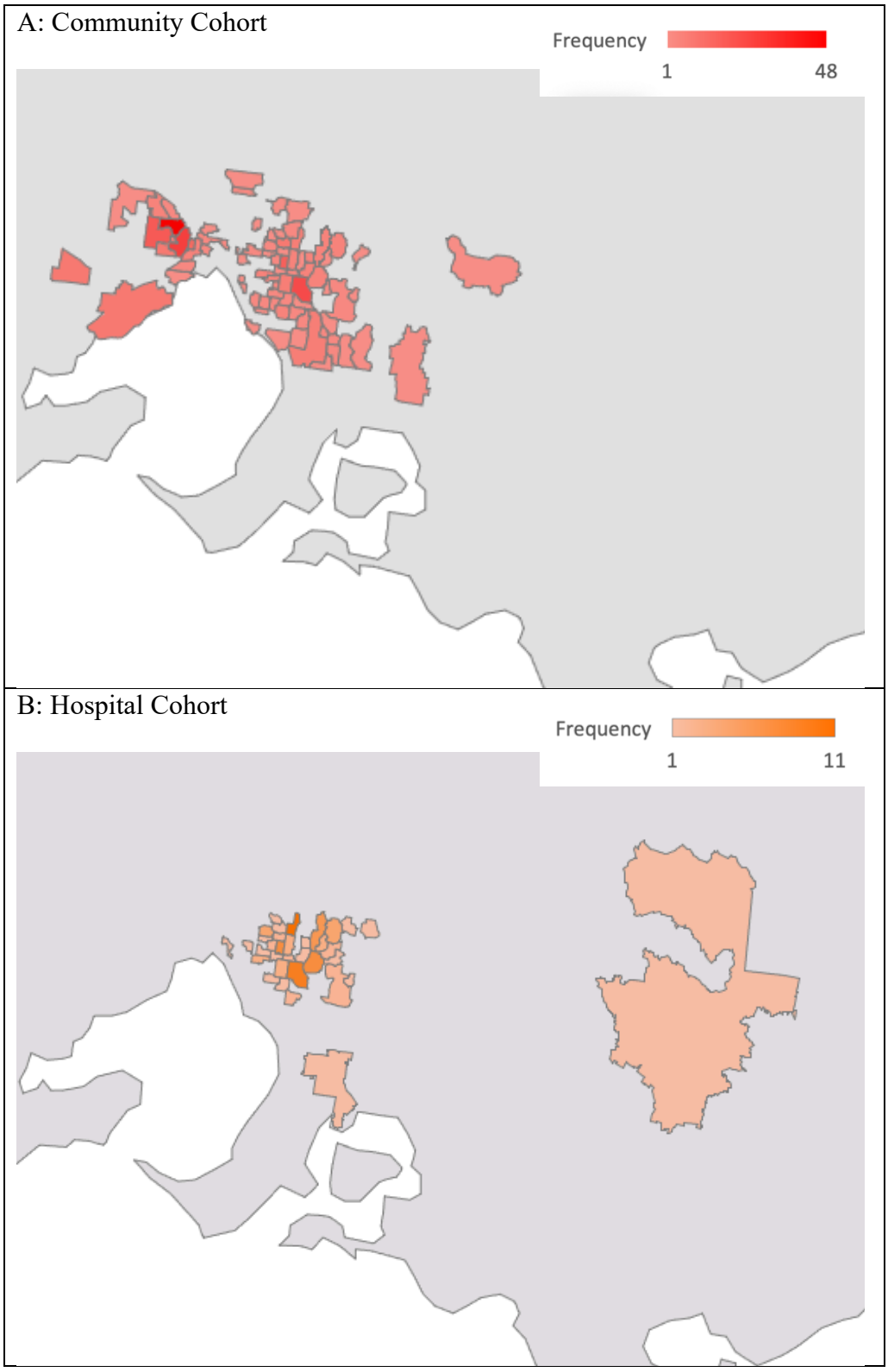
Figure 5-1 Flow chart of study recruitment



CHB: chronic hepatitis B virus infection; FTA: failed to attend; GP: general practitioner

Figure 5-2 demonstrates the patients' geographical location by postcode. The geographical distribution of the community cohort (Figure 5-2 A) of patients was more varied than the hospital cohort (Figure 5-2 B) due to the recruitment locations.

Figure 5-2 Geographical distribution of patients by postcode in community and hospital cohorts. Victoria, Australia



5.2. Factors associated with morbidity and mortality at initial assessment

The aim of this section is to determine the prevalence of a high probability of cirrhosis based on LSM ≥11kPa or ultrasound findings of cirrhosis, in a hepatitis phase or who required HCC surveillance, as well as the percentage with other factors associated morbidity and mortality. These include age, years of infection, gender, history of dual infection with CHC, at-risk alcohol intake, family history of HCC and BMI. Pathology results will also be assessed, namely platelets, ALT, AST, GGT, albumin, total cholesterol and AFP, along with indirect biomarker algorithms (APRI, FIB4, Forn's index and 4AGP).

5.2.1. Results

5.2.1.1. Baseline characteristics

Table 5-1 shows the baseline variables and differences between the community and hospital cohorts of patients. The community cohort had a longer estimated duration of infection than the hospital cohort although the difference was small (36.3 years versus 31.6 years, p = .007, Cohen's D = 0.3). The other variables were all similar between the cohorts (age, dual infection with CHC, gender, history of cigarette smoking, cannabis use, at-risk alcohol, IVDU, psychiatric diagnosis, personal history of cancer, family history of HCC and BMI, p > .5 for all). One patient was diagnosed with dual HIV infection from the community cohort.

Table 5-1 Baseline characteristics and variables in community and hospital cohorts. Univariate analysis.

Variable	Community n=308	Hospital n=90	p-value
Age (years, mean, SD)	44.5 (10.7)	42.7 (10.9)	.2
Years of infection (years, mean, SD)	**36.3 (13.9)**	**31.6 (14.3)**	**.007**
Dual Infection CHC, n (%)	15 (4.9)	2 (2.2)	.3
Gender, n (female, %)	162 (52.6)	46 (51.1)	.8
Cigarette smoking, n (%)	21 (6.8)	3 (3.3)	.2
Cannabis use, n (%)	12 (4.0)	4 (4.5)	.8
Alcohol, n (%)	22 (7.1)	6 (6.7)	.9
History of IVDU, n (%)	15 (4.9)	4 (4.4)	.9
History of psychiatric diagnosis, n (%)	10 (3.2)	3 (3.3)	.0
Personal history of cancer, n (%)	2 (0.6)	0 (0)	.4
Family history of HCC, n (%)	43 (14.0)	13 (14.4)	.9
BMI (kg/m^2, median, IQR)	23.4 (4.5)	22.9 (5.3)	.1

Bold: significant (p<.5); SD: standard deviation; CHB: chronic hepatitis B virus infection; cigarette smoking: > 15 pack-year history; alcohol: > 100g/week; IQR: interquartile range; IVDU: intravenous drug use as a risk factor for viral hepatitis; HCC: hepatocellular carcinoma; BMI: body mass index; kg: kilograms; m: metres

The ethnicity of patients was assessed. There were 92.8% who were of Asian ethnicity in the community cohort and 88.9% in the hospital cohort; 4.9% who were white in the community cohort and 10.0% in the hospital cohort; African (n=1, community cohort); Arab (n=2, community cohort); Indigenous Oceanic (n=1 in each of the cohorts); Sub-Continent (n=1 in the community cohort) and mixed ethnicity (n=2 in the community cohort). There were no differences in ethnicity distributions between the cohorts ($p = .3$).

To examine the relationship between CHB and socioeconomic status, patient postcode was linked to socioeconomic disadvantage quintiles using ABS data. There were significant differences in socioeconomic disadvantage quintiles between the cohorts with the community cohort having higher levels of socioeconomic disadvantage (i.e. the community cohort was more disadvantaged, $p < .001$, Table 5-2). There were very few patients within the 'high' socioeconomic disadvantage quintile. There were no differences between socioeconomic disadvantage quintiles between ethnicities in either cohort ($p > .05$ for both).

Table 5-2 Socioeconomic disadvantage quintiles in community and hospital cohorts

	Socioeconomic disadvantage quintile %				
Cohort	Very high	High	Moderate	Low	Very low
Community	35.4	2.9	12.0	24.0	25.6
Hospital	3.4	1.1	6.7	46.1	42.7
Total	28.2	2.5	10.8	29.0	29.5

Each cell represents the percentage of patients from the Cohort (row) belonging to the Socioeconomic disadvantage quintile (column). Very high: very high level of disadvantage, meaning most disadvantaged

Given there may be differences in rates of smoking, history of psychiatric diagnosis, IVDU, cannabis use and at-risk alcohol intake between areas of different socioeconomic status, these factors were also assessed. There were no differences in these factors between socioeconomic disadvantage quintiles, in either the community or hospital cohorts ($p>.5$ for all).

Examination of pathology results (Table 5-3) found that platelets and cholesterol were higher in the community cohort although both had very small effect sizes (Cohen's D = 0.3 for both) meaning that the differences were small. The community cohort had lower ALT with a negligible difference (Cliff's Delta = 0.1 [0-0.3]). There was a much lower hepatitis B viral load in the community than the hospital cohort with a moderate difference ($p < .001$, Cliff's Delta = 0.3 [0.2-0.5]). The other pathology results (AST, GGT, albumin and AFP) were similar between the cohorts ($p > .05$ for all).

Table 5-3 Baseline pathology results in community and hospital cohorts. Univariate analysis

Variable	Community n=308	Hospital n=90	p-value
Platelets (x109/L, mean, SD)	**229.0 (50.6)**	**215.3 (55.3)**	**.03**
AST (U/L, median, IQR)	22 (8)	24 (11)	.1
ALT (U/L, median, IQR)	**23 (15)**	**25 (18)**	**.04**
GGT (U/L, median, IQR)	19 (17)	19 (16)	.7
Albumin (g/L, mean, SD)	40.5 (2.7)	40.4 (3.0)	.6
Cholesterol (mmol/L, mean, SD)	**5.0 (1.0)**	**4.8 (1.0)**	**.02**
AFP (ug/L, median, IQR)	2 (1)	3 (2)	.09
Hepatitis B viral load (IU/mL, median, IQR)	**294 (1609.5)**	**2340 (42722.5)**	**< .001**

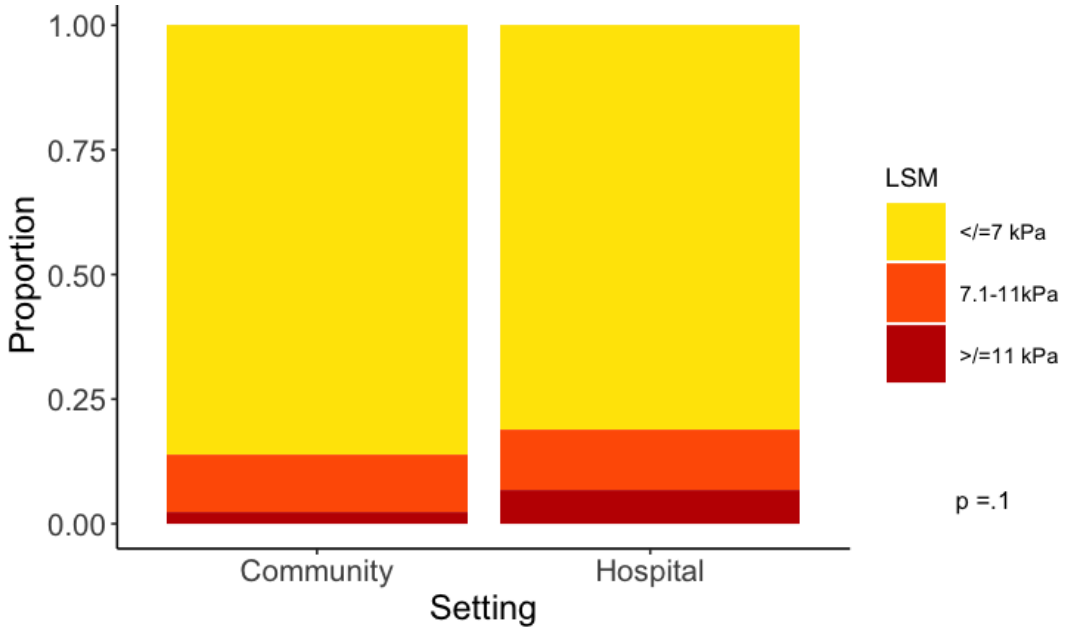
Bold: significant (p<.05); SD: standard deviation; AST: aspartate aminotransferase; U/L: units per litre; IQR: interquartile range; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; g/L: grams per litre; mmol/L: millimoles per litre; AFP: alpha fetoprotein; ug/L: micrograms per litre; IU/mL: international units per millilitre

To summarise, the patient characteristics and pathology results were similar between the community and hospital cohorts. The main differences showed the community cohort had slightly longer duration of infection, higher levels of socioeconomic disadvantage and lower hepatitis B viral load. Although platelets, ALT, cholesterol and AFP were different between the cohorts, effect sizes indicate these differences were negligible.

5.2.1.2. Severity of liver disease as assessed by liver stiffness measurements and indirect biomarker algorithms

LSM and indirect biomarker algorithms were very similar between the two cohorts. Rates of LSM ≥11kPa and ≥7kPa were no different between the community and hospital cohorts (p = .1, Figure 5-3). When LSM was assessed as a continuous variable, there were no significant differences between the hospital and community cohorts (p = .2, Table 5-4). Indirect biomarker algorithms were also very similar between the community and hospital cohorts. APRI was slightly lower in the community cohort than the hospital cohort although the difference was negligible clinically (Cliff Delta = 0.2 [0.0-0.3]). FIB4, Forn's index and 4AGP were all similar between the cohorts (p > .05 for all).

Figure 5-3 Baseline liver stiffness measurements in community and hospital cohorts



LSM: liver stiffness measurements; kPa: kilopascals

Table 5-4 Baseline liver stiffness measurements and indirect biomarkers algorithms in community and hospital cohorts. Univariate analysis

LSM and algorithms of indirect fibrosis markers	Community n=308	Hospital n=90	p-value
LSM (median, IQR)	4.7 (2.0)	5.0 (2.2)	.2
APRI (median, IQR)	**0.29 (0.1)**	**0.32 (0.2)**	**.006**
FIB4 (median, IQR)	0.9 (0.5)	0.9 (0.6)	.7
Forn's index (mean, SD)	6.3 (1.4)	6.2 (1.5)	.9
4AGP (mean, SD)	-6.5 (1.5)	-6.3 (1.6)	.3

Bold: significant (p<.05); LSM: liver stiffness measurements; IQR: interquartile range; APRI: AST to platelet ratio index; FIB4: Mean fibrosis index based on four factors; SD: standard deviation.

To summarise, LSM and indirect biomarker algorithms were very similar between the cohorts. Although APRI was slightly lower in the community cohort the effect size was small meaning the difference was negligible.

5.2.1.3. Baseline Associations with elevated liver stiffness measurements

There was 2.3% (n=7) of the community cohort and 6.7% (n=6) of the hospital cohort who had a high probability of cirrhosis based on LSM ≥11kPa. Due to these low numbers, meaningful statistical tests for predictors of LSM ≥11kPa could not be performed. As such, this section has used a cut-off of ≥7kPa to determine factors associated with patients who have

a high probability of advanced fibrosis, however, there are still low numbers of patients with LSM≥7kPa so some statistical tests could not be performed. There was 13.6% (n=42) of the community cohort and 18.9% (n=17) of the hospital cohort who had an LSM ≥7kPa.

Variables associated with LSM ≥7kPa were assessed (Table 5-5). In both cohorts, history of IVDU and increasing AST, ALT and GGT were associated with LSM ≥7kPa. In the community cohort, lower rates of LSM ≥7kPa were seen in those of female gender and in those with decreasing platelets and cholesterol. There were higher rates of LSM ≥7kPa seen in those with dual infection with CHC, cigarette smoking history, at-risk alcohol intake, history of psychiatric diagnosis, history of IVDU and increasing BMI, AST, ALT, GGT and AFP. The other variables assessed (age, years of infection, albumin) were not associated with LSM ≥7kPa in the community cohort.

Table 5-5 Odds ratio with 95% confidence intervals for liver stiffness measurements ≥ 7kPa in community and hospital cohorts. Univariate analysis.

	Odds ratio (95% CI)	
Variable	**Community Cohort**	**Hospital Cohort**
Age	1.03 (1.0-1.06)	1.02 (0.97-1.07)
Years of infection	0.99 (0.97-1.01)	1.01 (0.97-1.05)
Gender (female)	**0.17 (0.08-0.38)**	0.33 (0.1-1.02)
Dual Infection CHC	**4.82 (2.64-8.80)**	*
Cigarette smoking	**3.6 (1.36-9.53)**	*
Cannabis use	**15.64 (4.46-54.78)**	5.0 (0.65-38.54)
Alcohol	**3.35 (1.28-8.78)**	2.3 (0.39-13.73)
History of IVDU	**16.31 (2.25-50.73)**	**15.43 (1.49-159.28)**
History of psychiatric diagnosis	**4.56 (1.23-16.91)**	2.22 (0.19-26.0)
BMI	**1.14 (1.05-1.25)**	1.07 (0.95-1.19)
Platelets	**0.99 (0.98-0.99)**	0.99 (0.98-1.00)
AST	**1.06 (1.03-1.09)**	**1.05 (1.01-1.09)**
ALT	**1.03 (1.02-1.04)**	**1.01 (1.00-1.03)**
GGT	**1.01 (1.01-1.02)**	**1.02 (1.00-1.05)**
Albumin	1.01 (0.90-1.14)	0.92 (0.76-1.1)
Cholesterol	**0.59 (0.40-0.87)**	0.70 (0.38-1.27)
AFP	**1.26 (1.11-1.43)**	1.12 (0.90-1.39)

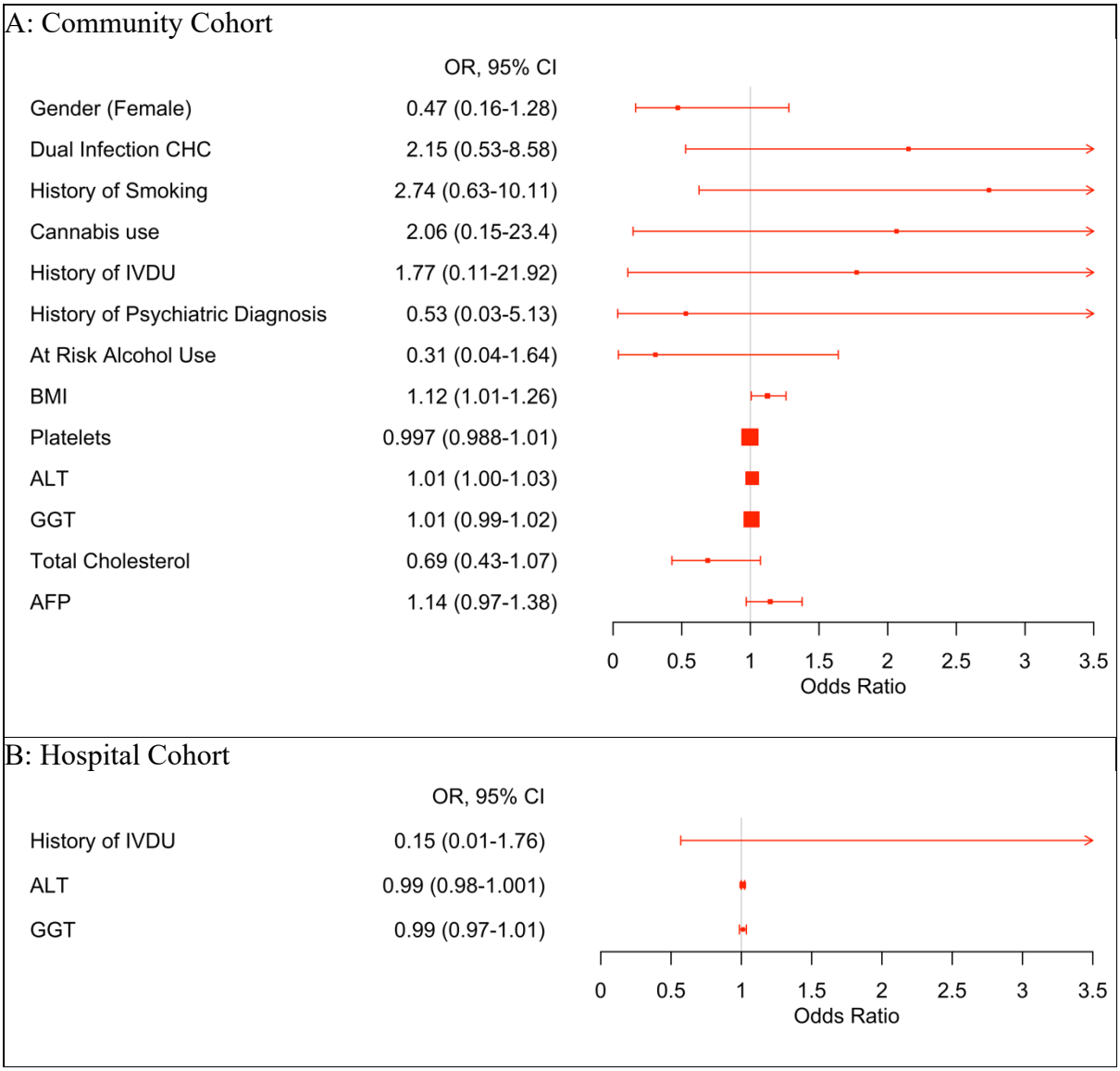
* odds ratio cannot be calculated accurately as too low numbers of dual infection and smoking in the hospital cohort for meaning statistical tests**.** Bold: significant ($p < .05$, confidence interval does not cross 1); CI: confidence interval. CHB: chronic hepatitis B virus infection; alcohol; >100g/week; IVDU: intravenous drug use as a risk factor for viral hepatitis; BMI: body mass index; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; AFP: alpha fetoprotein; cigarette smoking: > 15 pack-year history

In the hospital cohort, history of IVDU and increasing AST, ALT and GGT were associated with LSM ≥7kPa, however, none of age, years of infection, gender, cannabis use, at-risk alcohol intake, history of psychiatric diagnosis, BMI, platelets, cholesterol or AFP were associated with LSM ≥7kPa.

There were also no differences in socioeconomic disadvantage quintiles between those with LSM ≥7kPa and LAM<7kPa in either the community (p = .7) or hospital cohorts (p = .3).

To determine which factors were independently associated with LSM ≥7kPa and whether these differed between cohorts, two binary logistic regressions were calculated, one with the community cohort and one with the hospital cohort. The community cohort regression examined LSM ≥7kPa and gender, dual infection with CHC, smoking history, cannabis use history, history of at-risk alcohol intake, history of IVDU, history of psychiatric diagnosis, BMI, platelets, ALT, GGT, cholesterol and AFP (p = .019, Figure 5-4 A). Only BMI, GGT and ALT remained statistically significant in this regression analysis. The hospital cohort regression examined LSM ≥7kPa predicted by history of IVDU, ALT and GGT (p = .051, Figure 5-4 B). This showed that there was a trend towards LSM ≥7kPa with increasing ALT but not GGT or history of IVDU.

Figure 5-4 Odds ratio with 95% confidence intervals for liver stiffness measurements ≥ 7kPa in community and hospital cohorts. Multivariate Analysis



Statistical test: binomial logistic regression**;** OR: odds ratio; CI: confidence interval; history of smoking: cigarettes: > 15 pack-year smoking history; Alcohol: > 100g/week; BMI: body mass index; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; AFP: alpha fetoprotein.

Lastly, to determine the prevalence of a high probability of cirrhosis based on combining LSM and ultrasound findings of cirrhosis, an LSM cut-off of 11kPa was again used (Table 5-6). Of those who had an ultrasound, the rates of cirrhosis were unable to be accurately compared due to low numbers, although there was a trend towards higher rates of cirrhosis on imaging in the hospital cohort at 6.4% (n=5) compared to 1.8% (n=4) of the community cohort. Combining LSM ≥11kPa and ultrasound findings consistent with cirrhosis produces 2.9% (n=9, 7 + 2) of the community cohort and 8.9% (n=8, 6 + 2) of the hospital cohort who had a

high probability of cirrhosis: the hospital cohort had a higher prevalence of a high probability of cirrhosis than the community cohort (p = .014).

Table 5-6 Percentage of patients with ultrasound findings of cirrhosis by liver stiffness measurements and cohort

Cohort	LSM (kPa), n	US performed, n (%)	US findings of cirrhosis, n (%)
Community	≥11, **7**	5 (71.4)	2 (40.0)
	<11, 301	217 (72.1)	**2** (0.9)
Hospital	≥11, **6**	6 (100.0)	3 (50.0)
	<11, 84	72 (85.7)	**2** (2.8)

Bold: values used to calculate the number with high probability of cirrhosis using both ultrasound and LSM data.
LSM: liver stiffness measurements; kPa: kilopascals; US: ultrasound

5.2.1.4. Phases of disease

Determining the phase of CHB is an important part of management: phases help to guide treatment decisions and certain phases require closer monitoring. At baseline, using an ALT cut-off of 30 IU/mL for women and men based on the cut-off suggested by the laboratory used by CATCH, most patients had HBeAg negative infection in both cohorts, however, with a higher percentage of patients with HBeAg positive hepatitis and HBeAg negative hepatitis in the hospital cohort (p < .001, Table 5-7). There was also a significant percentage in both cohorts who were not in a clearly defined phase. Most of these had HBeAg negative infection with viral load less than 2000 IU/mL but with an ALT above 30 IU/mL, followed by HBeAg negative disease with viral load more than 2000 IU/mL and an ALT of 30 IU/mL or less.

Table 5-7 Chronic hepatitis B phases at baseline with alanine transaminase cut-off of 30 IU/mL for women and men in community and hospital cohorts

Phase	Community, n (% of total cohort), n=308	Hospital, n (% of total cohort), n=90
HBeAg positive infection	6 (1.9)	8 (8.9)
HBeAg positive hepatitis	11 (3.6)	9 (10.0)
HBeAg negative infection	180 (58.4)	32 (35.6)
HBeAg negative hepatitis	24 (7.8)	17 (18.9)
No clear phase		
HBeAg negative infection but high ALT	50 (16.2)	12 (13.3)
HBeAg negative high viral load normal ALT	32 (10.4)	12 (13.3)
No viral load available	5 (1.6)	0 (0)
Total	89 (28.6)	24 (26.7)

ALT: alanine aminotransferase

Using the cut-off of an ALT of 19 IU/L for women reclassified 45 patients from the community cohort at baseline: 2 patients from HBeAg positive infection to HBeAg positive hepatitis; 7 from HBeAg negative high viral load with normal ALT to HBeAg negative hepatitis; and 36 patients from HBeAg negative infection to HBeAg negative low viral load with elevated ALT. In the hospital cohort, using the same ALT cut-off for women reclassified 14 patients at baseline: 2 patients from the HBeAg positive infection to HBeAg positive hepatitis; 4 from HBeAg negative high viral load with normal ALT to HBeAg negative hepatitis; and 8 patients from HBeAg negative infection to HBeAg negative low viral load with elevated ALT. The phases with the ALT cut-off of 19 IU/mL for women is shown in Table 5-8.

Table 5-8 Chronic hepatitis B phases at baseline with alanine transaminase cut-off of 19 IU/mL for women and 30 IU/mL for men in community and hospital cohorts

Phase	Community, n (%), n=308	Hospital, n (%), n=90
HBeAg positive infection	4 (1.3)	6 (6.7)
HBeAg positive hepatitis	13 (4.2)	11 (12.2)
HBeAg negative infection	144 (46.8)	24 (26.7)
HBeAg negative hepatitis	31 (10.1)	21 (23.3)
No clear phase		
HBeAg negative infection but high ALT	86 (27.9)	20 (22.2)
HBeAg negative high viral load but normal ALT	25 (8.1)	8 (8.9)
No viral load available	5 (1.6)	0 (0)
Total	116 (37.7)	28 (31.1)

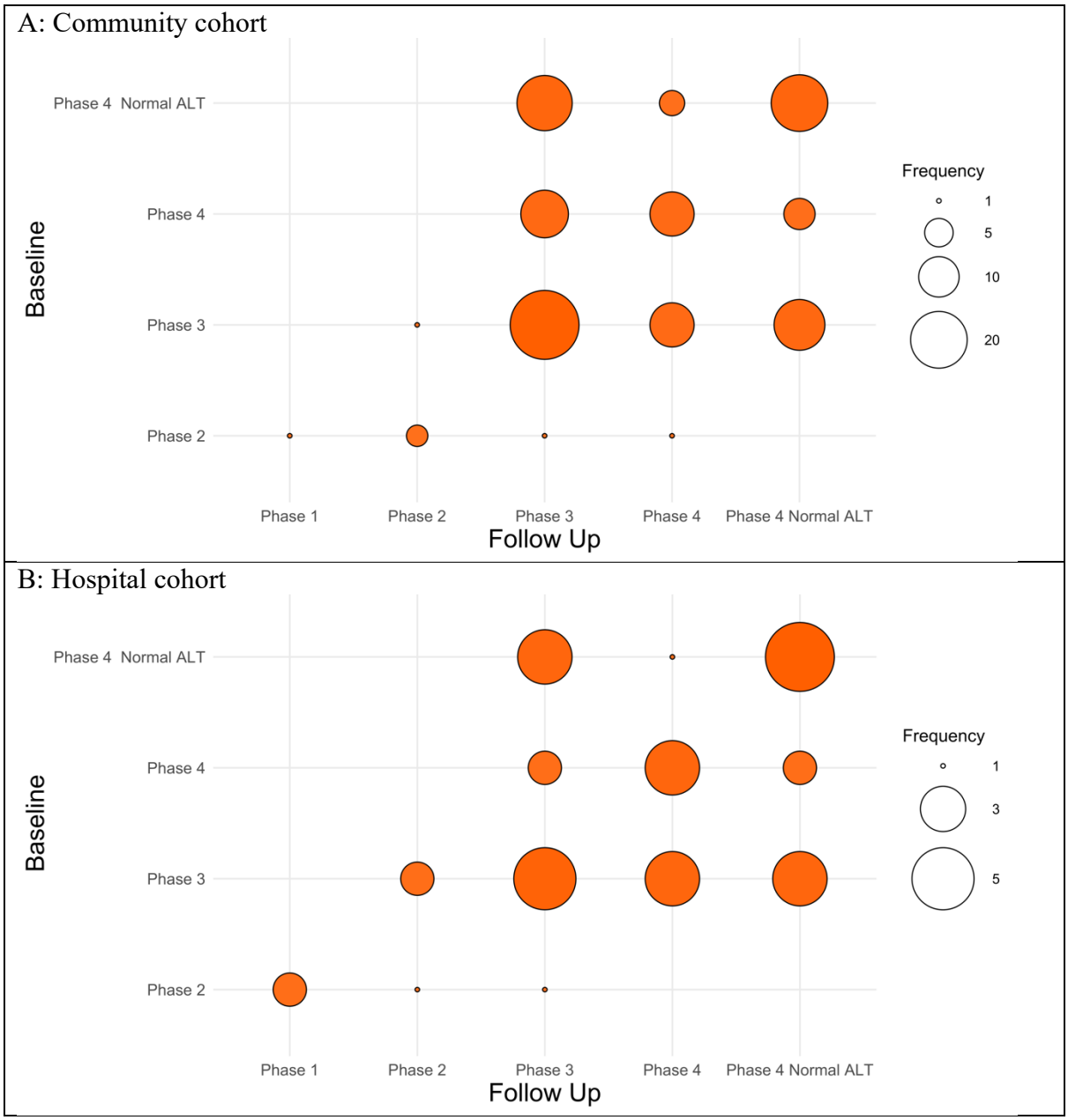
ALT: alanine aminotransferase

To determine the differences between the percentage of patients in each cohort who were in a hepatitis phase at baseline, those in a hepatitis phase were combined using ALT cut-off of 19 IU/mL for women and 30 IU/mL for men. The hospital cohort had a higher percentage of patients in a hepatitis phase than the community cohort (44.4% versus 22.4%, $p < .001$). Predictors of being in a hepatitis phase at baseline were analysed. None of age, years of infection, gender, dual infection with CHC, at-risk alcohol intake, smoking history, history of IVDU or psychiatric diagnosis, cannabis use or BMI were predictors in either cohort ($p > .05$ for all).

At time of last follow-up, 180 patients had been reassessed prior to antiviral therapy commencement, 142 in the community cohort and 38 in the hospital cohort. For these patients, mean follow-up was for 102.3 weeks +/- 36.8. Figure 5-5 is a bubble graph that shows

movement between phases at baseline and at the time of last follow-up (before antiviral therapy was commenced). This graph is interpreted by looking at the horizontal lines which represent the baseline phase, then the vertical lines which represent the phase at follow-up, the larger the bubble, the more patients in that group. This graph shows that a high percentage were in the same phase at baseline and at follow-up, however, there was also a lot of movement between phases over time. In the community cohort, of those who were in a hepatitis phase at baseline, 65.0% remained in a hepatitis phase. Of those not in a hepatitis phase at baseline, 14.2% moved into a hepatitis phase. In the hospital cohort, of those who were in a hepatitis phase at baseline, 66.7% remained in a hepatitis phase. Of those not in a hepatitis phase at baseline, 9.1% moved into a hepatitis phase.

Figure 5-5 Bubble graph demonstrating phases at baseline and at follow-up in community and hospital cohorts



Phase 1: HBeAg positive infection; Phase 2: HBeAg positive hepatitis; Phase 3: HBeAg negative infection; Phase 4: HBeAg negative hepatitis

5.2.1.5. Hepatocellular carcinoma surveillance

To determine the percentage of patients who required HCC surveillance, anyone with a high probability of cirrhosis based on LSM ≥11kPa and/or ultrasound findings of cirrhosis, those where surveillance was recommended based on age/gender/ethnicity criteria and those with a family history of HCC were included. Non-Asian and non-African patients with non-cirrhotic

CHB were classified using the guidelines for those of Asian ethnicity given the lack of data for this sub-group of patients who are not on antiviral therapy.

There were no differences in percentage who required HCC surveillance between the community and hospital cohorts (59.4% compared to 40.6% respectively, p = .3). Of those who required HCC surveillance, the indications for surveillance were different between the cohorts, with a higher percentage of cirrhosis as the indication in the hospital cohort and a higher percentage of age/gender/ethnicity criteria in the community cohort (p = .019, Table 5-9). The percentage of patients with family history of HCC as the indication were similar between the two cohorts.

Table 5-9 Indication for hepatocellular carcinoma surveillance in community and hospital cohorts

Indication for surveillance	Community Cohort, n=183 n (%)	Hospital Cohort, n=48 n (%)
Cirrhosis	9 (4.9)	8 (16.7)
Age/gender/ethnicity	149 (81.4)	33 (68.8)
Family history of HCC	25 (13.7)	7 (14.6)

HCC: Hepatocellular carcinoma.

5.2.1.6. Cirrhosis, disease phase and hepatocellular carcinoma surveillance

To determine the prevalence of patients requiring closer monitoring, patients with cirrhosis or in a hepatitis phase or needing HCC surveillance were combined. There were no differences between the cohorts with 69.8% (n=216) in the community cohort and 70.0% (n=63) in the hospital cohort having one or more of the above listed factors (p = .9). The primary factors were different between the cohorts (p < .001, Table 5-10). There was a higher percentage of patients with cirrhosis and patients in a hepatitis phase in the hospital cohort, and higher rates of patients where HCC surveillance was recommended in the community cohort.

Table 5-10 Factors associated with morbidity and mortality in community and hospital cohorts

Factor	Community Cohort, n=216, n (%)	Hospital Cohort, n=63, n (%)
Cirrhosis		
Cirrhosis only	1 (0.5)	4 (6.3)
Cirrhosis and dual infection CHC	3 (1.4)	1 (1.6)
Cirrhosis and CHB phase	5 (2.3)	3 (4.5)
Total	9 (4.2)	8 (12.7)
CHB phase		
CHB phase only	24 (11.2)	14 (22.2)
CHB phase and dual infection CHC	1 (0.5)	0 (0)
CHB phase and HCC surveillance	38 (17.7)	22 (34.9)
Total	63 (29.4)	36 (57.1)
HCC surveillance required		
HCC surveillance only	131 (61.4)	18 (28.6)
HCC surveillance and dual infection CHC	4 (1.9)	0 (0)
Total	135 (63.3)	18 (28.6)
Dual infection CHC	6 (2.8)	1 (1.6)
HIV	1 (0.5)	0 (0)

Cirrhosis: high probability of based on LSM and ultrasound findings; CHC: chronic hepatitis C virus infection; CHB: chronic hepatitis B virus infection; CHB phase: in a hepatitis phase; HCC: hepatocellular carcinoma; HCC surveillance: as per Australian guidelines; HIV: human immunodeficiency virus.

The community cohort had a lower percentage of patients who had two or more of the above listed factors compared to the hospital cohort (24.1% compared to 41.3%, p = .007).

5.2.2. Summary

Overall, the rates of factors associated with morbidity and mortality were similar between a CHB community and hospital cohort of patients. However, there are clear differences between the cohorts. The community cohort had longer duration of infection and were also from areas of higher socioeconomic disadvantage. Although the percentage of patients with additional risk factors was similar between the cohorts at around 70% of patients for both cohorts, the underlying factors between the two cohorts were different. The hospital cohort had a slightly higher percentage of patients with a high probability of cirrhosis than the community cohort and had a higher percentage of patients in a hepatitis phase. The community cohort had a higher percentage of patients at risk of HCC. The hospital cohort also had a higher percentage of patients who had two of more factors that had a potential impact on morbidity and mortality. Both cohorts also had a significant percentage of patients who moved between phases as well, highlighting the need for ongoing monitoring.

5.3. Adherence with medical appointments and management

All people living with CHB need regular monitoring and management. This section will thus focus on all patients and those who have a higher risk of liver-related outcomes. This includes those who have a high probability of cirrhosis, are in a hepatitis phase or require HCC surveillance. First, repeat attendance rates within CATCH will be assessed for all patients. In those with a high probability of cirrhosis, retention in non-GP specialist care, antiviral treatment and HCC surveillance rates have been assessed. Those in a hepatitis phase will have treatment rates assessed and those who require HCC surveillance will have these rates assessed. Predictors of adherence for all these aspects will also assessed.

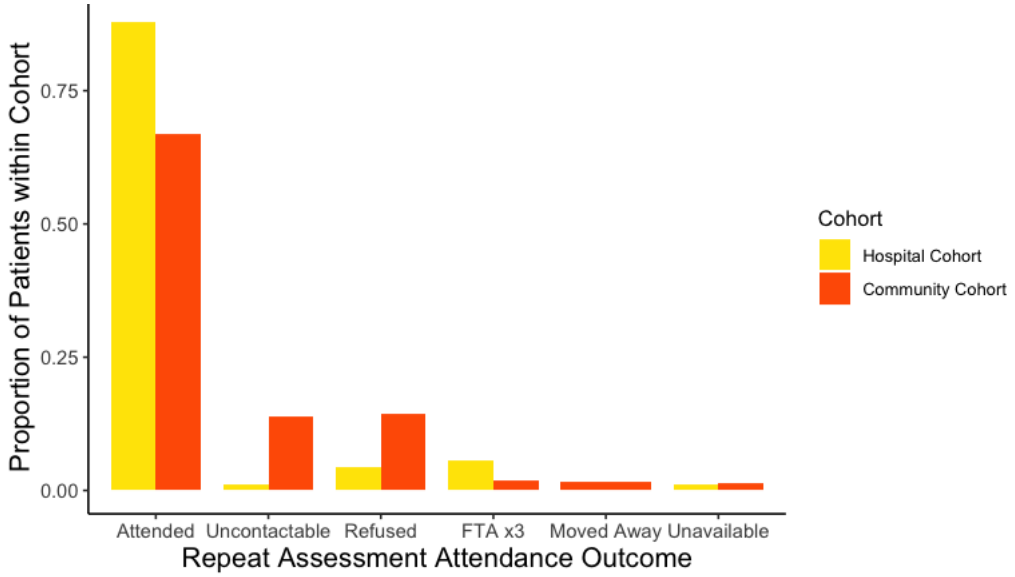
5.3.1. Results

Follow-up was for a mean of 3.7 +/- 0.6 years, indicating 1464.0 patient years. There was no difference in follow-up time between the community and hospital cohorts ($p > .5$). During the study period, only 2 patients were incarcerated, both from the community cohort.

5.3.1.1. Repeat attendance rates within the study

Of the 398 patients, 71.6% attended a repeat assessment with CATCH. There were lower attendance rates in the community than the hospital cohort (66.9% versus 87.8%, $p < .001$) and higher rates of being uncontactable in the community cohort (13.8% versus 1.1% respectively, $p < .001$). Other reasons for non-attendance were refusing a repeat appointment (12.2%); accepting an appointment then failing to attend more than 3 times (2.8%); moving away (1.3%); followed by being unavailable on multiple occasions (1.3%). This is shown in Figure 5-6.

Figure 5-6 Repeat attendance to the study appointments and reasons for not attending in hospital and community cohorts



FTAx3: failed to attend appointments after accepting appointment booking

To determine factors associated with repeat attendance within CATCH, patients' characteristics were analysed including age, gender, at-risk alcohol intake, history of IVDU or psychiatric diagnosis, smoking history, dual infection with CHC, cannabis use and socioeconomic disadvantage quintiles. LSM and the indirect biomarker algorithms including APRI, FIB4, Forn's index or 4AGP were also assessed. In the community cohort, there were no differences in attendance rates for any of these variables ($p > .05$ for all).

Many of the above analyses were unable to repeated with the hospital cohort due to low numbers. Of the variables where statistical tests could be performed, none of gender, age or any of the indirect biomarker algorithms or LSM were associated with attendance in the hospital cohort ($p > .05$ for all).

To summarise, the community cohort had lower repeat attendance rates within CATCH and higher rates of being uncontactable.

5.3.1.2. Retention in non-general practitioner specialist management

As discussed in chapter 3, some of the community cohort of patients were referred onwards by CATCH for non-GP specialist management. The reasons for the referral onwards included a high probability of cirrhosis or advanced fibrosis, dual infection with CHC, discordant results

or being in a hepatitis phase. All the hospital cohort had an appointment made with a non-GP specialist. This section has focused on the groups where non-GP specialist management is warranted for longer term: those with a high probability of cirrhosis based on LSM ≥11kPa and/or ultrasound findings of cirrhosis or those in a hepatitis phase. The reason for this decision is that these are the patients who most benefit from long-term non-GP specialist management for monitoring and consideration of antiviral therapy. Of those who were not retained in non-GP specialist care, it is unclear whether they were lost to follow-up due to being uncontactable or having multiple FTAs or whether they were discharged due to no longer requiring management by non-GP specialists. This section has also assessed factors associated with retention in non-GP specialist care. None of the GP clinics involved with the community cohort of CATCH were S100 prescribers for CHB antiviral therapy, thus all the community cohort of patients who should have been assessed for antiviral therapy were referred onwards.

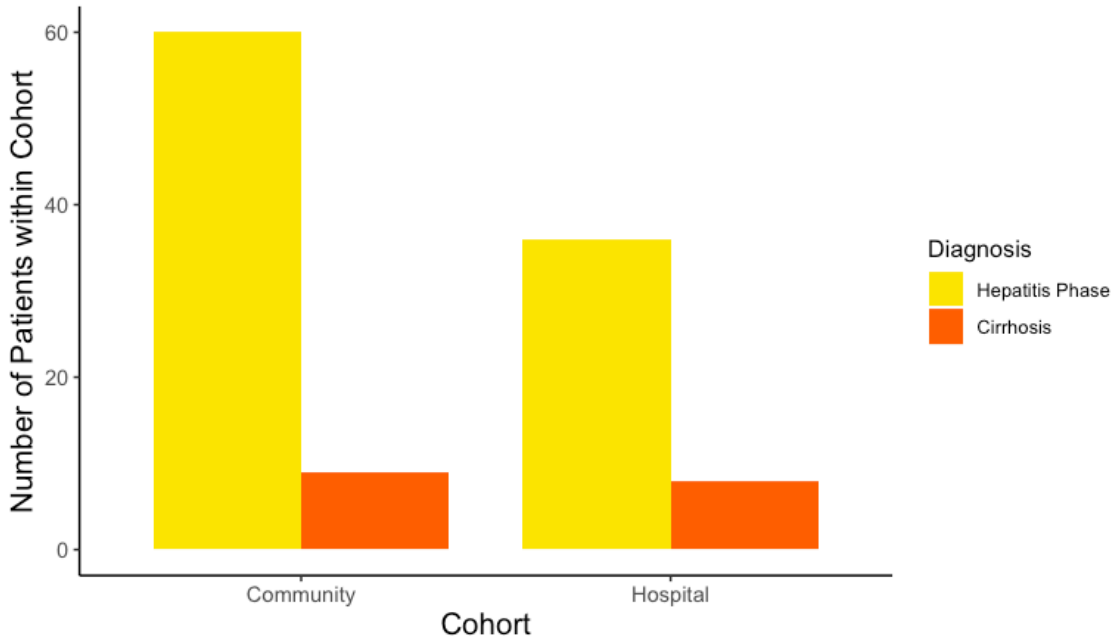
Those who did not meet one of these indications but required HCC surveillance were either referred onwards for non-GP specialist care or remained in the care of their GP with a management plan for surveillance depending on patient preference. HCC surveillance rates will be discussed in section 5.3.1.3.

Those with dual infection CHC have not been included in this analysis unless they had a high probability of cirrhosis or were in a hepatitis phase. The reason for this decision is that once these patients are treated and cured from CHC, long-term non-GP specialist management is not required. In the CHB community cohort, there were 15 patients with dual infection CHC who did not have a high probability of cirrhosis and were not in a hepatitis phase; 10 were treated and cured from CHC; 3 did not start treatment; one patient who self-cleared and one patient where treatment status is unknown. In the hospital cohort, there were two patients who were both treated and cured from CHC.

There were also 3 patients in the community cohort who were not referred onwards for non-GP specialist management, all with very low LSM and who wanted GP follow-up: two males who both had HBeAg positive hepatitis but with an ALT of 31 and 33 IU/mL and viral load just above 20,000 IU/mL and one patient had HBeAg negative disease with very low ALT and viral load just above 2000 IU/mL. There was one patient diagnosed with HIV dual infection who was referred onwards who was not included in this analysis; they are still retained in non-GP specialist management.

Of the 308 community patients, 25.6% (n=69) were referred onwards to a non-GP specialist: 87.0% (n=60) due to being in a hepatitis phase and 13.0% (n=9) due to a high probability of cirrhosis. Of the 98 hospital cohort patients, 48.9% (n=44) of patients met one of the criteria above: of these, 81.8% (n=36) were in a hepatitis phase and 18.2% (n=8) had a high probability of cirrhosis. This is shown in Figure 5-7.

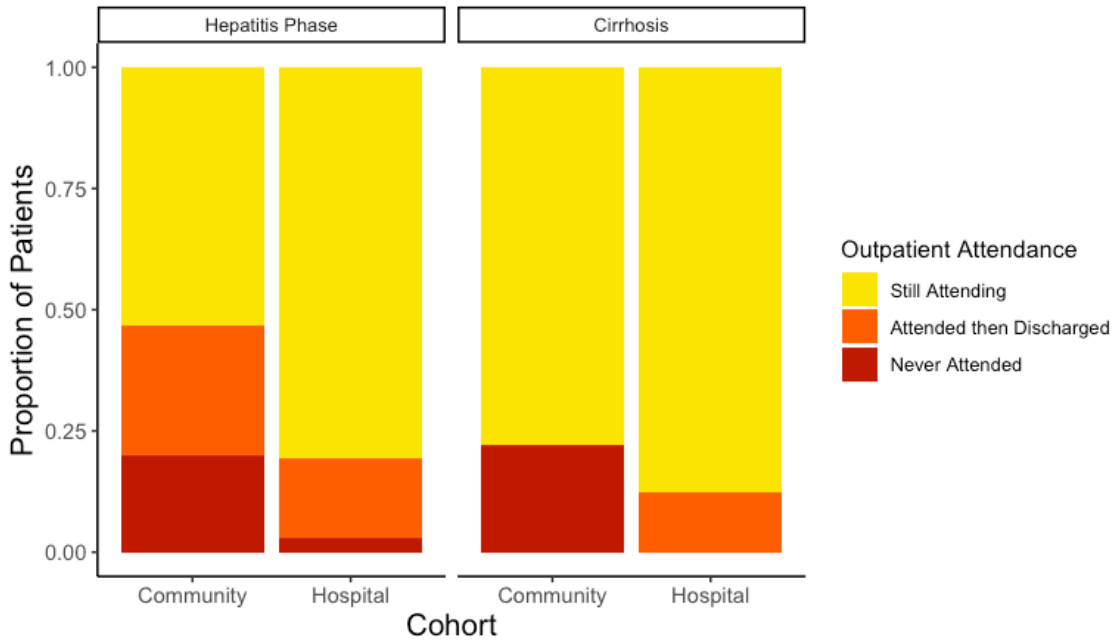
Figure 5-7 Number of patients in a hepatitis phase or with a high probability of cirrhosis in community and hospital cohorts



Cirrhosis/Advanced Fibrosis: high probability of based on ultrasound and LSM assessment

In the community cohort, in those with a high probability of cirrhosis, 77.8% are still attending, the remainder never attended an appointment with a non-GP specialist. Of those from the community cohort in a hepatitis phase, 53.3% are still attending, 16.7% attended at least one appointment but are no longer being seen and 20% never attended an appointment with a non-GP specialist. In the hospital cohort, in those with a high probability of cirrhosis, 87.5% are still attending, the remainder attended at least one appointment with a non-GP specialist but are no longer being seen. Of those from the hospital cohort in hepatitis phase, 80.6% are still attending, 16.7% attended at least one appointment but are no longer being seen and 2.7% never attended an appointment with a non-GP specialist. Those from the community cohort were less likely to be retained in non-GP specialist care than the hospital cohort (56.5% versus 81.8%, p = .006). This is shown in Figure 5-8.

Figure 5-8 Retention in non-general practitioner specialist care in community and hospital cohorts



Cirrhosis/Advanced Fibrosis: high probability of based on ultrasound and LSM assessment

To determine factors associated with retention in care, within each cohort, patient factors including indication, age, gender, history of psychiatric diagnosis or IVDU, smoking history, at-risk alcohol intake, incarceration during the study period, cannabis use and socioeconomic disadvantage quintiles were assessed. In the community cohort, there was no difference in any of these variables ($p > .05$ for all) although there were too few patients with a history of smoking to assess this variable. In the hospital cohort, there was no difference between those retained and those not retained in non-GP specialist care based any of these variables either ($p > .05$ for all) although there were too few patients with a history of psychiatric diagnoses and cannabis use to assess these variables.

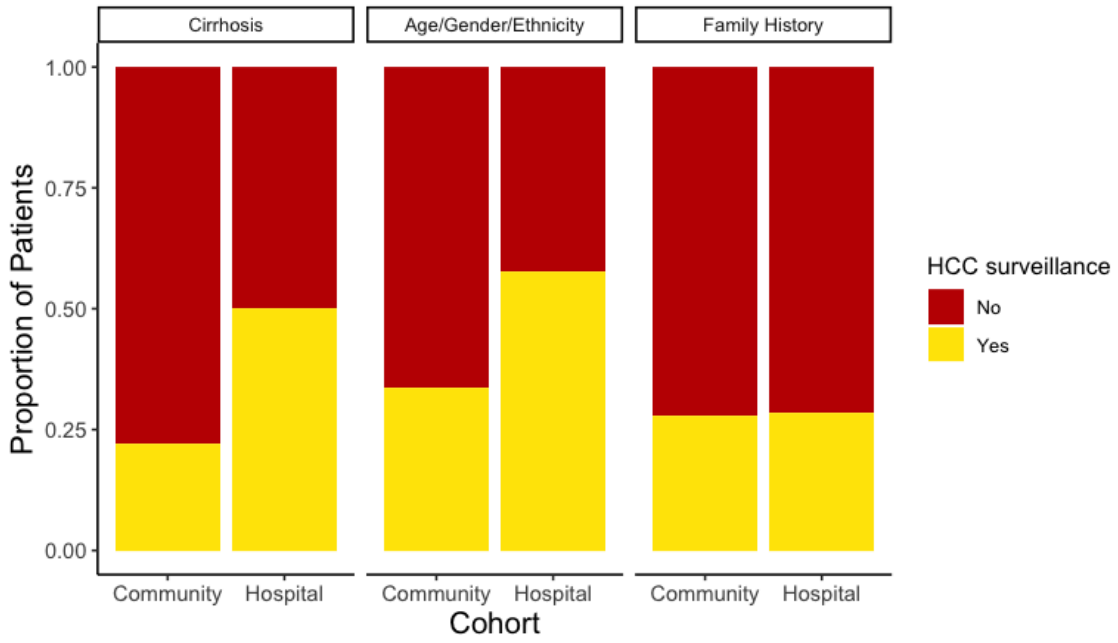
To summarise, retention rates in both cohorts within both CATCH and non-GP specialist attendance rates was variable. The hospital cohort was more adherent cohort with higher repeat attendance rates within CATCH and higher retention rates in non-GP specialist care. Reassuringly, patients with a high probability of cirrhosis had a high retention rate within non-GP specialist care within both cohorts.

5.3.1.3. Hepatocellular carcinoma surveillance

This section has focused on HCC surveillance rates in patients where HCC surveillance is recommended. All community cohort patients had a treatment plan provided to their GP; if HCC surveillance was required, a written recommendation for a six-monthly ultrasound was provided. Patients were assessed whether they had had an ultrasound within the preceding 12 months to capture most patients who were having surveillance and those who were clearly not having surveillance. This was assessed both at baseline and at time of last follow-up.

There were 183 patients in the community cohort and 48 patients in the hospital cohort who required HCC surveillance as presented in section 5.2.1.5. At baseline, the hospital cohort had a higher rate of HCC surveillance than the community cohort (52.1% versus 32.2%, $p = .01$). Predictors of having had HCC surveillance at baseline were assessed including age, gender, history of psychiatric diagnosis or IVDU, smoking history, at-risk alcohol intake, incarceration during the study period, cannabis use and socioeconomic disadvantage quintiles. None of these were significant in either cohort ($p > .05$ for all). There was also no difference in HCC surveillance rates between the indications for surveillance, in either cohort ($p > .05$). Figure 5-9 shows the rates of surveillance at baseline recruitment, grouped into the indication for surveillance and cohort.

Figure 5-9 Indications for and percentage with hepatocellular carcinoma surveillance at baseline in community and hospital cohorts



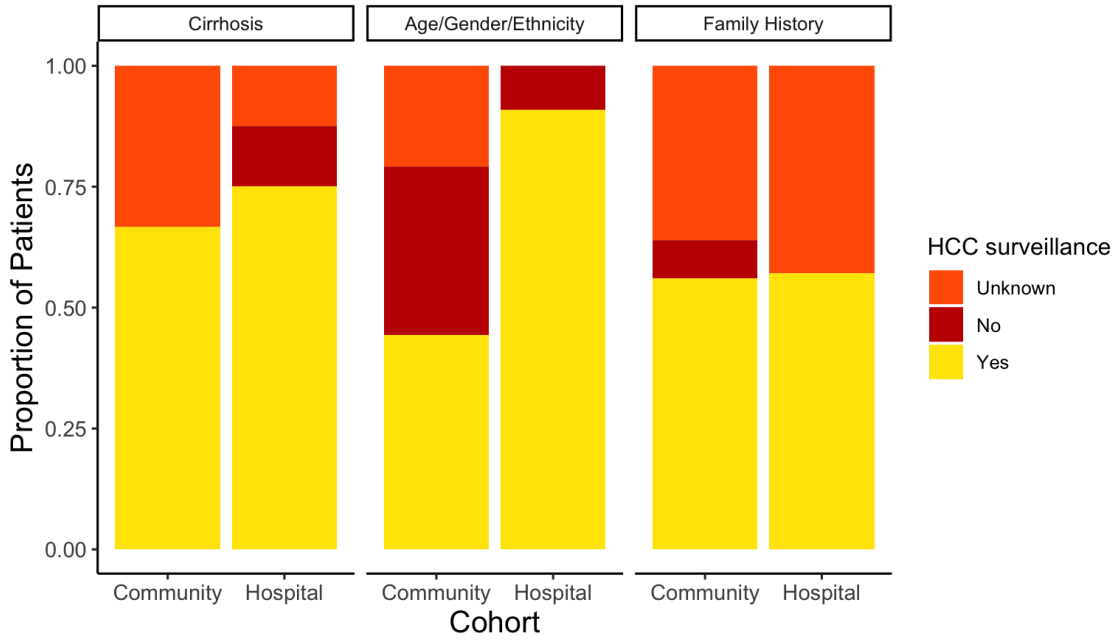
Cirrhosis: high probability of based on ultrasound and LSM assessment; Age/Gender/Ethnicity: as per Australian Guidelines [11]; Family history: of HCC; HCC: hepatocellular carcinoma

At time of last follow-up, some patients were lost to follow-up, where it is unknown if they had had HCC surveillance. These patients are excluded from the following analysis (lost to follow-up: community n=43, hospital n=4) leaving 140 patients in the community cohort and 44 in the hospital cohort included in the following analyses. These patients are excluded as some had moved interstate or between non-GP specialists so potentially some may have had ultrasound surveillance. An intention to treat analysis, where those lost to follow-up were assumed to have not had HCC surveillance is included within appendix 3.

At time of last follow-up/record review, the hospital cohort again had a higher rate of HCC surveillance than the community cohort (90.9% versus 61.4%, $p < .001$) with higher rates at time of last follow-up compared to baseline in both cohorts. Predictors of having had HCC surveillance at follow-up were assessed including age, gender, history of psychiatric diagnosis or IVDU, smoking history, at-risk alcohol intake, incarceration during the study period, cannabis use, socioeconomic disadvantage quintiles and having had HCC surveillance at baseline, in both cohorts. In the community cohort, there were different rates of HCC surveillance at follow-up based on indication: of those with a high probability of cirrhosis,

92.3% had HCC surveillance, compared to 90.0% in those with a family history of HCC and 63.6% where the indication was age/gender/ethnicity criteria (p = .009). Those with a smoking history had lower rates of HCC surveillance than non-smokers (25.0% versus 64.8%, p = .007). There was also a trend towards higher rates of having HCC surveillance at follow-up if performed at baseline: 72.0% of those who had HCC surveillance at baseline had HCC surveillance at follow-up compared to 55.6% of those who did not have HCC surveillance at baseline (p = .055). None of the other above listed variables were statistically significant (p > .05 for all). In the hospital cohort, none of the variables were associated with HCC surveillance (p > .05 for all), although history of IVDU was not assessed due to low numbers. Indications for HCC surveillance and percentage performed at follow-up by cohort is shown in Figure 5-10.

Figure 5-10 Indications for and percentage with hepatocellular carcinoma surveillance at last follow-up in community and hospital cohorts



Cirrhosis: high probability of based on ultrasound and LSM assessment; Age/Gender/Ethnicity: as per Australian Guidelines [11]; Family history of HCC

To determine whether retention in non-GP specialist care influenced HCC surveillance rates at time of last follow-up, those from the community cohort who were referred onwards were assessed (n=104). Retention in non-GP specialist care was associated with higher rates of HCC surveillance than those who were lost to follow-up (94.2% versus 39.4%, p < .001). In the

hospital cohort, retention in non-GP specialist care was also associated with higher rates of HCC surveillance than those who were lost to follow-up (100% versus 55.6%, p < .001).

To determine whether the indication for HCC surveillance, retention in non-GP specialist care or cohort were independently associated with HCC surveillance at follow-up in the community cohort, a binomial logistic regression was performed (p < .001, Table 5-11). Only retention in non-GP specialist care was associated with having HCC surveillance at follow-up.

Table 5-11 Regression analysis for predictors of hepatocellular carcinoma surveillance at follow-up

Predictors	Significance	Odds ratio	95% CI
Community Cohort	.1	0.34	(0.09, 1.38)
Retention in non-GP specialist care	**< .001**	**36.1**	**(9.12, 143.1)**
Indication:			
Cirrhosis	*reference	.1	(1,1)
Age/gender/ethnicity criteria	.8	1.3	(0.1, 15.3)
Family history of HCC	.3	7.1	(0.3, 192.4)

Bold: significant (p < .05 and 95% CI does not cross 1); CI: confidence interval; GP: general practitioner

To summarise, at baseline there were very few patients who are having appropriate HCC surveillance, although at time of last follow-up, rates had increased. There were consistently lower rates of HCC surveillance in the community cohort than the hospital cohort. Retention in non-GP management was associated with higher rates of HCC surveillance at follow-up.

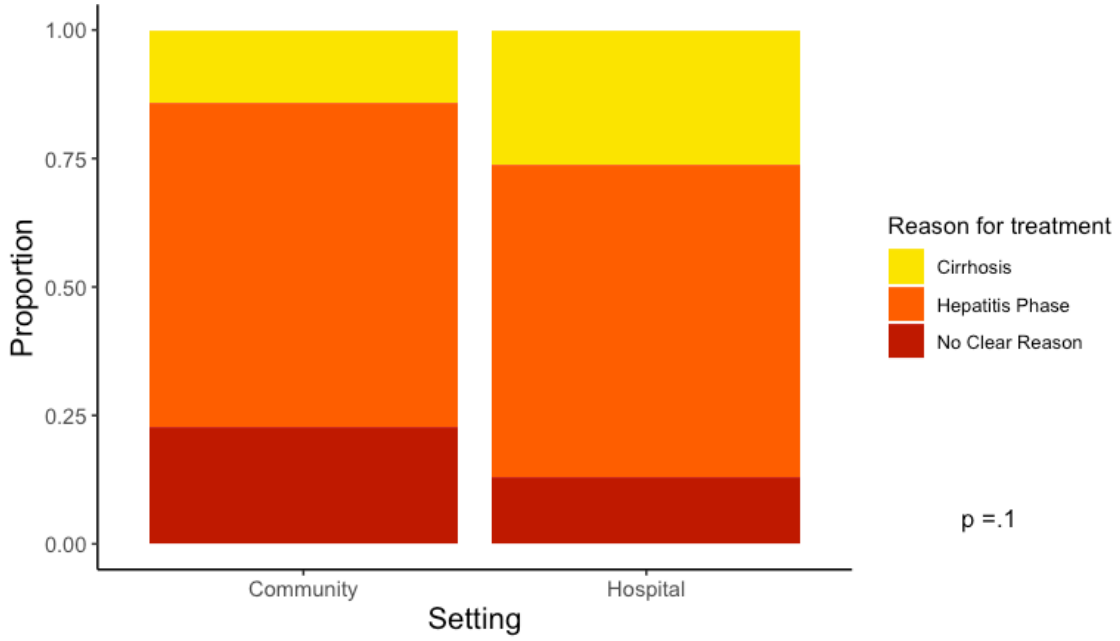
5.3.1.4. Antiviral therapy

To determine the indication for antiviral therapy, the phase of disease was determined at baseline and latest time of follow-up (pre-treatment). If a patient was in a hepatitis phase at either time point, then this was listed as the indication for treatment. The phase was determined using an ALT cut-off of 19IU/mL for women and 30IU/mL for men, as discussed in section 5.2.1.4. In patients where the treatment indication was unclear, it could be that they were in a hepatitis phase at another time point, however, this data was not collected. Factors associated with having antiviral therapy were not assessed as the numbers of patients treated was too low for meaningful statistical tests.

There were lower treatment rates in the community cohort at 11.4% (n=35) compared to 25.6% (n=23) of the hospital cohort (p < .001). In the community cohort, the reasons for treatment were phase of disease (62.9%); having a high probability of cirrhosis (14.3%); and

not having a clear indication for antiviral therapy (22.9%). In the hospital cohort, the reason for treatment included phase of disease (60.9%); having a high probability of cirrhosis (26.1%); and not having a clear indication for antiviral therapy (13.0%). None of the patients without a clear indication for treatment had a family history of HCC, in either cohort. The numbers in each of these indications were too low for meaningful statistical tests. This data is shown in Figure 5-11.

Figure 5-11 Reasons for antiviral therapy in community and hospital cohorts



Cirrhosis/Advanced Fibrosis: high probability of based on ultrasound and LSM assessment; HCC: hepatocellular carcinoma

In the community cohort, of the 9 patients with a high probability of cirrhosis, 55.6% (n=5) commenced antiviral therapy. Of the 69 patients in a hepatitis phase at baseline, 36.2% (n=25) commenced antiviral therapy. In the hospital cohort, of the 8 patients with a high probability of cirrhosis, 75.0% (n=6) commenced antiviral therapy. Of the 40 patients in a hepatitis phase at baseline, 45.0% (n=18) commenced antiviral therapy.

5.3.1.5. Liver-related outcomes

There was one liver-related outcome in in the CHB CATCH study. This patient was diagnosed with HCC; they were from the hospital cohort and had the diagnosis confirmed 3 months after recruitment into CATCH. They were stage BCLC-B at diagnosis and underwent DEB-TACE three times with PD followed by systemic therapy; they are still alive. No one else

with CHB developed HCC and there were no cases of liver decompensation or death due to liver disease.

5.3.2. Summary

The community cohort was a less adherent cohort overall, with lower repeat attendance rates within CATCH and retention in non-GP specialist care, lower HCC surveillance rates both at baseline and follow-up and lower treatment rates. Their main reason for not attending repeat appointments within CATCH was being uncontactable, with a higher rate of this occurring in the community cohort. HCC surveillance rates were consistently both at baseline and at time of last follow-up in the hospital compared to the community cohort, however, both cohorts' rates of HCC surveillance increased from baseline to time of last follow-up. The hospital cohort also had higher antiviral treatment rates than the community cohort. Although the community cohort had a lower adherence rates than the hospital cohort, there were high rates of retention in non-GP specialist care in those with cirrhosis and HCC surveillance rates increased after recruitment into CATCH. There was only one liver-related outcome in people living with CHB in this study.

5.4. Chapter Discussion

This chapter has shown that the prevalence of factors associated with morbidity and mortality were similar between the cohorts. The actual factors were different however: the hospital cohort had a higher percentage of patients with a high probability of cirrhosis and in a hepatitis phase, and the community cohort had a higher percentage who required HCC surveillance and were also from lower socioeconomic status. This chapter also showed that there was a lot of movement between phases highlighting the need for ongoing monitoring for CHB.

Secondly, the community cohort was consistently a less adherent cohort, however, a key finding is that patients at highest risk of complications (those with a high probability of cirrhosis) had high rates of adherence. HCC surveillance rates also increased in both cohorts after recruitment into CATCH. This chapter has also shown that patients are less likely to have HCC surveillance if they are not retained in non-GP specialist care. The implications for this are that to increase HCC surveillance rates, we either need to improve linkage into care or

change the way that HCC surveillance is performed. It has also highlighted that the community cohort of patients had much lower treatment rates, far below the Australian 2022 goal of 20%.

Chapter 6. Discussion and Conclusion

Australia has set a goal to decrease mortality by 65% for people living with CHB and CHC by 2030.[1, 2] This thesis set out to examine multiple factors that have an impact on morbidity and mortality for people living with CHB and/or CHC in Australia via a community assessment program. Previous characterisation of these factors has been limited by the methodological approaches of previous research.[13-19] Past studies have been performed in patients who are managed in a hospital setting, veterans or current PWID. Larger studies including a more varied population have been based on Medicare diagnosis and other linkage data, or only include patients who developed the outcome of interest. Other studies have been performed overseas with different health care systems and patient populations so generalisation of these results to an Australian population is complex. To overcome these limitations, any patient diagnosed with CHB or CHC were included and assessed in a community setting. This was performed via a community assessment program targeted at staging fibrosis in people living with CHB and/or CHC. Earlier results from the CATCH study showed that patients with CHC had similar rates of elevated LSM between the cohorts[7, 12] and patients with CHB had higher rates of elevated LSM in the community cohort compared to the hospital cohort.[7] The first aim of this thesis was to better clarify the prevalence of cirrhosis as estimated by LSM and ultrasound findings as well as indirect biomarker algorithms and viral hepatitis associated risks factors for morbidity and mortality. The second aim was to explore the rates of adherence: the percentage of patients retained in non-GP specialist care, who had appropriate HCC surveillance and who had appropriate antiviral therapy. The last aim was to determine the risk of liver-related outcomes. This community cohort of patients was compared to one of the current standards of care, being a hospital cohort of patients to determine differences between patient cohorts. The main findings from this thesis have shown that significant changes to the care pathways for people living with CHB and/or CHC are required to meet the Australian 2030 goals.

6.1. Key Findings

6.1.1. Factors associated with morbidity and mortality

The first main aim of this thesis was to clarify the incidence of cirrhosis in a community setting. It also aimed to determine the percentage with additional risk factors for development of fibrosis and non-liver-related morbidity and mortality, such as at-risk alcohol use, history of

IVDU or psychiatric diagnosis. In people living with CHC, the percentage with elevated LSM and/or ultrasound findings of cirrhosis was similar between the hospital and community cohort. The indirect biomarker algorithms were also very similar between the cohorts. The community cohort were younger and had higher rates of IVDU, history of psychiatric diagnosis and were from lower socioeconomic status. Associations with elevated LSM were also similar to previous studies. These findings are significant in that the CHC community cohort had more risk factors for morbidity and mortality than the CHC hospital cohort.

In people living with CHB, both cohorts had approximately 70% of patients with one of elevated LSM, being in a hepatitis phase or needing HCC surveillance. The actual factors associated with morbidity and mortality were different between the cohorts. The community cohort had lower rates of patients with a high probability of cirrhosis and in a hepatitis phase, but higher rates of patients requiring HCC surveillance. The community cohort was also from lower socioeconomic status. The hospital cohort, however, did have more patients with more than one risk factor. Based on these results, overall, the two cohorts' risk of liver-related outcomes and non-liver morbidity and mortality may be similar although this is hard to say definitively.

6.1.2. Adherence with medical management

The second main aim of this thesis was to determine adherence with medical management. The cascade of care for CHB and CHC are similar. First, patients need to be diagnosed, then linked into care and, if appropriate, treated. The current cascade of care and management aims have treatment as the end point and monitoring with blood tests as the measure for linkage into care. One concern is that HCC surveillance is a vital part of management for patients at risk of HCC, and current goals do not include this part of management within measurements of adherence.

The CHC community cohort were a consistently less adherent cohort than the hospital cohort. At the time of recruitment, there were higher FTA rates in the community cohort compared to the hospital cohort and the community cohort had lower repeat attendance rates within CATCH and higher rates of being uncontactable. In those with a high probability of cirrhosis, the community cohort also had lower rates of retention in non-GP specialist care. HCC surveillance rates were also consistently lower both at baseline and at follow-up in the community cohort. Retention in non-GP specialist care had a positive effect on HCC surveillance rates in both cohorts. Older age was also consistently associated with higher

adherence rates and those incarcerated were, not surprisingly, less likely to adhere to advice and interventions. Treatment rates were also lower in the community cohort than the hospital cohorts (84.1% versus 97.7% respectively). The CHC community cohort who were treated with DAAs were also less likely to be tested for SVR than those from the hospital cohort (71.5% versus 94.3%). SVR rates were similar between the cohorts when tested.

The CHB community cohort were also a consistently a less adherent cohort than the hospital cohort. These patients had lower repeat attendance rates in CATCH; higher rates of being uncontactable; lower rates of retention in non-GP specialist care; lower HCC surveillance rates at both baseline and follow-up; and lower treatment rates (11.4% versus 25.6%). One major finding, however, was that those who were diagnosed with a high probability of cirrhosis had high rates of HCC surveillance rates at time of follow-up, in both cohorts.

Another finding in both people living with CHB and/or CHC was that the rates of HCC surveillance were higher at follow-up compared to baseline in both cohorts.

These results have highlighted that significant gaps in patient care are occurring in all of the assessed aspects, especially in those patients from the community cohort.

6.1.3. Incidence of liver-related outcomes

There was one liver-related outcome in people living with CHB being an HCC in the hospital cohort. For people living with CHC, there were two main findings for this aim: the community cohort of patients had a lower rate of HCC diagnosis but the rates of a composite of liver-related outcomes was similar between the cohorts. Predictors of liver-related outcomes were very similar to previous studies, being older age, at-risk alcohol intake and higher BMI. LSM, APRI, FIB4, Forn's index and 4AGP were also able to predict liver-related outcomes, however, in this cohort, a cut-off of 4.2 for Forn's index was possibly too low to determine risk of liver-related outcomes.

Overall, the major findings of this thesis have shown that a CHC community cohort may have slightly higher risk of morbidity and mortality compared to a hospital cohort; and people living with CHB likely have a similar risk in both cohorts. The CHC community cohort had a similar prevalence of elevated LSM and ultrasound findings of cirrhosis compared to the hospital cohort. This was further supported by the finding that both cohorts had similar morbidity and mortality rates. This was an unexpected finding as the assumption at the CATCH study inception was that there would be a referral bias with patients with cirrhosis being

referred for hospital management. It was possibly underappreciated that there may be patient factors that impact the likelihood to engage in hospital-based management. This was also supported by the finding that the community cohort was a less adherent cohort, with the only factor independently associated with poor adherence being younger age. For people living with CHB, the assumption that there would be a referral was bias was correct with higher rates of elevated LSM in the hospital cohort, however, the community cohort did have a similar percentage of patients with rates of factors associated with morbidity and mortality 70%. The CHB community cohort were also overall a less adherent cohort than the hospital cohort.

6.2. Implications of the findings from this thesis

The baseline results have significant implications for health resource utilisation and highlight the need that further testing and management of patients in a community setting is required. Not diagnosing this population of people living with CHB and/or CHC with cirrhosis or other risk factors for liver disease may lead to lack of appropriate management and treatment and thus worse health outcomes. These findings also raise issues regarding patients not diagnosed or diagnosed but not linked into GP care, as the percentage of these patients with cirrhosis, at risk of HCC or in a hepatitis phase is unknown. One of the assumptions made when designing this study was that there would be a referral bias where patients with more advanced liver disease were referred for hospital outpatient management, however, this did not seem to be the case. This finding also has implications that previous research results may be able to be generalised to anyone with CHC, although the other significant differences between the cohorts need to be considered. This includes younger age, higher rates of IVDU and history of psychiatric diagnosis and lower socioeconomic status in the community cohort.

This thesis has also shown very similar predictors of elevated LSM as previous studies. In people living with CHC, increasing age, BMI, ALT, GGT, AFP and at-risk alcohol, and lower platelets, albumin and cholesterol were associated with elevated LSM. In people living with CHB, increasing BMI, ALT and GGT were associated with elevated LSM. Years of infection was not a predictor in people living with CHB. This could perhaps be due to memory/recall errors whereas age is a variable that doesn't rely on recall. Indirect biomarkers were also highly correlated with elevated LSM; 4AGP was designed to identify variables that predicted an

LSM≥12.5kPa using people living with CHC from CATCH so it would be expected for it to be highly correlated.

There were also multiple gaps occurring in patient care that have been identified in this thesis. Identification of patients at high risk of cirrhosis, retention in care, HCC surveillance, treatment and HCC diagnosis rates are far lower than ideal. Retention in non-GP specialist care was low, this is concerning as this was associated with lower rates of appropriate HCC surveillance. Although it was not measured, non-retention in non-GP specialist care may also have a negative impact on other aspects of liver disease management such as variceal surveillance which has clear morbidity and mortality benefits. In the CHC community cohort, those who were younger and had a history of IVDU were more likely to not attend, highlighting a group that could be targeted for further interventions to improve the medical care for these patients. This is a very heterogenous group of patients and keeping this population engaged in medical care can be difficult due to factors such as unstable accommodation, change of GPs and change phone numbers. One pitfall of this data is that the reasons patients were lost to follow-up from non-GP specialist care was not able to be captured. This warrants further research as clarifying the reasons will hopefully add insight into potential interventions to improve their attendance rates. Incarceration also, not surprisingly, had a negative impact on retention in non-GP specialist care. Although adherence was lower overall in the community cohorts of patients, at time of follow-up, HCC surveillance rates had increased in both cohorts suggesting CATCH may have had a beneficial effect. HCC surveillance improves outcomes so to improve health outcomes, these rates need to be increased. HCC surveillance rates at baseline were concerningly low in both cohorts, highlighting that prior to referral to CATCH or for hospital-based outpatient management, patients were not having appropriate surveillance. To improve surveillance rates, retention in non-GP specialist care needs to improve or another model of care with GPs or other community management options is required.

Viral treatment rates were also consistently lower in the community cohort of patients for both CHB and CHC. This is also a concern given Australia's goal to eradicate CHC and have 20% of people living with CHB on antiviral therapy. Given lower rates of retention in non-GP specialist care in the community cohort, this may have influenced treatment rates along with this cohort being a less adherent cohort. Another reason for lower treatment rates could be that patients are less likely to have treatment by their GP than if they were seeing a non-GP

specialist. GPs manage a very broad spectrum of diseases and for some patients, CHB and/or CHC may not be a priority for management, as opposed to those seeing a non-GP specialist who is only managing one aspect of their health care. There are other models of care for people living with CHB. There were no S100 prescribing GPs who also were CHB antiviral prescribers in this study. This may be due to there being less benefit for this type of program in GP clinics where patients potentially have already had a similar type of assessment. However, as discussed in chapter 2, Australia is behind its own targets for diagnosis and treatment for people living with CHB and/or CHC, and thus changes to current standard of care are required.

Testing for SVR is an important part of treatment for people living with CHC; those who were younger, treated by their GP and were part of the community cohort were less likely to have testing for SVR. Unfortunately, the data about whether the test had been requested was not available for analysis. There are likely multiple reasons that patients who had treatment by their GPs were less likely to have testing for SVR; patient factors, GP's factors and setting factors. Firstly, those treated by their GP's may represent a group of patients who may be less adherent as those treated by non-GP specialists have to attend hospital outpatient settings and thus are a group more engaged in their health care. Also, there was a higher percentage of patients treated by GPs in the community cohort, which has been shown to be a less adherent cohort with a younger population and higher rates of IVDU and psychiatric diagnoses. GPs also manage a broad spectrum of diseases and there are likely times when testing for SVR is not a health priority. There are also different systems in place for GPs and non-GP specialists: GPs may be seeing patients for other reasons and testing for SVR may be opportunistic, compared to those seeing non-GP specialists who will have an appointment made specifically for the results of SVR. Resourcing for primary care is also different. Most GP clinics do not have funding for nurses to call patients to have testing for SVR, whereas a hospital outpatient setting, where most patients would be seeing their non-GP specialist, most often have a hepatitis C nurses who will call patients. These system and patient differences will need to be addressed to increase rates of testing for SVR for patients treated in a community setting. There were high rates of SVR in those that had it tested; there weren't any definite predictors of DAA failures in this study aside from incomplete treatment course. There were not enough liver outcomes to assess whether treatment influenced liver outcomes, however, with future linkage data as discussed above this will be able to be assessed.

The CHC community cohort were also less likely to be diagnosed with HCC during the study period compared to the hospital cohort. This may be due to lower incidence; however, it is more likely that the incidence is similar, but the diagnosis rates were lower. There were much lower rates of retention in non-GP specialist care and HCC surveillance in the community cohort making the probability of low diagnosis the more likely explanation. The composite of liver-related outcome rates was similar between the cohort, which also highlights the clinical need for patients from the community cohort to be linked into care and have a liver fibrosis assessment. These are both very concerning findings, and further research with data linkage at 10 years will be performed to address this further.

4AGP has been shown to potentially be an alternative measure to predict risk of outcomes for people living with CHC prior to commencing treatment; it comprises of standard demographic data and pathology test results so is readily available. It was however, developed to predict those with an LSM >/= 12.5kPa within CATCH people living with CHC and although it has now also been shown to be able to predict liver-related outcomes it needs to be validated with another cohort of patients before being used in clinical practice.

CATCH as a new model of care is likely to have benefit for patients. Firstly, it was able to determine patients' risk of cirrhosis. Diagnosis of cirrhosis has previously been shown to improve clinical outcomes by behaviour change and treatment of the underlying condition.[66] Secondly, it facilitated referrals onwards for non-GP specialist care and, although the community cohort was, as a whole, a less adherent cohort, those at highest risk of complications (those with a high probability of cirrhosis) had high rates retention in non GP specialist care. Thirdly, rates of HCC surveillance also consistently increased from recruitment to time of last follow-up. There may also have been other unmeasured beneficial effects: behaviour change, for example decreased alcohol intake after diagnosis of cirrhosis, GP confidence in treatment of patients and perhaps DAA treatment rates in a community setting with the structured management plan provided. Another implication from this study is that changes to the models of care are required, perhaps with more access to community based ongoing management for patients even if they are higher risk for liver-related outcomes.

6.3. Limitations

There were limitations with the CATCH study. There was likely bias in which GP practices participated in CATCH. There were five patient recruitment bias issues that may have affected some of the results of this study. First, for both cohorts, patients had to be linked into care to be referred to the CATCH program. Those who were not referred for hospital outpatient management, those who were not being managed by a GP who was involved in the study and those unaware of or not diagnosed with CHB and/or CHC would not have been included. Second, the hospital cohort of patients may have been a more adherent cohort from the method of their recruitment. GP's may not have referred patients for hospital outpatient management when they knew there was a high chance the patient will not attend. Also, for a hospital cohort patient to be recruited, the patient had to attend a hospital site for CATCH assessment. Third, in the community cohort, there may have been bias with which GP clinics opted to take part in CATCH. The clinics with higher case load of people living with CHB and CHC who opted to participate may be fundamentally different to other GP clinics, for example opiate replacement therapy clinics and clinics with interests in managing refugee health. This may lead to overestimation in the percentage of patients from the community cohort with a history of IVDU as the risk factor for viral hepatitis or from areas with higher levels of socioeconomic disadvantage for example. However, recruitment locations were varied with clinics that had both high and low viral hepatitis caseloads and opiate replacement therapy prescriber clinics and non-opiate prescriber clinics. This would have hopefully minimised this bias. Fourth, in the community cohort, there may also have been bias in which patients were referred to be part of CATCH. We relied on GPs to identify, discuss with and then refer the patient to the study. There will be occasions where GPs are not aware of the patient's CHB and/or CHC diagnosis. There may also have been a bias where some patients did not have the study discussed with them. Appointment structure timing can lead to time constraints, as there may have been limited time for the referring GP to be able to discuss the study with the patient and obtain consent for passing their information along, in a standard consultation whilst addressing other issues. Patients who refused to participate or who failed to attend will also potentially contribute to a recruitment bias. Unfortunately, data regarding refusal to have information passed along by their GP was not collected, data was only collected regarding refusal once the study was discussed with the patient by one of the study doctors. Lastly, the referral process for GPs was unlikely to be a limitation as the referral process was made as simple as possible

to ensure that if patients agreed, there was minimal work for the GPs or the clinics to refer the patient to the study. Also, potential incentives with a structured management plan and facilitated referrals onwards if required would have minimised this limitation. Fifth, the hospital cohort may have been a cohort of patients who were referred due to their GP having concerns about their liver disease, for example cirrhosis on imaging. However, the community CHC cohort had a similar proportion of people with cirrhosis on imaging compared to the CHC hospital cohort. Although the rates of cirrhosis on imaging were slightly higher in the CHB hospital cohort than the community cohort, the numbers were too low to draw any conclusions. The CHB hospital cohort did have a higher hepatitis B viral load and higher rates of patients in a hepatitis phase than the CHB community cohort. Some of these limitations may warrant further research to determine whether GPs were referring patients based on the patient's likelihood to attend or other factors. Even though there are likely to be recruitment biases, these were unlikely to significantly affect the study results. First, the aim of this study was for patients already diagnosed to be assessed, not to increase diagnosis rates. Second, some of the aims within the study was to compare the standard of care (hospital cohort) with the new model of care (community cohort) and determine differences in patient characteristics, results, adherence and outcomes. Lastly, although the responsibility of identification of patients and discussing with patients was placed on GPs, a significant number of patients were recruited. Future studies or even implementation of a management program for viral hepatitis could be performed in a different way, perhaps with linkage data to invite diagnosed patients to participate, similar to the NBCSP.

Patient recruitment bias was also minimised by recruiting patients sequentially, inviting many clinics to participate and by recruiting from a hospital cohort that included multiple sites around Eastern and outer Eastern Melbourne. We also gave patients multiple opportunities to attend and tried to maximise attendance rates by the methods discussed in section 3.1.5. One of the strengths of this study, however, is that participation was offered to all people living with chronic viral hepatitis rather than specific groups which previous studies have done, such as patients who currently use drugs, veterans or those who are managed in a hospital outpatient setting.

6.4. Future research

The CATCH study has multiple planned analyses and this thesis itself has findings that also warrant further research. Some of the planned future research will be to directly improve adherence and some is related to other aspects of testing and management for people living with viral hepatitis.

6.4.1. Linkage data

The CATCH study included consent for data linkage to registries including cancer registries, hospital admission and discharge data as well as the Australian Registry of Birth, Deaths and Marriages. This is planned to be performed at 10 years post the last recruitment date. This will answer multiple questions including whether the lower rate of HCC diagnosis seen in the community cohort is due to true lower rates, or a lack of surveillance and thus diagnosis. It may also address whether a community management program of this sort will lead to earlier HCC diagnosis rates by comparing with cancer databases and historical cases. One of the findings from this thesis was the number of patients who were lost to follow-up. Although it is a limitation, it is also itself a significant finding. The lost to follow-up rates were minimised as much as possible via multiple methods: contacting the patients in multiple different ways including text, phone call, mailed messages and contact by the GP clinics themselves. Patient record reviews were also performed within GP clinics and hospitals and pathology results from private providers were also reviewed. Future linkage studies will hopefully negate this limitation and determine what has happened to these patients which may provide information regarding reasons for being lost to follow-up.

6.4.2. Repeated measures

The CATCH study also has data for repeated LSM assessments, pathology and serum samples at multiple time points. This data was not presented in this thesis as there were not enough liver-related outcomes for meaningful data analysis in those who had repeated measures. However, 10-year linkage data will likely find more liver-related outcomes so this data will be able to be analysed in a more meaningful way. This research will assess whether baseline LSM, LSM at 1 year or change in LSM best predicts liver-related outcomes. It will also look at whether the repeat LSM was performed prior to antiviral treatment or after antiviral treatment was commenced to determine which timepoint best predicts liver-related outcomes.

6.4.3. Serum samples

The CATCH study has also collected serum samples from patients each time they were assessed by CATCH. These frozen samples will be used in future research examining markers of fibrosis and liver regeneration. This will include comparing these samples to LSM but will also determine whether any markers can predict the development of HCC or other liver-related outcomes.

6.4.4. 4AGP

4AGP was developed as part of another aspect of the CATCH study and needs validation studies with another cohort of people living with CHB and/or CHC to determine its clinical utility.

6.4.5. Improving adherence – retention in care

This thesis has shown issues with adherence, especially in the community cohorts of patients. First, the reasons for non-adherence for each of these need to be explored further to determine if patient, doctor or system issues or a combination of all of these are driving this. Further information can be obtained by patient and doctor questionnaires and patient record reviews to identify the specific barriers and reasons for poor adherence. In depth case reviews for those who were not retained in non-GP specialist care can be performed to determine if a clinical reason, such as determining cirrhosis is unlikely, is the cause of non-retention. Previous studies have shown that patient factors include having other health priorities,[330, 405] finding attendance too hard[405]or costly[330] or a lack of knowledge.[320-322] Doctor factors may include having other health priorities for the patient, appointment timing structure constraints or knowledge. System factors may include patients not being notified of appointments, physical distance,[329-331] parking [329-331] and other transport issues[329-331] and recall systems. We have shown that one major factor for being lost to follow-up within CATCH was being uncontactable so other novel ways of contacting patients could also be assessed. Studies have found positive results with retention in studies using social media. One study of patients aged 16-24 years where they were monitored for sexually transmitted diseases study found retention in the study was improved by using social media (Facebook®).[448] Another study assessing men who have sex with men found increased rates of retention in an HIV study using social media.[449] There are ethical and privacy issues surrounding use of social media in health research which would need to be addressed. Financial incentives have also been shown to

increase engagement in care[14] and could be used to improve retention in research studies. Retention is care is complex but certainly more research regarding reasons and methods to improve it is required.

6.4.6. Improving adherence – hepatocellular carcinoma surveillance

This thesis has shown HCC surveillance rates were far below ideal especially at baseline and in the community cohort. First, further studies are required to determine the extent of the problem. This could be done with linkage data for patients diagnosed with CHB and Medicare billings for abdominal ultrasound based on age/gender criteria although ethnicity criteria may be more complex. Second, a national measure for HCC surveillance rates within the National Hepatitis B and C strategies should be considered. Third, assessing methods to increase rates of surveillance would assist in determining the best methods to implement to increase rates. These could include funded nursing support in high case load clinics, online patient centred management systems and change in recall systems for GPs. A previous study in a single Aboriginal rural health service found that although recall systems, nursing support and patient reminder systems increased surveillance rates in people living with CHB, these rates were still poor (10% at baseline and 56% after intervention).[299] Clearly, the issues are multifactorial and multiple changes need to be made.

6.4.7. Cost-benefit study

As discussed in section 6.2, expansion of a community management program such as CATCH would be complex. A cost-benefit analysis using data from this thesis using risk factors for morbidity and mortality and cost for the program should be performed to determine whether expansion is warranted and where the economy of scale for benefit is. To implement a program such as CATCH as standard of care would face significant challenges. To extend the program to assess patients from remote and regional areas would not be simple: an economy of scale and cost effectiveness would need to be performed to determine the benefit and time required to assess patients in this way and in rural and remote settings.

6.5. Conclusion

In conclusion, the work presented in this thesis has identified that a CHB and/or CHC community cohort of patients have significant rates of factors associated with morbidity and

mortality compared to a hospital cohort. People living with CHC had similar rates of elevated LSM and ultrasound findings of cirrhosis in a community and hospital cohort. People living with CHB had higher rates of elevated LSM and ultrasound findings of cirrhosis in a hospital cohort compared to the community cohort, however, the community cohort had a similar percentage of patients with one of elevated LSM/ultrasound findings of cirrhosis, in a treatment or needing HCC surveillance to the hospital cohort. This highlights a significant gap in care with a large population of patients being underdiagnosed and thus not having appropriate management and treatment. This thesis has also highlighted significant gaps in patient care with potential negative health outcomes. The community cohorts were a consistently less adherent cohort. Rates of retention in non-GP specialist care, HCC surveillance and treatment were lower in the community cohorts, and lack of retention in non-GP specialist care was associated with lower rates of HCC surveillance. The CHC community cohort also had lower rates of HCC diagnosis than the hospital cohort which is likely due to lack of diagnosis rather than true lower rates. HCC surveillance goals should also be included within the National Strategies for CHB and CHC.

Community management of patients' needs to be explored further with multi-pronged changes to the models of care for people living with CHB and/or CHC in Australia, including diagnosis, treatment, management and appropriate HCC surveillance. More extensive government support is needed to meet the goal of elimination of CHB and CHC as public health threats by 2030.[1, 2]

Chapter 7. Appendix

1. Patient information and consent form

easternhealth
GREAT HEALTH AND WELLBEING

Participant Information Sheet/Consent Form

Non-Interventional Study - *Adult providing own consent*

Eastern Health - Box Hill Hospital

Title	Community Approach Targeting Cirrhosis & Hepatocellular Carcinoma
Short Title	CATCH
Protocol Number	[Version 3]
Project Sponsor	Victorian Cancer Council
Coordinating Principal Investigator/ Principal Investigator	Dr. John Lubel
Associate Investigator(s)	Dr. William Kemp Dr. Stephen Bloom Dr. Diana Lewis
Location	Eastern Health / Alfred Health

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1. Introduction

You are being invited to take part in a research study. You are invited to take part because you have Hepatitis B and/or Hepatitis C and are not currently undergoing regular review at a hospital-based liver clinic.

This information and consent form has information to help you decide if you want to participate. Take your time, read this form carefully, and ask the study doctor or staff any questions you may have. You should not sign this form until you understand all of the information presented in the following pages and until all of your questions about the research have been answered to your satisfaction.

Eastern Health has received a research grant from the Victorian Cancer Council to allow this study to be performed. Participation in this research is voluntary. If you don't wish to take part, you don't have to.

If you decide you want to take part in the research project, you may be asked to sign the consent section. By signing it you are telling us that you:

- understand what you have read;
- consent to take part in the research project;
- consent to be involved in the procedures described;
- consent to the use of your personal and health information as described.

You may decide to change your mind at any time during the study. You may leave the study at any time, even if you have signed this form. You do not have to give a reason.

You will be given a copy of this Participant Information and Consent Form to keep.

About this study

Scarring of the liver can occur silently without any physical signs. This scarring can occur as a result of various liver conditions including hepatitis B and C. In some individuals the scarring becomes very extensive. This is called cirrhosis. When this occurs, the risk of medical problems including liver cancer increase substantially. This project is about identifying those individuals who have either cirrhosis or severe scarring and providing them with access to appropriate treatment and follow-up.

Worldwide, primary liver cancer (hepatocellular carcinoma - HCC) is the fifth most common cancer in men and seventh in women. Eighty percent of cases develop in the presence of cirrhosis and if found early, this cancer may be curable. It is currently recommended that high-risk patient and individuals with cirrhosis undergo regular screening with ultrasound every 6 months to increase early detection. However, cirrhosis can be unrecognised and it is possible that only a small portion of patients at risk are being screened effectively.

Through the process of scarring, the liver becomes increasingly stiff. In some cases this can be detected on physical examination but in many cases there are no physical signs. Transient elastography is a method of measuring the stiffness or hardness of the liver and is performed by a device called FibroScan®. This device has been approved by the Australian Therapeutic Goods Administration (TGA) for this use. The measurement is painless, quick and reproducible. It uses ultrasound to measures the speed of a vibration (shear wave) through the liver. This measurement can predict the degree of scarring of the liver and detect cirrhosis. This measurement is currently used in hospitals throughout the world for the management of people with liver disease. It can identify those who may develop complications secondary to liver scarring and help prioritise treatment where appropriate.

This study is a cohort study that will take place throughout Melbourne. The study will follow a group of individuals with hepatitis B and/or C over time to determine whether this measurement can increase the detection of cirrhosis and hepatocellular carcinoma. It will attempt to assess 2000 individuals. The purpose of this study is to:

1. Determine whether screening in the community with transient elastography can increase the early detection of advanced liver scarring and cirrhosis
2. Determine whether early detection of cirrhosis improves detection and management of hepatocellular carcinoma
3. Assess community-based treatment practices of viral hepatitis
4. Provide timely preventative health education and early implementation of risk reduction strategies for patients without immediate risk of hepatocellular carcinoma (such as Hepatitis C and hepatitis B treatment, alcohol reduction and weight reduction)

There may be reason that you are not allowed to take part in this study

- Age under 18
- Age over 80
- Inability to provide informed consent
- You are pregnant
- Formal involvement with hospital hepatology unit in the last 18 months
- Formal involvement with private gastroenterologist or Hepatologist in the last 18 months
- Prior transient elastography in the last 18months
- Current or prior diagnosis of hepatocellular carcinoma

The results from this research will be used by Dr. Stephen Bloom and Dr. Diana Lewis (Eastern Health, Melbourne) to obtain PhD degrees.

This research has been funded by Victorian Cancer Council

What will I be asked to do?

If you take part in this study, you will be asked to visit either your local medical service or a nearby community health centre. If you decide to participate in this research project, the study doctor will inform your local doctor.

Prior to your review you will be requested to:

- Fast for at least 2 hours as this improves the accuracy of the test
- Complete a questionnaire regarding your medical history
- Take your regular medications as prescribed.

During this visit your study doctor will:

- Take a medical history
- Collect routine blood specimens from you to assess the health of your liver
- Collect blood for hepatitis C or hepatitis B viral counts and for sequencing the genotype of the virus.
- Collect vital signs including blood pressure, heart rate, weight, height and waist circumference
- Perform a clinical examination to assess for signs of liver disease

- Perform an assessment of liver stiffness, Transient Elastography (TE) via FibroScan®
- Residual blood that would normally be discarded will be stored for further analysis pending funding. These tests include your IL28B genotype that may affect how individuals respond to treatment. Your DNA will be taken from your blood, and a test will be done to find out your IL28B gene status. These results are for research only. Since these tests are exploratory research only, they will have no clear implications about you or your family medical conditions.

This initial evaluation will take between 20 to 30 minutes. Following this consultation you and your primary care physician will be given a copy of your FibroScan report. Following the processing of your blood samples, a full management plan will be delivered to your primary care physician regarding future management of your liver disease.

During your participation in this study, you may be found to have significant liver fibrosis or cirrhosis. As a result of this you may require further evaluation and ongoing monitoring by a gastroenterology or hepatology unit. This would be done at the discretion of your primary care provider. Specialist referral information will be provided to your primary care provider.

Further investigations would be at discretion of you specialist and not directed by the study group. These investigations may include a liver biopsy and repeat fibroscan to determine whether you have cirrhosis. If required we may quest your permission to use this information in the study.

If you are determined to be at high risk of developing hepatocellular carcinoma according to existing management guidelines, it will be recommended that you enter a screening program consisting of liver ultrasound and blood testing on a 6-monthly basis. This can either occur through your primary care physician or through a gastroenterologist/hepatologist.

This study will request that we can contact either yourself or your primary care physician in the future to monitor your ongoing management and screening. This follow-up would be indefinite unless you otherwise withdrawal consent. This study also requests that we can contact registries of cancer, birth, death and marriages to identify the development of hepatocellular carcinoma, liver-related hospitalization and death in the study group in the future.

What effects could the tests have on me?

You may feel discomfort during some of these tests or may experience some inconveniences. Some procedures may also have risks, which may include:

- **Blood Samples**: drawing blood from your arm may cause discomfort, bruising, light-headedness and, rarely, infection.

- **FibroScan®**: FibroScan is a non-invasive procedure to assess liver stiffness (liver elasticity) using a specialised machine. This result is immediate and it shows the extent of fibrosis caused by the liver disease. This will assist the doctor to diagnose the amount of liver fibrosis or hardening of the liver. FibroScan examination is painless. During the measurement, you may feel a slight vibration from the tip of the probe which is placed on your skin. This test will carried out at either your place of primary care (general practitioners practice) or at a community health care center. To carry out the tests, you will be asked to lie on your back with the right arm positioned behind your head and be required to expose the skin area around your abdomen. The doctor or technician will apply some gel onto the skin and will place the probe in between your ribs on the right side where the liver is situated. The examination includes a minimum of 10 consecutive measurements made at the same location and this will take 10-15 minutes. Occasionally the measurement is repeated a few more times over other locations in your liver in order to get an accurate assessment. In about 10% of individuals a measurement either cannot be obtained or the quality of the measurement is poor. In this circumstance, you will be offered the option to attend a FibroScan® clinic which has a different sized probe. In some instances the only way of accurately determining the extent of scarring is through a liver biopsy.

Are there any pregnancy risks?

Currently the manufacturer of FibroScan® do not recommend its use in pregnant women. This recommendation is based on limited safety data and uncertainty regarding the effects of pregnancy on results of the test. The

FibroScan® uses ultrasound to measure stiffness and pregnant women have ultrasound examination as part of their routine antenatal care. However, if you are or may be pregnant please inform the study doctor.

What will happen to my test samples?

Blood samples will be taken as part of this research project. Specimens will be stored in a coded manner so that your privacy is maintained at all times. We are also asking your permission to store excess blood that is usually discarded for possible future research into other non-genetic markers that are involved in predicting the development of hepatocellular carcinoma and cirrhosis. This part of the study is optional and will not affect the rest of this study.

How will my privacy be protected?

Information of a personal and medical nature collected about you will be kept confidential. Samples and information will be coded and stored without any of your personal information. The code will allow researchers to link the participant to their clinical record. Samples will be stored in a locked laboratory and clinical records will be stored digitally on a secure database. Only the researchers involved in this study will have access to this information and it will not be used for commercial purposes.

Results from the research project will be used to write articles in medical journals, may be presented at relevant medical conference and will be used by the researcher, Dr Stephen Bloom to obtain a PhD degree. The data presented will be the results of group analyses and no personal or identifying information will be used.

This is a research project and we may find new information about you. This information will be shared immediately with you and your treating doctor if it is critical or important to your health. This information and information regarding your participation may be recorded in your health records.

Information obtained from this study that is not helpful to you and your doctor in managing your healthcare (as is often seen with research) will not be given to you, your family, your employer or anyone involved in your healthcare management.

In accordance with relevant Australian and/or Victorian State privacy and other relevant laws, you have the right to request access to the information collected and stored by the research team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the research team member named at the end of this document if you would like to access your information.

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project.

What benefits could there be from taking part in the study?

This assessment will improve the management of liver disease. It may indicate that you need treatment for your underlying liver disease and improve your health. It will increase the knowledge of your primary care provider regarding your health and management of viral liver disease. Information learned from the study may help other people in the future.

Will I be paid for participating in the study?

You will not be paid for your participation in the study.

Will there be any charge for me to be in this study?

The majority of the tests performed in this study are part of standard care and will be billed in the usual way. Any costs associated with extra procedures will be covered by the researchers.

What are my options if I am not in the study?

Should you decide not to participate in the study, your primary care provider can recommend ongoing evaluation of your liver disease. This can either be carried out via your primary care provider or through specialist involvement.

All assessments being carried out in this study are currently available via metropolitan hospital centers. You do not need to participate in this study to have your liver disease assessed.

Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Eastern Health – Box Hill Hospital or your primary care provider.

What happens when the research project ends?

Participation in this study may improve you long-term medical management. Upon completion of your participation, all ongoing medical treatment will be organised by your primary care physician. If your require specialist input, referral information to tertiary liver centers will be provided to you primary care provider. All information gathered from this study will be available to primary care provider and yourself on request through the freedom of information act.

What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law.

Who is organising and funding the research?

This research project is being organised by Dr John Lubel at Eastern Health, Melbourne and Dr William Kemp at the Alfred Hospital, Melbourne.

This research project is an investigator-initiated study being conducted by Eastern Health Melbourne. The study is partially supported through a grant from the Victorian Cancer Council.

Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Eastern Health, Melbourne.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

For further information or appointments:
If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the *Dr John Lubel*, on *9094 9548* or any of the following people:

Clinical Contact Person

Name Dr. Stephen Bloom

Position Study Investigator
Telephone 90949532
Email stephen.bloom@monash.edu

Complaints:

For matters relating to research at the site at which you are participating, the details of local site complaints person:

The Manager - Office of Research and Ethics - Eastern Health: 9895 3398

Research Participant Rights:

If you have any questions about your rights as a research participant, then you may contact the Executive Officer Research at Eastern Health on Telephone: 9895 3398

Consent Form

Title	Community Approach Targeting Cirrhosis & Hepatocellular Carcinoma
Short Title	CATCH
Protocol Number	Version 3
Project Sponsor	Victorian Cancer Council
Coordinating Principal Investigator/ Principal Investigator	Dr. John Lubel
Associate Investigator(s)	Dr. William Kemp Dr. Stephen Bloom Dr. Diana Lewis
Location	Eastern Health - Box Hill

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the project without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Eastern Health concerning my condition and treatment for the purposes of this project. I understand that such information will remain confidential.

I understand that, if I decide to discontinue the research project treatment, I may be asked to attend follow-up visits to allow collection of information regarding my health status. Alternatively, a member of the research team may request my permission to obtain access to my medical records for collection of follow-up information for the purposes of research and analysis. I understand that information may be gathered from governmental registries for assessment of significant outcomes; death, hospitalization or development of malignancy.

Yes / No (circle one) – I agree to a sample being stored for this research project only; genetic testing related to this research; other closely related research; any further research

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is <u>not</u> to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may <u>not</u> act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher†(please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I consent to the storage and use of blood and tissue samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

* Witness is <u>not</u> to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may <u>not</u> act as a witness to the consent process. Witness must be 18 years or older.

Name of Study Doctor/
Senior Researcher†(please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation

Title	Community Approach Targeting Cirrhosis & Hepatocellular Carcinoma
Short Title	CATCH
Protocol Number	Version 3
Project Sponsor	Victorian Cancer Council
Coordinating Principal Investigator/ Principal Investigator	Dr. John Lubel
Associate Investigator(s)	Dr. William Kemp Dr. Stephen Bloom Dr. Diana Lewis
Location	Eastern Health - Box Hill

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Eastern Health.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

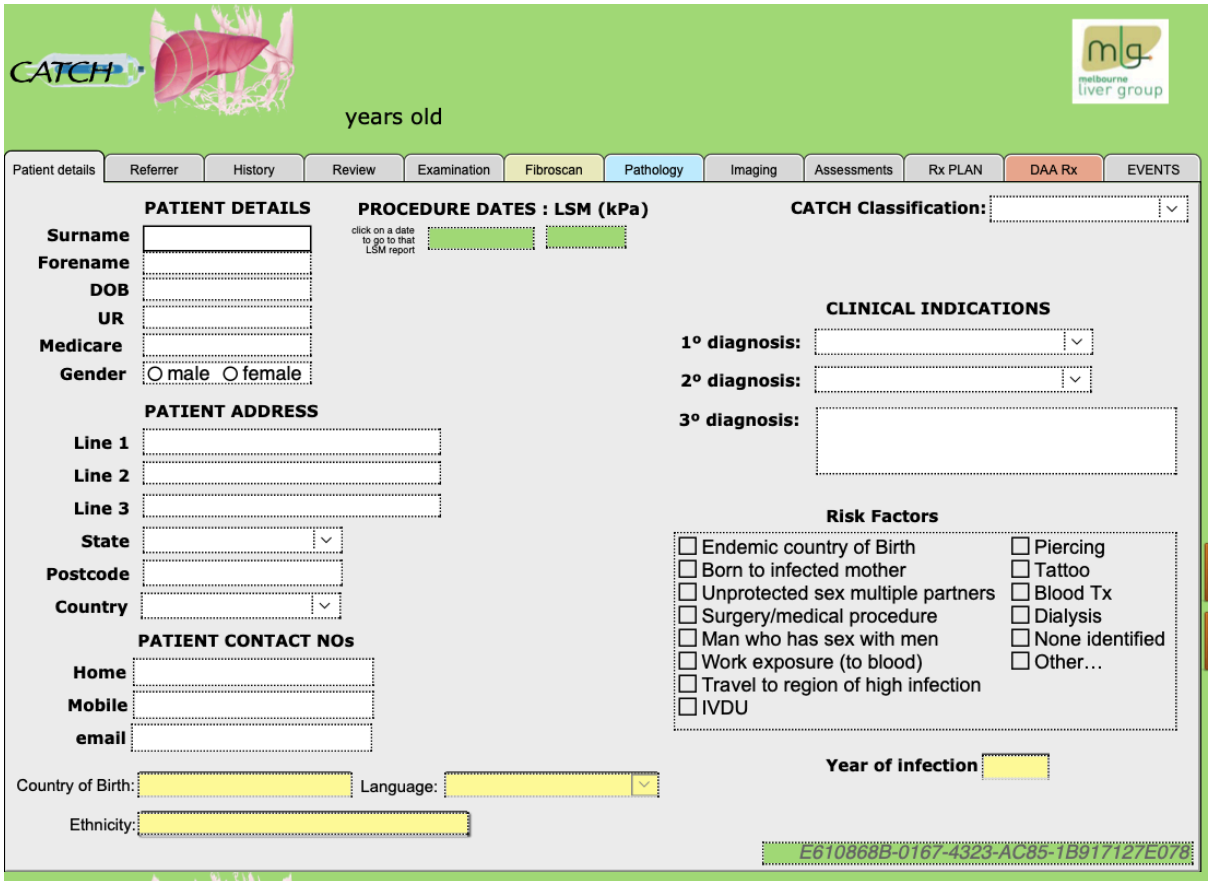
Name of Study Doctor/
Senior Researcher†(please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

2. Filemaker® Database images


CATCH
years old
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Patient details
Referrer
History
Review
Examination
Fibroscan
Pathology
Imaging
Assessments
Rx PLAN
DAA Rx
EVENTS
PATIENT DETAILS
Surname
Forename
DOB
UR
Medicare
Gender
male
female
PROCEDURE DATES : LSM (kPa)
click on a date to go to that LSM report
CATCH Classification:
CLINICAL INDICATIONS
1º diagnosis:
2º diagnosis:
3º diagnosis:
PATIENT ADDRESS
Line 1
Line 2
Line 3
State
Postcode
Country
Risk Factors
Endemic country of Birth
Born to infected mother
Unprotected sex multiple partners
Surgery/medical procedure
Man who has sex with men
Work exposure (to blood)
Travel to region of high infection
IVDU
Piercing
Tattoo
Blood Tx
Dialysis
None identified
Other…
PATIENT CONTACT NOs
Home
Mobile
email
Year of infection
Country of Birth:
Language:
Ethnicity:
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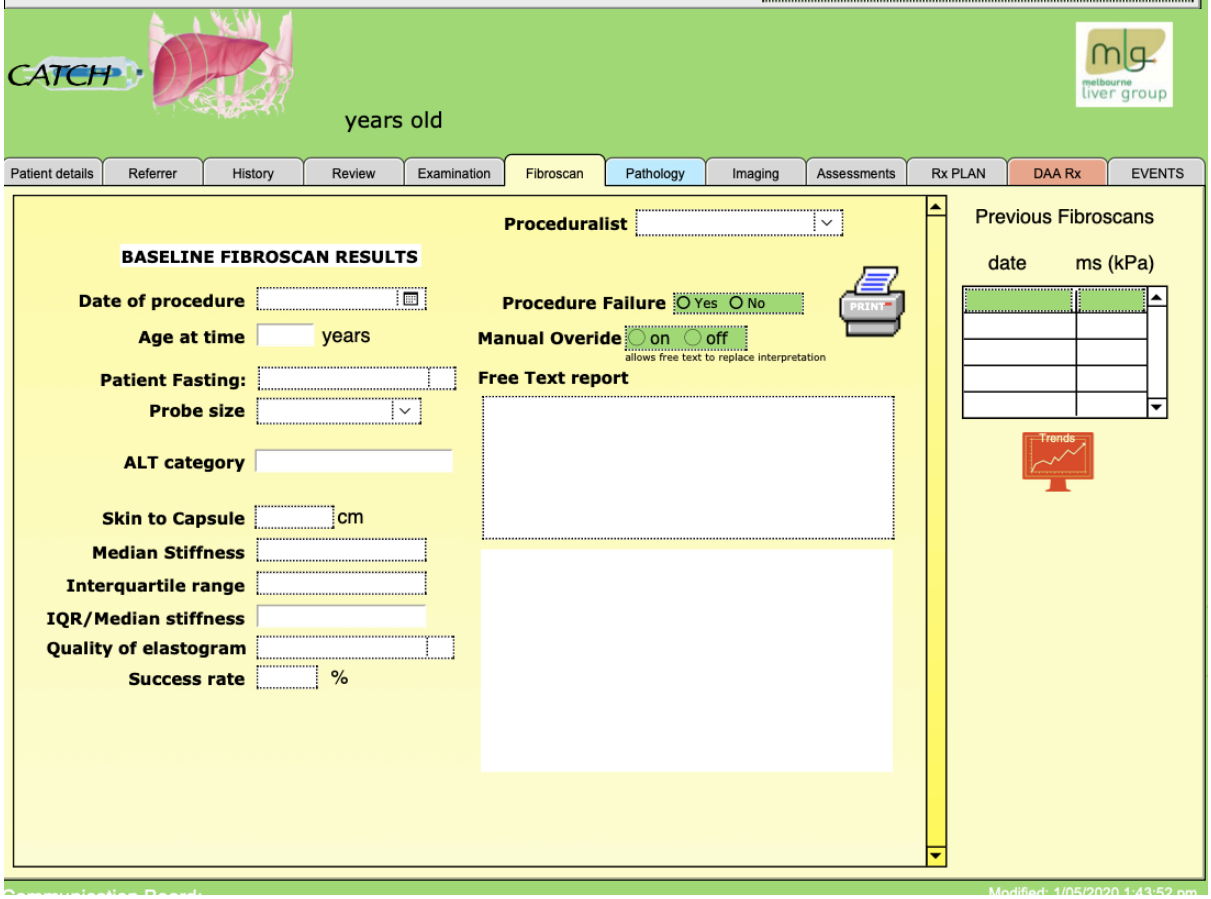
CATCH
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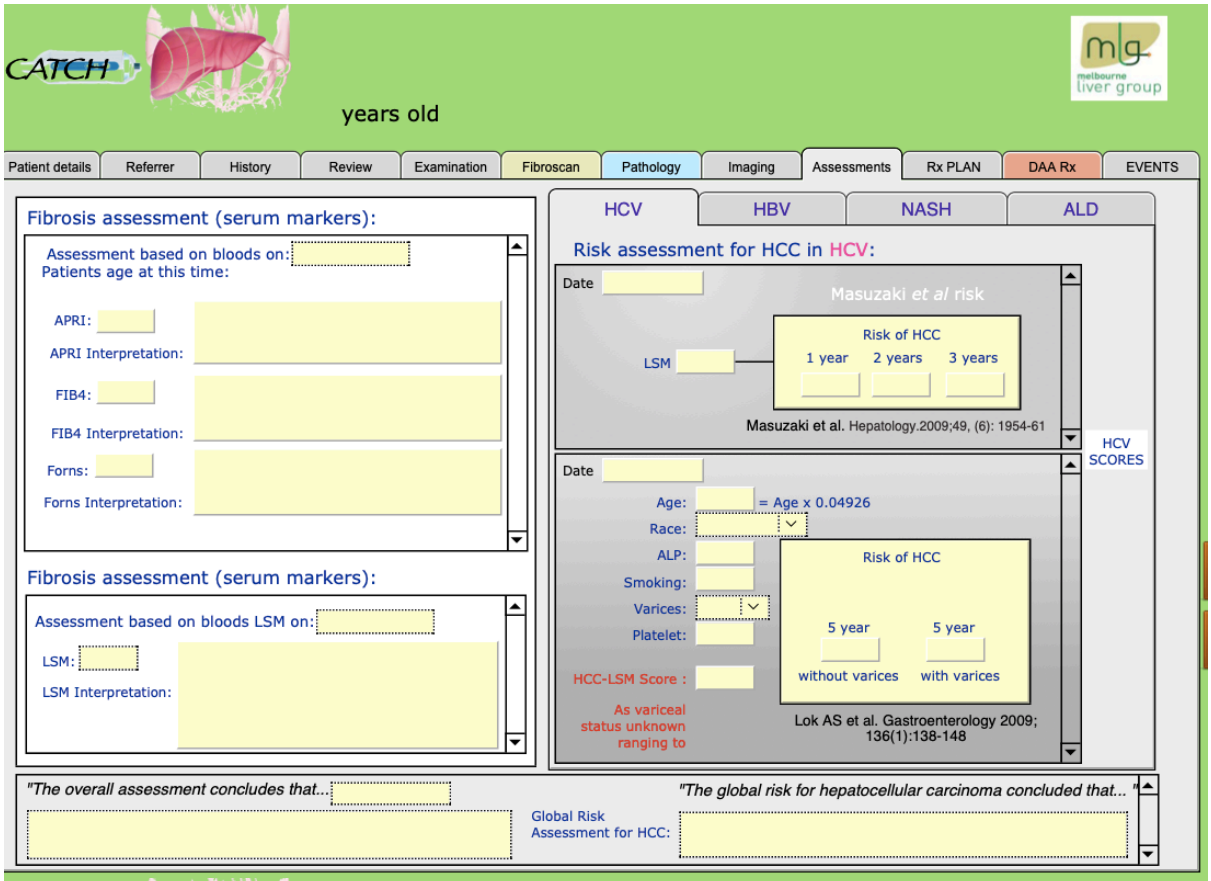
DAA Rx
EVENTS
Proceduralist
BASELINE FIBROSCAN RESULTS
Date of procedure
Age at time
years
Patient Fasting:
Probe size
ALT category
Skin to Capsule
cm
Median Stiffness
Interquartile range
IQR/Median stiffness
Quality of elastogram
Success rate
%
Procedure Failure
Yes
No
Manual Overide
on
off
allows free text to replace interpretation
Free Text report
Previous Fibroscans
date
ms (kPa)
Trends


CATCH
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Examination
Fibroscan
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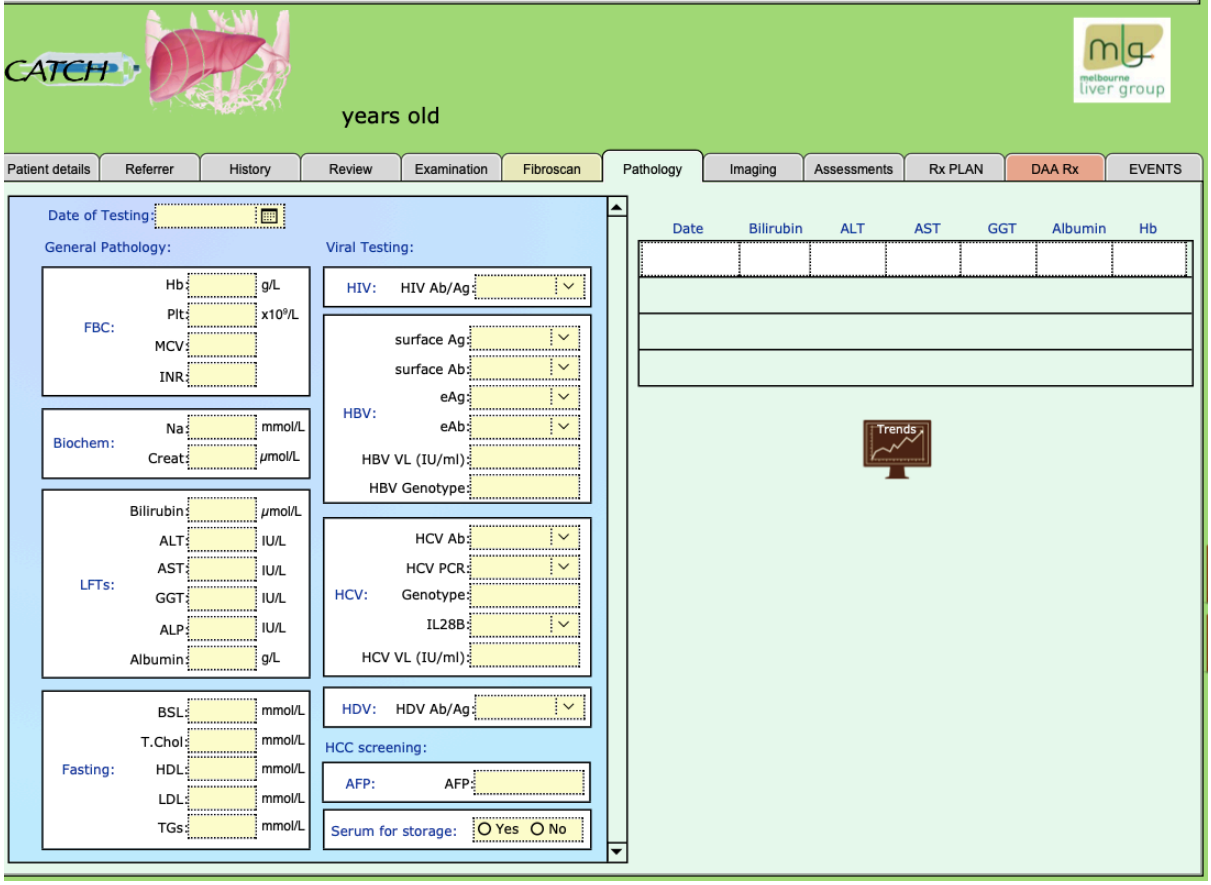
Imaging
Assessments
Rx PLAN
DAA Rx
EVENTS
Fibrosis assessment (serum markers):
Assessment based on bloods on:
Patients age at this time:
APRI:
APRI Interpretation:
FIB4:
FIB4 Interpretation:
Forns:
Forns Interpretation:
Fibrosis assessment (serum markers):
Assessment based on bloods LSM on:
LSM:
LSM Interpretation:
HCV
HBV
NASH
ALD
Risk assessment for HCC in HCV:
Date
Masuzaki et al risk
LSM
Risk of HCC
1 year
2 years
3 years
Masuzaki et al. Hepatology.2009;49, (6): 1954-61
HCV SCORES
Date
Age:
= Age x 0.04926
Race:
ALP:
Smoking:
Varices:
Platelet:
HCC-LSM Score :
As variceal status unknown ranging to
Risk of HCC
5 year
without varices
5 year
with varices
Lok AS et al. Gastroenterology 2009; 136(1):138-148
"The overall assessment concludes that...
Global Risk Assessment for HCC:
"The global risk for hepatocellular carcinoma concluded that..."


CATCH
years old
melbourne liver group
Patient details
Referrer
History
Review
Examination
Fibroscan
Pathology
Imaging
Assessments
Rx PLAN
DAA Rx
EVENTS
Date of Testing:
General Pathology:
FBC:
Hb g/L
Plt x10⁹/L
MCV
INR
Biochem:
Na mmol/L
Creat µmol/L
LFTs:
Bilirubin µmol/L
ALT IU/L
AST IU/L
GGT IU/L
ALP IU/L
Albumin g/L
Fasting:
BSL mmol/L
T.Chol mmol/L
HDL mmol/L
LDL mmol/L
TGs mmol/L
Viral Testing:
HIV:
HIV Ab/Ag:
HBV:
surface Ag:
surface Ab:
eAg:
eAb:
HBV VL (IU/ml):
HBV Genotype:
HCV:
HCV Ab:
HCV PCR:
Genotype:
IL28B:
HCV VL (IU/ml):
HDV:
HDV Ab/Ag:
HCC screening:
AFP:
AFP:
Serum for storage:
Yes
No
Date
Bilirubin
ALT
AST
GGT
Albumin
Hb
Trends

FIBROSCAN REPORT

. / -. / -0. . .

Patient name: **Test Tester**

Patient DOB: **01/01/1900**

Patient UR: **123456**

Referring clinician: **Dr Noname**

Indication: **Hepatitis C**

Anthropometry:

Weight: 100 kg

Fasting status: Fasted >3 hours

FIBROSCAN REPORT

Procedure (performed on 10/10/2000)

An abdominal ultrasound was performed with the patient supine to determine the position of the right lobe of the liver and the best intercostal space for positioning of the Fibroscan® probe. The skin to capsule distance was 1.6 cm.
The Medium probe was used to take 10 measurements of transient elastography (TE) within the right liver lobe. Fasting status:Fasted >3 hours.

Results:

Median stiffness: 5.2 kPa

Interquartile range (IQR): 0.4

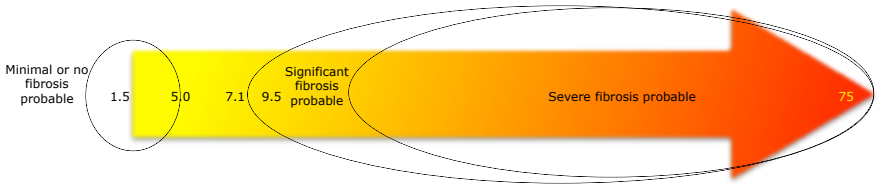
IQR/Median stiffness: 0.08

Elastogram quality: Excellent

Success rate: 100 %

Interpretation:

This value is within the range seen in individuals without any liver disease. However, some patients with mild fibrosis may also have values in this range.



Thank you for your referral,

Dr Diana Lewis
01/01/2000

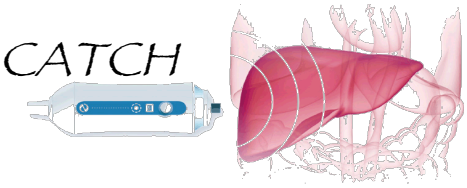
References:

Castera et al. Gastroenterology 2005;128:343–350
Ziol et al. Hepatology 2005; Vol. 41, No. 1, 2005

Notes:

The Fibroscan does not always replace the need for Liver biopsy, nor does it replace the need for diagnostic ultrasound to determine the presence of abnormalities within the liver or biliary tree. The results should always be interpreted within the clinical context of the patient.

Clark



Community Approach Targeting Cirrhosis and Hepatocellular Carcinoma

Hepatitis C Assessment and GP Management plan

Patient:	**Test Tester**
DOB:	**01/01/1900**
Date Assessed:	**01/01/2000**
Primary Diagnosis:	**Hepatitis C**

CATCH SUMMARY:

Global Assessment:	**Cirrhosis is unlikely to be present.**
Risk of Hepatocellular Carcinoma (HCC):	**HCC risk is NOT increased based on LSM**

MANAGEMENT PLAN:

This patients hepatitis C PCR is negative ~ 1 year after DAA treatment = CURE. We recommend a repeat PCR 12 monthly if ongoing IVDU.

The CATCH project is happy to facilitate referral to a tertiary centre within your area of practice in those with evidence of cirrhosis or urgent need of assessment and treatment.

Regards,

Dr John Lubel (MRCP FRACP PhD)
Principal Investigator
Gastroenterologist and Hepatologist

Dr. William Kemp (FRACP PhD)
Principal Investigator
Gastroenterologist and Hepatologist

Dr. Stephen Bloom (FRACP)
Principal Investigator
Hepatology Fellow

Dr. Diana Lewis (FRACP)
Principal Investigator
Hepatology Fellow

Emma Dimitri
Research Coordinator
Registered Nurse

3. R code and analyses and results

The code for data cleaning and statistical tests and results is more than 650 pages long. As such, it has been uploaded to Open Science Framework and can be accessed at:

https://osf.io/fbk8n/?view_only=e39aff45e7a74bdd9afbed3a0706c89c

4. Human research Ethics committee approval

5 Arnold Street, Box Hill
Victoria 3128 Australia
PO Box 94, Box Hill 3128
Tel (03) 9895 3281
Fax (03) 9895 4896
info@easternhealth.org.au
ABN 68 223 819 017

www.easternhealth.org.au

Human Research Ethics Committee - Scientific and Ethical Review

Ethical Approval – Granted

Commencement of Research at Eastern Health
has been authorised

3 October 2014

Dr J Lubel, Dr W Kemp & *Dr S Bloom*
Level 2
5 Arnold Street
Box Hill VIC 3128

Eastern Health Human Research
Ethics Committee
Ph: 03 9895 3398
Fax: 03 9094 9610
Email:
ethics@easternhealth.org.au
Website:
www.easternhealth.org.au/ethics

Dear Dr Lubel

E38/1314 *Community approach targeting cirrhosis and hepatocellular carcinoma*

Principal Investigator: Dr John Lubel, Dr William Kemp

Associate Investigators: None

Student Investigator: Dr Stephen Bloom

Other approved personnel: Nil (if none)

Eastern Health Site: Box Hill Hospital

Approval Period: On-going - subject to a satisfactory progress report being submitted annually.

The above study was considered by the Eastern Health Research and Ethics Committee at its meeting on 19 June 2014 and was approved subject to amendments and clarifications. Following receipt of amended documents and additional information (received on 18 September 2014), **final approval** can now be given for the study to proceed.

List of documents approved:
- NEAF Application
- Site Specific Assessment Form
- Victorian Specific Module
- Participant Information and Consent Form version dated 31 July 2014

easternhealth
GREAT HEALTH AND WELLBEING

5 Arnold Street, Box Hill
Victoria 3128 Australia
PO Box 94, Box Hill 3128
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Fax (03) 9895 4896
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- Protocol version 2 dated 5 August 2014
- Catch study Patient Information Brochure version 3 dated 17 September 2014
- CATCH Week 4 Patient Survey version 1 dated 28 May 2014
- CATCH – Participant Questionnaire undated
- CATCH – Primary Care Physician Post Assessment Satisfaction version 1 dated 28 May 2014
- CATCH – Participant Flyer version 1 dated 28 May 2014

Additionally the following documents have been submitted:

- Curriculum vitae: Dr William Kemp

Reporting Requirements:

Please note, **a progress report is due by 31 December Annually** until project completion. This would cover the preceding calendar year. Continuing approval is subject to the timely submission of a satisfactory progress report. Progress report template can be downloaded from our web-page:
http://www.easternhealth.org.au/research/ethics/progressreports.aspx

Please ensure you notify the Ethics Committee of all personnel changes and any serious adverse events that may affect study conduct. Any changes to the approved Protocol or other approved documents must be submitted for ethical review and approval prior to use.

Eastern Health Research and Ethics Committee

The Eastern Health Research and Ethics Committee is constituted and functions in accordance with the National Health and Medical Research Council Guidelines (National Statement on Ethical Conduct in Human Research 2007). No member of the Committee adjudicates on research in which that member has any conflict of interest including any personal involvement or participation in the research, any financial interest in the outcome or any involvement in competing research.

Please refer to the National Statement on Ethical Conduct in Human Research (2007) http://www.nhmrc.gov.au/publications/synopses/e35syn.htm and Declarations by Investigators in the NEAF for researchers' obligations. **Continuing approval is subject to the adherence of these guidelines and the fulfilment of researchers' obligations.**

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Please quote our reference number ***E38/1314*** in all future correspondence.

Yours sincerely

Ms Pat Sterling
Ethics Officer
Office of Eastern Health Research and Ethics

Encl: Committee Composition letter

- Copy all above listed personnel

Chapter 8. References

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