Non-invasive assessment of chronic liver disease in vulnerable and homeless adults in the community

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Abstract

People who are homeless (PWAH), are at high risk of developing chronic liver disease (CLD) due to the high prevalence of alcohol use disorder (AUD) and injecting drug use (IDU). Nonetheless, their access to healthcare and overall engagement with liver services remain suboptimal. Moreover, this group represents a hard-to-reach population when it comes to the implementation of hepatitis C (HCV) elimination plans. Various models have been proposed to develop community liver screening services for PWAH employing passive and active case finding strategies. Our systematic review of these models suggests that community-based FibroScan is the most common method for liver fibrosis assessment; the prevalence of clinically significant hepatic fibrosis (CSHF)/≥F2 fibrosis (liver stiffness measurement ≥8kPa) being 37%. Additionally, quality of evidence assessing the effectiveness of interventions in PWAH remains poor, but where good quality evidence exists it highlights that community-based interventions for PWAH can improve their linkage to care and HCV treatment outcomes.

In Brighton, the Vulnerable Adults LIver Disease (VALID) study was modelled on our previous successful ITTREAT model based at Addiction centres. In VALID Study, we focused primarily on homeless adults and established a hostel-based liver screening service offering alcohol (AUDIT) questionnaire and substance misuse assessment, blood-borne viruses (BBVs) testing, mobile transient elastography (TE) and dedicated treatment for CLD. Our primary outcome was the prevalence of CSHF. Secondary outcomes included service uptake (BBV screening, FibroScan, HCV treatment), prevalence of HCV, IDU, alcohol dependence, and cirrhosis and HCV treatment outcomes. We also assessed correlation between LSM and peripheral cytokines (Th17 panel, IL-6, TNF and IFN-γ), hepatocyte senescence markers

[Matrix metalloproteinase-2 (MMP-2), cytokeratin -18 (CK-18)] and Enhanced Liver Fibrosis (ELF) score [Hyaluronic acid (HA), tissue inhibitor of metalloproteinase-1 (TIMP-1) and procollagen III amino-terminal peptide (PIIINP)] in a community setting.

Of 131 individuals approached, service uptake was 97% (n=127). At baseline 96 (76%) were homeless, half (n=63) were alcohol dependent (AUDIT questionnaire) with 49 (39%) being HCV PCR positive. Using TE, CSHF and cirrhosis were detected in 33 (26%) and 21 (17%), respectively, with AUD being an independent predictor of both. There was moderate agreement between LSM and ELF score for CSHF (Kappa value 0.536, $p<0.001$). In comparison to ELF, APRI had a lower degree of agreement with LSM for CSHF (Kappa value 0.452, $p<0.001$). Serum concentrations of TNF, IFN-γ, IL-6, IL-10 hepatic senescence biomarkers and ELF biomarkers were significantly elevated in those with CSHF.

Of the 29 who received DAA-based HCV treatment, sustained virological response rates were 83% with 93% successfully completing treatment.

In conclusion, this work demonstrates the significant burden of CLD in PWAH; the two main aetiological factors being AUD and HCV, leading to a high prevalence of CSHF (as assessed by LSM). This work is also amongst the first to assess additional non-invasive markers of hepatic fibrosis (ELF, APRI), as well as cytokines and hepatic senescence biomarkers in PWAH and their correlation with LSM. Despite the vulnerable nature of the cohort, service uptake and HCV treatment outcomes were excellent. Our work endorses the need for a national model evaluating community-based interventions to address CLD amongst PWAH to improve overall liver health.

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List of Abbreviations

ABBVIE 3D	Ombitasvir/paritaprevir/ritonavir + dasabuvir
ACLF	Acute-on-Chronic Liver Failure
ALD	Alcohol related liver disease
ALT	Alanine transferase
APRI	AST: Platelet Ratio Index
AST	Aspartate transaminase
AUD	Alcohol use disorder
AUDIT	Alcohol Use Disorders Identification Test
BBVs	Blood-borne Viruses
BHH	Brighton Homeless Healthcare
BHWC	Brighton Health and Wellbeing Centre
BMI	Body mass index
CI	Confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CIRU	Clinical Investigations and Research Unit
CK	Cytokeratin
CLD	Chronic liver disease
COVID-19	Coronavirus disease 2019
CT	Computed tomography
DAA	Direct-acting antivirals
DBST	Dried Blood Spot Testing

EBR/GZR	Elbasvir/grazoprevir
ELF	Enhanced liver fibrosis
EOTR	End of treatment response
GP	General Practice/Practitioner
HA	Hyaluronic Acid
HC	Healthy controls
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B Surface Antibody
HBsAg	Hepatitis B Surface Antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HCC	Hepatocellular carcinoma
HDAS	Healthcare Databases Advanced Search
HEARTH	Homeless Emergency Assistance and Rapid Transition to Housing
HepCATT	Hepatitis C Awareness Through to Treatment
HIV	Human immunodeficiency virus
HRQoL	Health-related quality of life
IC	Integrated care
ID	Infectious diseases
IDU	Injecting drug use
IFN	Interferon
IL	Interleukin
IQR	Interquartile range
ITTREAT	Integrated community-based Test – stage – TREAT

ITT	Intention to treat
mITT	modified ITT
kPa	kiloPascals
LFT	Liver function tests
LSM	Liver stiffness measurement
LTFU	Loss/lost to follow up
MELD	Model for end-stage liver disease
MeSH	Medical Subject Headings
MMP	Matrix metalloproteinases
MRI	Magnetic resonance imaging
MRE	Magnetic resonance elastography
MSD	MesoScale Discovery
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
OST	Opiate substitution therapy
ODN	Operational delivery network
PIIINP	Amino-terminal propeptide of procollagen type III
PBC	Primary biliary cholangitis
PCR	Polymerase chain reaction
PEG	Pegylated interferon
PHE	Public Health England
PICOS	Participants, interventions, comparators, outcomes, and study design

PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PWAH	People Who Are Homeless
PWID	People who inject drugs
RBV	Ribavirin
RCT	Randomised controlled trial
RR	Responder relapse
SD	Standard deviation
SIM	Simeprevir
SMS	Substance misuse service/s
SOF/LDV	Sofosbuvir/ledipasvir
SPSS	Statistical Package for Social Sciences
STAT3	Signal transducer and activator of transcription 3
SVR	Sustained virological response
TB	Tuberculosis
TE	Transient Elastography
Th	T-helper cell
TIMP	Tissue inhibitors of metalloproteinase
UC	Usual care
UK	United Kingdom
USA	United States of America
USG	Ultrasound/Ultrasonography
VALID	Vulnerable Adults LIver Disease
VCTE	Vibration-Controlled Transient Elastography
VEL	Velpatasvir
WHO	World Health Organization

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Author's Declaration

I declare that the research contained in this thesis, unless otherwise formally indicated within the text, is the original work of the author. The thesis has not been previously submitted to this or any other university for a degree and does not incorporate any material already submitted for a degree.

Signed ……*A. Hashim*  ……

Dated……04/06/2021…

CHAPTER 1: Introduction & literature review

In the UK, mortality from chronic liver disease (CLD) has increased by almost 400% since 1970 (Public Health England, 2017). Liver disease is considered the third most common cause of premature death and the rise in the incidence of liver disease is considerably higher in the United Kingdom (UK) than in other parts of Western Europe according to the UK liver report released in 2014 (Williams et al., 2014).

Chronic hepatitis C virus (HCV) infection remains a major national health burden in the UK (Public Health England, 2020). In 2015, the global mortality from viral hepatitis (1.4 million/year) surpassed that of the human immunodeficiency virus (HIV) (1.3 million/year), malaria (1.2 million/year), and tuberculosis (TB) (0.5 million/year) (Global Burden of Disease, 2015). This led to introducing the first-ever World Health Organization (WHO) Global Health Sector Strategy for eliminating viral hepatitis by 2030 (World Health Organization, 2016). Following this, Public Health England (PHE) published a vision statement which adopted the WHO HCV elimination strategy (Public Health England, 2017).

In 2014, the UK Lancet liver report advocated for strengthening and prioritising the detection of CLD in the community (Williams et al., 2014). One of the top recommendations highlighted in the report was the need to improve support services in the community to screen vulnerable adults and people at high risk. This recommendation should be coupled with early detection of liver disease in order to prevent complications of CLD in these vulnerable high-risk groups. For instance, HCV infection is readily treatable using the new direct-acting antivirals (DAAs).

These antivirals have cure rates [sustained virological response (SVR)] in the high 90% (Bell et al., 2016, Feld et al., 2014). Likewise, early treatment of chronic hepatitis B virus (HBV) with antivirals infection results in a significant reduction of the risk of CLD complications and hepatocellular cancer (HCC), especially with successful virological suppression (Chen and Yang, 2011).

1.1 Definition of a vulnerable adult

There is no consensus as to what exactly defines a vulnerable adult. The term generally refers to any individuals who are unable to take care of themselves or are unable to protect themselves against neglect, exploitation, or harm.

An early definition in the UK was made by the Lord Chancellor department and described that a vulnerable adult might be defined as a person over the age of 18 years who *"'is or may be in need of community care services by reason of mental or other disability, age or illness; and who is or may be unable to take care of him or herself, or unable to protect him or herself against significant harm or exploitation*" (Lord Chancellor's Department, 1997).

The vulnerable adult term is often used interchangeably with "adult at risk" or adults at risk. However, the latter terms are more increasingly preferred as a description of this group. Although the definition of adults at risk varies slightly depending on the context, in the UK, the Safeguarding Vulnerable Groups Act (2006) has developed criteria that can be used to define vulnerable groups or adults at risk. These criteria involve any adult who:

- "*is in residential accommodation,*

- *is in sheltered housing,*

- *receives domiciliary care,*

- *receives any form of health care,*

- *is detained in lawful custody,*

- *by virtue of an order of a court, is under supervision per Criminal Justice Act 2003 sections regarding community sentences.*

- *receives a welfare service of a prescribed description,*

- *receives any service or participates in any activity provided specifically for persons who have particular needs because of his age, has any form of disability or has a prescribed physical or mental problem. (Dyslexia, dyscalculia and dyspraxia are excluded disabilities),*

- *has payments made to him/her or to an accepted representative in pursuance of arrangements under the Health and Social Care Act 2012, and/or*

- *requires assistance in the conduct of own affairs.*"

Other definitions include that of the Care Act 2014 (Care Act, 2014) in England which defines the person who should be subject of a safeguarding enquiry as an adult who:

- "*has needs for care and support (whether or not the local authority is meeting any of those needs) and;*

- *is experiencing, or at risk of, abuse or neglect; and;*

- *as a result of those care and support needs is unable to protect themselves from either the risk of, or the experience of abuse or neglect.*"

In Wales, the Social Services and Wellbeing Act 2014 (Social services and wellbeing act 2014, 2014) describes "adults at risk" as adults who

- "*are experiencing or is at risk of abuse or neglect,*
- *have needs for care and support (whether or not the authority is meeting any of those needs), and*
- *as a result of those needs are unable to protect himself or herself against the abuse or neglect or the risk of it.*"

The Adult Support and Protection Act (2007) in Scotland described another definition for adults at risk similar to the previous definitions and involved an adult who:

- "*is unable to safeguard their own well-being, property, rights or other interests,*
- *is at risk of harm, and*
- *because they are affected by disability, mental disorder, illness or physical or mental infirmity, are more vulnerable to being harmed than adults who are not so affected*."

In clinical practice, vulnerable adults have to be identified and diagnosed formally so that they are approached in a sensitive manner, especially due to issues related to consent and engagement with clinical services.

Many vulnerable adults have a higher risk of encountering specific chronic somatic and mental conditions. The vulnerable adults' groups that remain at greater risk of developing liver disease include those with mental health and substance misuse problems and groups at risk of immediate danger, such as refugees, those living in post-conflict zones, prisoners, homeless individuals, and some elderly adults. Homeless adults and those in prisons are, for instance, at

higher risk of developing CLD because of substance and alcohol misuse and/ high-risk sexual behaviour. Nevertheless, given their likely poor socioeconomic situations, they may have limited engagement with the healthcare services. Other vulnerable adults, like refugees and immigrants are also at risk of CLD, specifically due to the increased prevalence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. Furthermore, they may not gain easy or secure access to the healthcare system in the host country as the immigration rules may not allow, or they may have other competing life priorities related to their immigration circumstances.

Therefore, it is crucial to understand the extent of CLD among these special vulnerable groups and explore the possible implications of their complex health problems on the health care system. It is also essential to establish and delineate appropriate, feasible and efficient screening and treatment strategies for managing liver disease in these vulnerable populations.

1.2 Homelessness: definitions and prevalence

While there is no uniform definition of homelessness, the term includes unstable housing, rough sleepers, those who are unsheltered, and those who live in temporary accommodation including ‘sofa surfing’ or living with friends or family (Busch-Geertsema, 2010).

In the UK, however, there is no specific definition, but individuals are defined as homeless if they have no secure place in which they are entitled to or are not able to live in a place for strong reasons (such as domestic violence) (Housing Experimental Statistical First Release, 2018). A person is described as statutory homeless if the local housing department of his/her local council becomes obliged to provide housing-related support to that person (Housing Act, 1996, Homelessness Act, 2002). In the UK, the decision on delivery of care and housing needs

is generally left to the local housing authority within the area to make. These housing authorities are required to devise strategies for the prevention of homelessness in their respective districts. The Housing Act (1996) defines homelessness as:

"*(1) A person is homeless if he/she has no accommodation available for his/her occupation, in the United Kingdom or elsewhere, which he/she:*

(a) is entitled to occupy by virtue of an interest in it or by virtue of an order of a court,

(b) has an express or implied license to occupy, or

(c) occupies as a residence by virtue of any enactment or rule of law giving him the right to remain in occupation or restricting the right of another person to recover possession.

(2) A person is also homeless if he has accommodation but:

(a) he cannot secure entry to it, or

(b) it consists of a moveable structure, vehicle or vessel designed or adapted for human habitation and there is no place where he is entitled or permitted both to place it and to reside in it."

In view of the difficulty in estimating homelessness rates, partly due to the varied definitions of homelessness and poor engagement of this group with local authorities, UK data is mostly based on rough sleeping, being the most visible type of homelessness. Rough sleeping is, in turn, defined by The Housing Statistical Release (2019) as:

- *"people sleeping, about to bed down (sitting on/in or standing next to their bedding) or actually bedded down in the open air (such as on the streets, in tents, doorways, parks, bus shelters or encampments)*

- *people in buildings or other places not designed for habitation (such as stairwells, barns, sheds, car parks, cars, derelict boats, stations, or 'bashes')*".

In the United States of America (USA), the Homeless Emergency Assistance and Rapid Transition to Housing (HEARTH) Act 2009 (HEARTH, 2009) produced homelessness inclusion criteria which encompass:

- "*Individuals and families who do not have a fixed, regular, and adequate night-time residence, which includes individuals who live in emergency (but not transitional) shelters for the homeless and those who live in places not meant for human habitation.*

- *Individuals and families who will imminently lose their main night-time residence.*

- *Unaccompanied young people and families with children and young people who meet other definitions of homelessness.*

- *Individuals and families who are fleeing or attempting to flee domestic violence, dating violence, sexual assault, stalking, or other dangerous or life-threatening conditions that relate to violence against an individual or family member*".

The HEARTH subdivides the definition further, according to the risk of homelessness and circumstances that lead to homelessness, into *literally homeless* individuals, those with *imminent risk* of homelessness, homeless adults under other federal statues and finally those fleeing or attempting to flee domestic violence.

The European Typology of Homelessness and Housing Exclusion (ETHOS, 2016) defines a person as homeless if they have a deficit in at least two of three categories; the physical, legal, and social domains. This is a more holistic description that includes, in addition to roofless or houseless individuals, those living in insecure or inadequate accommodation. The latter group involves those living under the threat of eviction, living in extreme crowdedness, unfit housing, or non-conventional structures.

Another classification of homelessness which was described by (Chamberlain and Mackenzie, 1992) categorises the term into three tiers depending on the availability and type of accommodation: *primary homelessness* (i.e., those without regular accommodation), *secondary* (those living in emergency shelters or temporarily staying with family or friends), or *tertiary* (living in substandard housing such as boarding homes and caravans).

In general, homelessness is experienced in three different patterns: chronic or long-term homelessness, intermittent homelessness, and crisis homelessness (Fazel et al., 2014). Chronic homelessness occurs when an individual is homeless for more than one year or has at least 4 periods of homelessness in the two years' time. On the other hand, intermittent homelessness refers to those who alternate between periods of homelessness and housing in a rotating fashion. Those who experience homelessness for a short period of time, commonly following a major incident or personal crisis such as employment loss, are described as crisis or temporary homeless. These homelessness patterns tend to influence each other as in the USA, for example, 1 in 5 who experience a single episode of homelessness eventually become chronically homeless (Fazel et al., 2014). Chronic homelessness appears to carry the worst prognosis from a clinical outcome perspective compared to the other types or patterns of homelessness (Caton et al., 2005).

Many socio-demographic factors are linked to predisposition to homelessness. These include poverty, criminal or violence history, family conflicts, non-heterosexual orientation, mental illness and substance and alcohol misuse (Fazel et al., 2014, Caton et al., 2005). The latter two factors have been shown to cause homelessness and contribute to the persistence of the homelessness status leading to chronic homelessness (Patterson, 2012). Advancing age is another factor that is uniquely associated with chronic homelessness (Patterson, 2012). In addition to social factors, homelessness is also associated with structural and policy-related and economic elements such as houses prices, poor income and income inequality, and affordability (Fazel et al., 2014).

Establishing homelessness rates is rather a challenging process as measuring the prevalence using a single point of time count may overestimate chronic or long-term homeless, and similarly may result in underestimation of short periods of homelessness. In Europe, the number of people who have suffered a homelessness episode per year was estimated to be 4.1 million (European Commission, 2013). Homelessness appears to be rising across the whole of Europe, although there have been recessions in the rates of homelessness in a few countries, such as Finland and Norway (Feantasa, 2018). The rise in the prevalence is linked to increased housing costs, ageing of the population, in addition to social changes in the structure of families in the western world (Fazel et al., 2014). However, in the USA, homelessness is trending down since 2007 with evidence of 15% reduction in homelessness rates in general and a more significant drop amongst homeless veterans. Recent US data indicate that a total of 552,830 individuals were homeless on a single night in 2018 which is equivalent to 17 out of every 10,000 people in the United States (Department of Housing and Urban Development, 2018).

In England, the rates of homelessness and in particular rough sleeping have reached a concerning high level over the past decade. A report carried out by Local Authorities in

England in 2017 (The Housing Statistical Release, 2018), providing a snapshot figure of the number of people sleeping rough, estimated that 4,751 individuals were sleeping rough on any given night. This was the seventh consecutive year that the rates of rough sleeping continue to rise, and the figure had, in fact, increased by 15% from the year before and at least 73% over the preceding 3 years alone. The locality with the highest number of rough sleepers was Westminster, followed by Brighton & Hove council. The most significant regional increase was evident in the north-west (39%), where rough sleeping had almost doubled over the two years preceding the report. It is also crucial to bear in mind that these figures do not take into account "hidden homelessness" which, in essence, underscores that many homeless people (estimated to be up to be an additional 62%) are not included in the official figures as they seek temporary solution or accommodation by sofa surfing or staying with relatives or friends. Therefore, the rates of homelessness are estimated to be significantly higher than the currently available official figures.

1.3 General health problems among people who are homeless (PWAH)

Homelessness is a risk factor for many systemic problems (Figure 1.1). In view of the chronic debilitating medical conditions which frequently coexist with mental health problems in the context of the poor socio-economic status, the average life expectancy of people who are homeless (PWAH) is markedly reduced, and in one report it was estimated to be as low as 47 years (Hassanally and Asaria, 2018, Medcalf and Russell, 2014, Roncarati et al., 2018, Aldridge et al., 2019). Also, the rates of mortality in the homeless population are higher than the general population, both in absolute and relative figures (Fazel et al., 2014). In some studies, premature death amongst the homeless was described to be three to four times that of the general population (Kaduszkiewicz et al., 2017). Some studies suggest that age and female

gender carry an excess risk for mortality among the homeless (Nordentoft and Wandall-Holm, 2003, Nusselder et al., 2013). Moreover, deaths from homelessness have been steadily rising despite the numerous interventions made over the past few decades to tackle the concerning issue of increased mortality amongst this population of vulnerable adults (Fazel et al., 2014). However, there has been a shift regarding death's causes with fewer reported cases of HIV-related mortality but more deaths from overdose of drugs and illicit substance misuse (Baggett et al., 2013). In the USA, a slightly different pattern is observed with two spikes of increased mortality; one at a young age caused by external factors such as suicide and drug overdose, and a second spike in older homeless adults who tend to have similar causes of death to the general population but in a premature fashion (Baggett et al., 2013). In England, a study looking at mortality of homeless individuals in east London, specifically the boroughs of Tower Hamlets and Hackney between 2001 & 2016, found that of the 203 deaths examined, the average year at death was 47, and the leading three causes of death related to substance misuse, cardiac problems and liver disease (Hassanally and Asaria, 2018). Interestingly, those whose mortality was related to liver disease died at the age of 49, while those who died because of substance misuse died at an average of 38 years (Hassanally and Asaria, 2018).

In general, despite the challenges in collecting data in this cohort, the burden of health problems in homeless individuals is considerably high, with many accessing healthcare at secondary level during crisis admissions in emergency departments (Schanzer et al., 2007). Homeless people often present to accidents and emergency departments five times more than housed individuals, with homelessness being considered an independent factor for emergency admissions. They are also admitted to hospitals more than 3.2 as often, and the length of their hospital stay could be prolonged by at least three times (Medcalf and Russell, 2014). In another study, the length of hospital stays for homeless individuals following an acute admission was at least two days longer than that for the general population (Hwang et al., 2011). Hence, from

a health economic point of view, the overall utilisation of health services is higher amongst the homeless and has been estimated to cost eight times that of housed populations (Heatherington and Hamlet, 2015). The high costs could be partly explained by the poor access of PWAH to primary or preventative health services and the limited transportation means available to them to attend ambulatory or outpatient appointments.

As with the increased mortality, morbidity levels PWAH are similarly increased. This seems to be the case for those with long-term or chronic homelessness as well as those with acute homelessness (Adebowale, 2018). The high burden of disease among homeless adults constitutes a major healthcare barrier and is a widely recognised healthcare challenge, acknowledged worldwide in reports by the World Medical Association (World Medical Association, 2006).

In an early report, the interaction between diseases and homelessness was classified broadly into three categories by the Institute of Medicine (US) Committee on Health Care for Homeless People (The Institue of Medicine, 1988). These categories are diseases that predate but contribute to homelessness, health problems that occur due to homelessness, and illnesses aggravated by homelessness. There is a great deal of overlap between the three categories. The first category includes those problems that predispose to homelessness, of which mental illness, alcohol and drug abuses are major contributors. Without appropriate and effective interventions, mental health and substance misuse problems can lead to many patients ending up in the streets or being unemployed. On the other hand, other diseases can be influenced by a homelessness state, and these include skin disorders, unintentional trauma and foot injuries, malnutrition, tuberculosis and more importantly liver disease, whether it is alcohol or viral hepatitis-related. Finally, homelessness contributes to worsening of already existing diseases. This occurs primarily due to the significant challenges facing the provision and delivery of care

to patients in the streets compared to domiciled individuals. In other words, existing chronic disease may progress due to the lack of an appropriate environment to provide therapeutic interventions. Progression of diabetes and development of its complications is a classic example in this respect as some of the crucial management interventions such as diet control and storage of insulin may not be easily achieved (if not virtually impossible) in a street environment. Moreover, even when interventions are initiated for chronic illnesses, there is usually a disruption of care continuity for homeless individuals with lack of long-term engagement and follow-up of cases and often poor interaction with health care providers (Anderson, 2012). This, in turn, impacts the quality of healthcare received by PWAH, given that an integrated management plan becomes challenging to implement.

In one study, alcohol and drug-related were the common causes of hospital admission in 27% of cases (Medcalf and Russell, 2014). These include, in addition to alcohol-related liver disease, drug injection site complications and leg ulcers. Mental health issues involving suicidal attempts, deliberate self-harm and drug overdose were the cause of hospital attendance in a similar proportion of homeless people (21%).

An Irish study reported that homeless people had a significantly higher proportion of alcohol and substance misuse related admissions, HIV and viral hepatitis infections, digestive disorders, skin problems and respiratory conditions (Romero-Ortuno et al., 2012). Moreover, the prevalence and risk for TB are higher in homeless people in several studies (Beijer et al., 2012). In particular, tuberculosis is linked to and complicated by poor diet and alcoholism, both of which are prevalent in PWAH (Romero-Ortuno et al., 2012).

HCV appears to be the most prevalent chronic infection in homeless adults with up to 36.2% prevalence for HCV with the other two common infections, HIV and TB having a prevalence of 0.3-21% and 0-8% respectively (Beijer et al., 2012). Unintentional injuries are also major

morbidity and constitute a significant proportion of cases attending the emergency department. In one report, the latter constituted up to 9% of the total attendances (Mackelprang et al., 2014) with the rates of traumatic brain injury being markedly higher among homeless adults than the general population (Topolovec-Vranic et al., 2012). Furthermore, the incidence of falls and cognitive impairment-related conditions in older homeless individuals is increased compared to non-homeless elderly (Brown et al., 2012). Brown and Steinman demonstrated that homeless adults aged 50 years or older had fewer mental health conditions diagnosed at discharge (10% vs 20%; $p = 0.002$) and lower percentage of drug abuse (7% vs 15%; $p = 0.003$) but conversely suffered from a significantly higher prevalence of alcohol abuse (31% vs 23%; $p = 0.03$) and were more likely to be admitted to the hospital (20% vs 11%; $p = 0.003$).

In addition to physical health problems, mental illness and both substance and alcohol use disorders contribute vastly to the overall health burden of homeless (Fazel et al., 2014). As indicated above, alcohol and substance misuse constitutes a significant cause of admission. While this appears to be the most prevalent psychiatric problem among the homeless, depression and personality disorders are also prevalent. Psychotic disorders are also common, with prevalence ranging from 3-42% (Fazel et al., 2008). Interestingly one study found that most homeless people with schizophrenia had a concomitant history of drug misuse, indicating an interaction between substance misuse and mental health disorders in PWAH (Nordentoft and Wandall-Holm, 2003). Furthermore, PWAH tend to have a higher prevalence of sexual abuse, which increases the incidence of psychiatric illness and self-harm (Torchalla et al., 2012).

Multiple barriers are hindering the optimal access of PWAH to the healthcare services, and this can often present as a dual burden to the homeless cohort, as homeless individuals may occasionally feel that the healthcare system treats them unequally or that healthcare

professionals have a hostile or uncompromising attitude towards them (Adebowale, 2018, Canavan et al., 2012). Secondly, many homeless individuals have low self-confidence levels with self-perceptions of worthlessness, leading them not even to approach healthcare services in the first instance (Adebowale, 2018, Fitzpatrick-Lewis et al., 2011). This is particularly prevalent amongst rough sleepers. A general recommendation for improving health services for the homeless, which appears to have a wide acceptance, is the integrated approach, whereby homeless health services are provided in dedicated centres that screen for chronic physical illness alongside psycho-social, mental and cognitive problems (Hwang and Burns, 2014, Davies and Wood, 2018, Fazel et al., 2014). The barriers to accessing healthcare systems experienced by PWAH and ways of overcoming them are summarised in Table 1.1 (below).

Barrier	Solutions
Interrupted care and lack of continuity.	- Multidisciplinary approach in integrated services. - Ensure community and social support once homeless patients are discharged from hospital. - Offering stable housing.
Feeling of being treated unequally by healthcare professionals and lack of confidence in the healthcare system.	- Development of dedicated primary care centres for the homeless that are more accessible to them. - Offering holistic approach to address the interaction between physical and mental health as well as substance misuse and alcohol problems.
Poor engagement with healthcare system. Late presentation with medical illnesses.	Offering hostel-based and street-based outreach services which can deliver care to the homeless in environments they feel more comfortable in leading to better engagement and improved outcomes.

Table 1. 1: Barriers to accessing healthcare system by homeless individuals and suggested solutions.

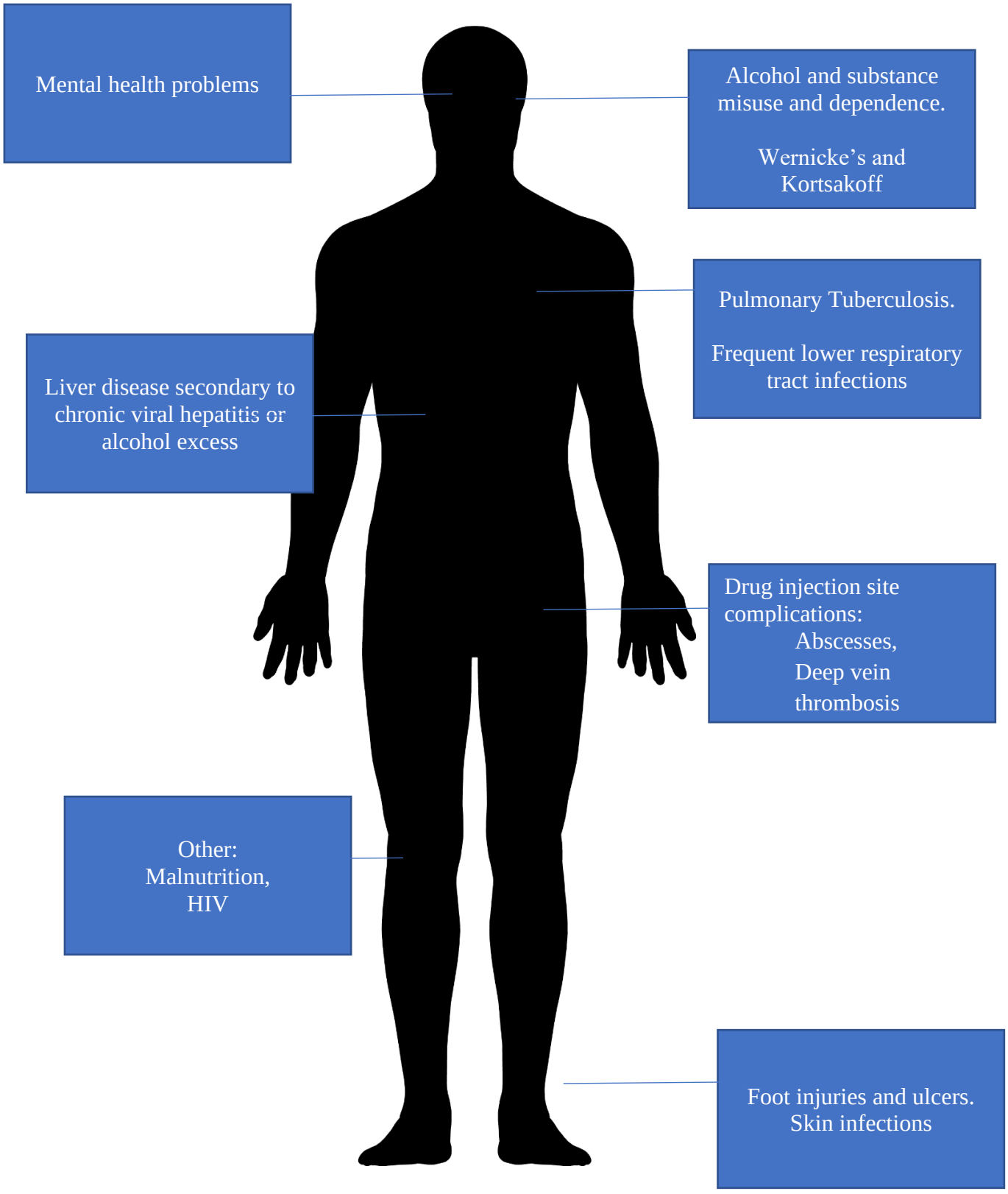


Figure 1. 1: Summary of the common and most prevalent health problems among homeless adults [adapted from Medcalf and Russell (2014)].

1.4 Liver disease among the homeless

People who are homeless (PWAH) are especially at risk of chronic liver disease as such individuals are often living in hostels or have a history of alcohol and substance misuse and psychiatric issues. The prevalence of alcohol abuse and CLD has been generally found to be higher among homeless groups. Studies from Asia, North America and Europe have addressed this issue though there is limited data available from other parts of the world, in particular Africa.

In a Dutch study, the prevalence of cirrhosis in the homeless was estimated to be 5% (van Laere et al., 2009). A case-control study from Boston, USA, demonstrated that one of the most important independent risk factors associated with high mortality among homeless individuals was liver disease, with an odds ratio of 3.8 (Confidence interval, CI: 1.2-11.5) (Hwang et al., 1998). Other factors identified in this study included AIDS/HIV and hypothermia. In Tokyo, a study of 1938 homeless individuals between 1992 and 1996 demonstrated that the observed morbidity from liver-related diseases was 96.5 patients/1000 person-year compared to the expected prevalence of 10.4 patients /1000 years in the general population (Takano et al., 1999). Another Japanese study revealed that in Osaka city's homeless population, leading risk factors for liver disease and HCC included HCV infection and alcohol excess (Sakai 1999). Moreover, most of the homeless patients with HCC presented in later stages; with only two individuals being eligible for curative treatment due to the advanced stage of the disease at the time of referral. In Takano et al.'s study, it was reported that the development of HCC in the homeless was significantly associated with low economic status and malnourishment.

In Philadelphia, homeless people's age-adjusted mortality rates were more than 3-fold higher than the general population (OR 3.5 CI: 2.8 – 4.5) (Hibbs et al., 1994). The main factor leading to this high mortality was substance abuse followed by poisoning, and injuries. More recent

data from a prospective cohort study of homeless individuals in Boston looking at age-standardized all-cause and cause-specific mortality rates revealed that the most common causes of death were non-communicable diseases (cancer and heart disease), alcohol use disorder, and CLD (Roncarati et al., 2018). A similar trend was noted in the UK as data from the United Kingdom's Office for National Statistics confirms that the most common causes of death amongst the homeless population were accidents and drug poisoning, followed by suicides and liver disease, accounting for 40%, 13% and 9% of mortality respectively (Office of National Statistics, 2018). Moreover, a Swedish study found that hospital admissions, especially amongst homeless women, were more likely to be due to viral hepatitis (Beijer and Andreasson, 2009).

Increased risk of HCV remains a common global theme in PWAH. The prevalence of HCV antibody in PWAH registered at eight homeless health care centres in the USA was 31% (Strehlow et al., 2012). Of those who had history of injection drug use, 70% were HCV antibody positive. Earlier USA studies estimated HCV prevalence in the homeless between 26.5% and 69.1% (Cheung et al., 2002). This is in keeping with a systematic review where the prevalence of HCV among homeless people was estimated to be between 3.9 to 36.2% (Beijer et al., 2012). This prevalence does not seem to have changed significantly following the advent of direct-acting antivirals (DAAs) for treatment of HCV as a more recent systematic review reported a comparable HCV prevalence of 28% (95% CI: 23-34) in PWAH (Hakobyan et al., 2018). Independent risk factors for HCV antibody positivity in PWAH are injection drug use (IDU), history of imprisonment, and tattoos. In a subgroup analysis, imprisonment and three or more years of IDU were reported to be the main risk factors for HCV in those with IDU, while amongst non-injectors, risk factors included imprisonment and tattoos (Cheung et al., 2002). Similarly, in Oxford-UK, 98 homeless individuals were tested for HCV with 26.5%

having a positive serology and the major risks being IDU and age (Sherriff and Mayon-White, 2003). The latter finding is probably because of the increased exposure to IDU.

In a study of 330 homeless individuals in São Paulo, Brazil, 30.6% had evidence of prior HBV exposure [positive HBV core antibody (HBcAb)], while the prevalence of active HBV infection being 3.3% (Brito et al., 2007). In the same study, HCV and HIV prevalences were 8.5% and 1.8% respectively. There was a significantly lower prevalence of serological markers of blood-borne viruses (BBVs) in those who reported consistent use of condoms - Hepatitis B Surface Antigen (HBsAg) (1.4%), HBcAb (21.4%) and HIV (0%). Nevertheless, the higher HCV seroprevalence in the UK (Oxford) vs the Brazilian study can be explained by the higher prevalence of IDU in the former study (57% vs 3%). As expected, the IDU cohort in the Brazilian study had higher rates of HIV and HCV positivity (10% and 50% respectively) compared to the non-IDU population. This difference in IDU prevalence suggests that intervention strategies should be based on the different risk factors and behaviours predisposing to HCV infection in each specific circumstance.

Evidence suggests that homelessness per se is a risk for HCV independent of IDU. Some studies demonstrated that the degree of homelessness correlates significantly with HCV seropositivity prevalence (Craine et al., 2009, Hall et al., 2004, Public Health England, 2020). This is mainly due to the chaotic living condition of the homeless but also relate to IDU as well as other risk factors such as mental health problems and unprotected sexual behaviour (Nyamathi et al., 2002). Many homeless adults have ongoing chronic substance use disorder, and in some European countries, a history of IDU may be present in 74% of this group (Read et al., 2017). A report from a previous service for vulnerable adults in Brighton accessing addition centres revealed a high prevalence of psychiatric problems and alcohol use in 70%, and 55%, respectively, with 46% hepatitis C virus seroprevalence (Marufu et al., 2012). It was

also shown that advanced liver fibrosis could be observed in about 40% of vulnerable adults with HCV at presentation (Verma et al., 2006). Alcohol is also a significant risk factor among PWAH, leading to alcohol-related liver disease (ALD). Additionally, alcohol and HCV appear to have a synergistic effect on the development and progression of liver disease as well as liver-related mortality among PWAH (Rigamonti et al., 2003, Singal et al., 2012). Data from a recent report from PHE indicate that 60% of deaths in those with HCV over the last ten years also had an alcohol-related cause of death documented on the death certificate (Public Health England, 2020).

Factors contributing to the HCV disease burden in PWAH include lack of knowledge regarding HCV transmission and prevention. In one study, PWAH had a mean score of only 7.8/15(55%), on a validated HCV knowledge questionnaire (Tyler et al., 2014). This score increased significantly to 12.5 (89%) with a simple nurse-led intervention that involved an educational element and improvement of social and behavioural skills. This demonstrates that a multidisciplinary approach is more useful in managing viral hepatitis in the homeless than the standard single intervention strategies. Similar strategies have been implemented and found to be useful in the context of HCV in substance misusers (Hagan et al., 2011).

Though prior HBV exposure (positive anti-HBc) amongst PWAH ranges between 27%-30% (Gilberg et al., 2001), active HBV infection (positive HBsAg) was present in only 3% in this study. Other studies reported a prevalence of HBsAg of 1-2% among the homeless (Noska et al., 2017, Haussig et al., 2018). While homeless adults may also be co-infected with HIV due to the shared risk factors and transmission routes with viral hepatitis, the prevalence of this co-infection is typically low (2%) (Cheung et al., 2002). In a Dutch study, the prevalence of HIV/AIDs was found to be 11% (van Laere et al., 2009), which is considerably higher than the

figures reported in other studies; but no data were provided on HCV and HBV prevalence in this study.

Lack of access to healthcare is a major factor leading to high morbidity and mortality rates from liver disease in the homeless. This may also result in poor compliance with vaccination programmes among the homeless. Compliance rates with HBV vaccination, for example, can be as low as 13% in these high-risk groups (Greengold et al., 2009). Nevertheless, reports aiming to improve vaccination compliance have demonstrated that simple and basic interventions, such as telephone reminders and incorporating vaccination with needle exchange services, can dramatically improve the engagement with vaccination (Shefer et al., 2006).

Finally, it should be highlighted that there are only a few studies screening for the degree of liver damage or liver fibrosis in PWAH. Non-invasive tests are becoming widely available and should be utilised to understand the magnitude and burden of liver disease in this cohort of patients. Therefore, there is a strong need to develop outreach services for PWAH to assess, stratify, and address liver fibrosis in this vulnerable cohort.

1.5 Nutritional problems of homeless individuals with liver disease

Patients with chronic liver disease tend to be at higher risk of malnutrition due to multiple reasons: reduced nutritional intake secondary to anorexia; early satiety due to ascites (Coufopoulos, 2012); catabolic state leading to muscle wasting (Evans and Dowler, 1999); and fat malabsorption with deficiency of micronutrients due to reduced bile flow and increased gastrointestinal loss through diarrhoea and vomiting. Increased prevalence of vitamin and mineral deficiencies in patients with chronic liver disease, reflecting the need for basic micronutrient assessment in this cohort of patients (Kozeniecki et al., 2020). Studies also indicate that the rates of glycogenolysis in patients with advanced liver disease is considerably

lower than healthy individuals (Saunders et al., 2010, Purnak and Yilmaz, 2013). Liver cirrhosis negatively impacts nutritional synthesis and affects specifically protein metabolism, leading to a reduction in essential proteins such as albumin (Saunders et al., 2010). Therefore, unsurprisingly, the prevalence of malnutrition in patients with liver cirrhosis is high ranging from 20% in those with compensated disease to as high as 60% in those with advanced CLD and being almost universal in patients awaiting liver transplantation (Saunders et al., 2010, Nutritional status in cirrhosis, 1994).

In the elderly homeless population, the effects and impact of liver disease on nutrition are expected to be higher than the average population. This is partly because elderly patients tend to have poor baseline nutritional status than the rest of the population (Hickson, 2006). Additionally, homelessness is likely to be an independent risk factor for malnutrition. Homelessness leads to a higher risk of malnutrition due to multiple factors encompassing low socio-economic status and poor knowledge of food choice, in addition to the lack of storage facilities (Wiecha et al., 1991, Coufopoulos, 2012, Evans and Dowler, 1999). The synergistic combination of homelessness and excessive alcohol use potentially magnifies the risk of malnutrition (Ijaz et al., 2018). The status of malnutrition in the homeless population, in turn, may have a significant impact on the progression of some chronic illness, including CLD.

In the UK, the literature on homelessness and malnutrition is scarce. However, homeless individuals in sheltered housing in England were estimated to have a 22% higher prevalence of malnutrition compared to hospitalized patients (Elia, 2015). This prompted attempts to improve the nutritional quality of food delivered to this high-risk population. Prior to this, Evans and Dowler (1999) looked at the dietary habits of the single homeless and marginalised people in London and highlighted that many failed to meet the dietary recommendations. A more recent study corroborated this finding, reporting that homeless women's dietary intake in

temporary accommodations in the north of England was poor in all aspects, including proteins, energy, and micronutrients (Coufopoulos, 2012). Additionally, ongoing substance misuse compounds the problem as it results in irregular and interrupted meals (Mahboub et al., 2020).

While the use of the subjective global assessment (SGA), a bedside nutritional assessment tool that includes focused history and physical examination, has been explored, its sensitivity in patients with liver disease has been questionable (Alvares-da-Silva and Reverbel da Silveira, 2005). The body mass index is perhaps the most widely utilized tool for assessing nutritional status in population screening. In patients with advanced liver disease, the body mass index (BMI) and waist/hip ratio may yield inaccurate results due to fluid overload and ascites, resulting in an overestimation of nutritional status. Nevertheless, the presence of low BMI of < 18.5 kg/m^2 is still accepted for selection of those requiring further nutritional assessment (Shi et al., 2014). Measurement of other anthropometric tools in particular mid-arm circumference and triceps skinfold thickness may give more accurate evaluation (Frisancho, 1981). The latter tools have comparative values to healthy individuals and have been shown to be good predictors of mortality in patients with liver disease (Alberino et al., 2001). A mid-arm muscle circumference of <23 centimetres together with a handgrip strength of <30 kilograms yielded a sensitivity of 94% and negative predictive value of 97% for malnutrition (Figueiredo et al., 2000). Moreover, laboratory tests, particularly the level of vitamins, minerals and micronutrients, have been used as surrogate markers of malnutrition and body stores' status in patients with liver disease (Hirsch et al., 1993, Kozeniecki et al., 2020). When micronutrient deficiencies are present, supplementation with multivitamin and replacement of electrolytes are usually recommended.

Therefore, taking the above evidence on board, when looking at the impact of liver disease in vulnerable adults, it is important to assess nutritional status.

1.6 Liver disease in vulnerable groups with high prevalence of homelessness

1.6.1 Liver disease among people who inject drugs (PWID)[1]

There appears to be a temporal relationship between injection of drugs and homelessness. In one study by Linton et al. (2013), 38% of 1,405 participants with current or former injection of drugs had at least one episode of homelessness. Furthermore, among those who ceased injecting drugs, homelessness was linked to relapse. Therefore, the authors concluded that a reduction of IDU behaviours could be achieved by preventing homelessness. Substance misuse disorders are generally considered to be associated with homelessness; the latter is a consequence of substance misuse and a predisposing factor. An Australian study revealed that 19% of 2396 needle exchange programme clients were in unstable housing at the time of the survey (Topp et al., 2013) while 66% had one instance of sleeping rough.

Injecting drug use is responsible for around 90% of all HCV infections in England (Public Health England, 2017), with 52% PWID having a positive HCV serology. The report estimates that about 50% of individuals with HCV may have already been diagnosed (Public Health England, 2017). However, only 5% of PWID sampled are aware of their HCV antibody positivity status (Unlinked Anonymous Monitoring Survey, 2017).

Despite the discovery of DAAs, however, we still need a three-five-fold increase in HCV diagnosis and treatment if we are to stem the national HCV burden (Wedemeyer et al., 2014). However, PWID remain a vulnerable cohort with suboptimal engagement with hospital services. Economic modelling suggests that prioritizing HCV treatment in PWID with a $\leq$40%

[1] This section is based on a published manuscript by the author of this thesis, Hashim et al. (2018)

HCV seroprevalence and mild to moderate liver disease (in combination with opioid substitution therapy (OST)/needle and syringe programs) is more cost-effective than treating other patient groups because of the additional benefit of avoiding onwards transmission also known as "treatment as prevention" (Martin et al., 2013, Martin et al., 2016).

However, an earlier study from Nottingham showed that, overall, only 49% of individuals with a positive HCV serology were referred to a specialist, 27% attended and 10% were treated (Irving et al., 2006). A re-audit about 10 years later showed improvement (80% referred, 70% attended, and 38% commenced treatment) though clearly there remained scope for improvement (Howes et al., 2016). Barriers to HCV treatment remain at all levels of care (patient, provider and national). These include the complex nature of HCV treatment (until recently), the inability of health care providers to appreciate the complex needs of vulnerable PWID, perceived stigmatisation and reluctance to treat those actively engaged in alcohol and substance misuse (Irving et al., 2006, Marufu et al., 2012, Dillon et al., 2016).

Locally in Brighton and as reported by others (Mehta et al., 2008, Lewis et al., 2016) we have been cognisant of the low uptake of HCV services by PWID. In 2011 a hepatitis C nurse was appointed at the largest substance misuse service (SMS) in Brighton to perform blood dry blood spot testing (DBST) for BBVs screening with onward referral to Hepatology services. Over a six-month period, of those identified with a positive BBV screen (n=73), 14 (19.1%) were known to Hepatology services (two previously treated). Of the forty individuals suitable for antiviral treatment, only two (5%) engaged with secondary care (42% declined a referral and 37% disengagement with SMS). No individual was eventually treated (Marufu et al., 2012). Poor uptake of HCV treatment may be contributing to Brighton and Hove having the highest hospital admission /100,000 population with HCV-related liver disease and hepatocellular cancer (HCC) (4.8, 95% CI 3.4-6.5), and highest mortality in those aged < 75yrs from HCV-

related liver disease and HCC (1.39, 95% CI 0.70-2.49) in the south-east (Public Health England, 2017).

These data indicate the value of developing innovative community HCV services. Such a novel strategy would represent patient-centred care with earlier diagnosis and treatment, prevention of onwards-viral transmission and potential for reduction in health inequalities. A community-based model with linkage to care is in line with the recently commissioned National Liver Report that advocates screening and treatment for chronic liver disease in the community (Williams et al., 2018).

NHS targets were to treat 10,000 individuals with HCV infection in 2016, increasing to 15,000/year by 2020 (Public Health England, 2017). If achieved, statistical modelling predicts that around 2620 people would be living with HCV-related cirrhosis or HCC (an 81% reduction) in England by 2030 (Harris et al., 2016) as mandated by the WHO (World Health Organization, 2016). This is, however, unlikely to be achieved without engaging PWID.

A number of models were described in the literature regarding community liver screening in PWID. Some of these models have overlap with the models used to screen for CLD and HCV PWAH. The model of specialist hepatitis nurses working in addiction centres has been implemented before, though care has been fragmented, with BBV screening in the community followed by referral to secondary care (Marufu et al., 2012). Even when nurse-led treatment had been provided at addiction centres, it was often delivered via out-reach sporadic clinics (Selvapatt et al., 2017) and did not always include assessment of hepatic fibrosis (Grebely et al., 2017b). In other models, homeless individuals attending addiction centres underwent review by a consultant Hepatologist and a hepatitis nurse but again only on an intermittent (monthly) basis (Wilkinson et al., 2009). Directly Observed Therapy with pegylated interferon (PEG) and ribavirin (RBV) have also been incorporated into opioid substitution clinics

(Bonkovsky et al., 2008). Nonetheless, these directly observed treatment models are limited to small randomised controlled trials and involve close collaboration with secondary and tertiary services- not always feasible in a community setting (Bruggmann and Litwin, 2013).

Group or peer-based treatment was also trialled, in which an experienced peer co-leads the treatment along with a medical provider. This has led to successful treatment outcomes in various settings but relies on pre-treatment engagement (Sylvestre and Clements, 2007). This model depends on excellent group dynamics and effective communication between peers (Bruggmann and Litwin, 2013).

In the general practice (GP) based model, a GP with additional HCV training offers treatment to PWID alongside OST (Seidenberg et al., 2013). While this model is simple, provision of addiction and HCV treatment by a single GP is demanding and requires great commitment, effort and training of the primary care provider (Seidenberg et al., 2013). Other primary care strategies involved a specialist nurse working in general practices (Jack et al., 2009). However, many PWIDs may not engage with their GPs. The Australians, nonetheless, have managed to treat > 20,000 individuals with HCV infection during Mar-Jun 2016 (previously 2,000-3,000 patients treated per/yr). Multiple factors contributed to this phenomenal success, including prescribing by GPs (The Kirby Institute, 2016). In a recent study in South West England, patients in 46 general practices were randomised to receive either standard care or a complex intervention comprising educational training, posters and leaflets display, the aim being to raise awareness and encourage opportunistic testing through risk prediction algorithms; Hepatitis C Awareness Through to Treatment (HepCATT) (Harrison et al., 2019). In the HepCATT study, interventions resulted in a rise in HCV testing as well as hepatology referrals and treatment initiation rates.

Other established community HCV programmes such as the American ECHO (The Extension for Community Healthcare Outcomes) project have also shown great promise (Arora et al., 2010). This model links Hepatologists with primary care physicians in local communities via telehealth technology. It allows optimal management of HCV patients through "knowledge networks," bringing together interdisciplinary expert specialists from the hospital and multiple community-based primary care practitioners (Arora et al., 2010). Similar outcomes have also been shown in the Veteran Affairs –ECHO programme (Beste et al., 2017). Other innovative strategies include the French mobile hepatitis team (Remy et al., 2016).

1.6.2 Liver disease in prisoners

Prisons are high-risk environments for the development of sexually transmitted and BBVs, which puts inmates at risk of encountering CLD. Most of the data on liver disease in prisons and detention centres come from America, with relatively limited data from elsewhere in the world. The relationship between incarceration and homelessness appears to be two-sided. On one side, there is evidence that homelessness may increase the risk of imprisonment, and on the other side, those who are released from prison may find themselves left homeless or at least become vulnerable to homelessness. In a random sampling survey in the USA, among federal prison inmates, 9% revealed an episode of homelessness in the year preceding their detention (Greenberg and Rosenheck, 2008). Compared to the general population, the survey also demonstrated that previous imprisonment, mental health problems, poor socio-demographic and substance use disorder were linked to homelessness among prisoners. Likewise, among PWAH living in sheltered accommodation in New York, 23.1% had a history of imprisonment within the last two years (Metraux and Culhane, 2006).

Cirrhosis was amongst the top six causes, accounting for 62% of the excess mortality post-release from prison in one study (Spaulding et al., 2011). Liver-related deaths were elevated relative to the reference population, with a standardised mortality ratio of 1.87 (95% CI: 1.44, 2.39). This reflects that CLD's risk and impact continue to be a burden even after release from prison. Regarding CLD complications, in a large prison in Texas, the prevalence of HCC was sevenfold higher than the general US male population (Baillargeon et al., 2009).

Viral hepatitis tends to be a significant factor leading to higher morbidity and mortality from liver disease in prisoners. However, the prevalence and aetiology of CLD amongst prisoners may considerably differ, depending on geographical and ethnic factors. A systematic review by Larney et al. (2013) found a prevalence estimate of HCV seroprevalence in general detainees of 26% (95% CI: 23%, 29%), and 64% (95% CI: 58%, 70%) in those with a history of IDU. However, a French study showed that alcohol-related liver disease was more common in prisoners than viral hepatitis, both in terms of frequency and severity (Jacomet et al., 2016). In this study, they surveyed 702 detainees, of which 357 agreed to participate (51%). The prevalence of HCV was 4.7%, while alcohol excess was observed in 53%. As assessed by transient elastography (TE) and Fibrometer, liver fibrosis was found to be significant in 16% of the prisoners, with the majority of them suffering from alcohol dependence (Jacomet et al., 2016).

In Africa, the picture is similar but not identical. A study looking at liver fibrosis in 703 African prisoners in Togo found an overall prevalence of significant liver disease [LSM >9.3 kilopascals (kPa)] of 3.3% with 12.6 % of the inmates infected with HBV (predominantly) or HCV (Jaquet et al., 2016). Factors associated with significant liver fibrosis after adjusting for other demographic variables were HIV and the use of traditional medicine, highlighting the different aetiological risk factors in Sub-Saharan Africa (Jaquet et al., 2016).

An Egyptian study seeking to determine the seroprevalence of BBVs in 500 prisoners in 2013, demonstrated that HCV antibody was positive in 15.8% with 77% of those with a positive antibody having viremia (Mohamed et al., 2013). HBV core antibody (HBcAb) was found in 9.8% of prisoners, but the prevalence of positive Hepatitis B surface antigen (HBsAg) was not provided. Interestingly, while other common risk factors like IDU were seen, two of the main predictors of viral hepatitis seroprevalence was a more extended stay in prison (>10 years) and shared toiletries. This indicates that long imprisonment can be considered an independent risk factor for BBVs.

The data above suggests that prisoners are at high risk of CLD specifically from viral hepatitis and alcohol and are also more likely to suffer or die from its complications. Hence, screening prisoners for liver disease generally, and particularly viral hepatitis, is imperative. This would require appropriate training of prison staff and engaging them in liver screening and management programmes. In England, it was highlighted by Public Health England (2020) that there is a need to screen for HCV in prisoners and provide appropriate guidance for prisons in delivering a high-quality HCV screening service, ensuring that relevant training is available for staff and that adequate psychosocial support is provided to patients.

Nonetheless, several barriers to detecting liver disease and viral hepatitis among prisoners have been described in the literature. Khaw et al. (2007) suggested that the major barriers to HCV screening in prisoners were lack of proactive approach, prisoner's anxiety and fears coupled with stigma and concerns about confidentiality, poor knowledge about HCV infection, and care interruptions related to transfer, and release of inmates. In the UK, the National Institute for Clinical Excellence (NICE) (National Institute for Health and Care Excellence, 2012) recommends testing for both HCV and HBV in prisoners and highlights the importance of continuity of care to avoid interruptions in managing these infections. The report suggests that

this approach is cost-effective and ensures that prisoners have the same right of access to healthcare as the general population, thereby, eliminating inequalities.

The introduction of dried blood spot testing (DBST) as a practical strategy to improve screening of viral hepatitis in prisoners has been assessed in many trials. A cluster randomised controlled trial involving 6 prisons in the UK (Hickman et al., 2008) assessed percentage point difference (percentage of patients tested 6 months after and 6 months before the introduction of DBS tests) in individuals tested for HCV. Results showed that the average percentage point difference between intervention and control sites was 14.5% (95% CI 1.3-28%, $p = 0.03$). Nurse-led models can also be useful for HCV assessment and treatment of prisoners (Lloyd et al., 2013). The peer-to-peer communication model has been shown to improve compliance of inmates (Sagnelli et al., 2012). It can also favour their access to screening, assessment and treatment. Finally, supportive and preventative measures such as supplying the inmates with personal toiletries, heightening vigilance to prevent tattooing and IDU and providing opiate substitution therapy (OST) for drug users can also be useful in reducing the transmission of viral hepatitis (Zampino et al., 2015).

1.6.3 Liver disease in immigrants and refugees

Over the past four decades, international migration has increased at an unprecedented rate. Many of the new migrants come from areas with a high prevalence of viral hepatitis, arriving in countries with a relatively low prevalence of the infection. Furthermore, the latter problem is compounded by the fact that once an asylum submission is refused, it may result in housing support being withdrawn in the absence of public fund entitlement or legal right to work (Macfarlane, 2020). Therefore, a considerable proportion of refugees may end up being

homeless or rough sleepers. For instance, The Housing Statistical Release (2018) indicated a 6% rise in the number of non-UK rough sleepers from 7014 to 760 between 2016 & 2017.

Several factors are involved in the development of liver disease in immigrants and refugees. The burden of liver disease depends on the country of origin, exposures, previous living conditions, health care access, migration pathways, and other factors. Refugees often differ from host individuals, in terms of access to healthcare, and hence reports have previously shown that refugees tend to experience poorer health outcomes (Pottie et al., 2011).

A systematic review of 110 studies showed that the pooled seroprevalence of HBV in immigrants and refugees worldwide was 7.2% (Rossi et al., 2012). Factors associated with increased prevalence of HBsAg were the region of origin, refugee status and decade of study. In a study in the UK, the prevalence of HBV in immigrants was slightly lower (around 4%) but varied depending on ethnicity and geographical location (Evlampidou et al., 2016).

Another systematic review aiming to establish the prevalence of HBV amongst immigrants showed that the prevalence was different between Western Europe and North America. In Western Europe, the prevalence ranged from 3.7% to 36.7%, but it varied significantly based on the country or areas of origin. In North America, however, the prevalence of HBsAg was estimated to be between 1.6% and 11.1% (Coppola et al., 2015). It also found high prevalence of HBsAg in those emigrating from South East Asia and sub-Saharan Africa due to the high incidence of HBV-related to vertical perinatal transmission (Coppola et al., 2015), showing that different countries may have to implement more aggressive screening programmes, depending on the specific risk of their cohort of immigrants.

A study in Toronto showed a lower prevalence of HBV (4%), with a higher rate among refugees from Asia (12%, $p < 0.001$). However, in this study, the number of Asian refugees was considerably lower than other studies (14%) (Redditt et al., 2015). Interestingly, in this study,

the prevalence of Schistosoma infection was relatively high (15%). The latter finding was also demonstrated by an American study looking at the persistence of untreated parasitic infections in Sudanese refugees in which almost half of the refugees were seropositive for *Schistosoma mansoni* (Quandelacy, 2010).

In the United States, a study in asymptomatic Brazilian immigrants found a 27.7% prevalence of Schistosoma antibodies (Rapoport et al., 2015). In African refugees in the USA, positive Schistosoma serology prevalence was 44% in Sudanese refugees and 73% in Somali Bantu refugees (Posey et al., 2007). Most patients with Schistosomiasis are asymptomatic; hence targeted screening of high-risk population is essential to identify the infection before the development of untoward sequelae. As infection can last many years, the treatment of asymptomatic patients is an important intervention (Rapoport et al., 2015).

On the other hand, HCV in immigrants and refugees is less common. A meta-analysis of 50 studies, representing more than 38,000 migrants worldwide showed that HCV antibody prevalence was 1.9% which is not markedly higher than that of the host population (Greenaway et al., 2015). The most significant factor for higher prevalence, similar to HBV, was the country of origin, with seroprevalence in those emigrating from Sub-Saharan Africa being more than 2%, which is higher than the prevalence in the host countries (Greenaway et al., 2015).

Another risk factor for liver disease amongst this group is drug-induced liver injury, resulting from the treatment of other common diseases in immigrants. The typical example is the treatment of TB, as the first-line antitubercular drugs are potentially hepatotoxic. Due to the increased prevalence of TB in immigrants and refugees originating from Asia and Africa (Lillebaek et al., 2002), close monitoring for drug-induced liver injury is required.

Unfortunately, the data on the clinical course of liver disease in immigrants and refugees is limited, and management remains complex mostly due to language barriers and socio-cultural

challenges. However, in one study, although all refugees with positive HBV screening were referred to their primary care physician, there were no follow-up mechanisms to ensure linkage to care, despite the majority of patients being young (10-39 years) (Museru et al., 2010). Another study from East London looked at the knowledge of immigrants on viral hepatitis. It concluded that immigrants lacked adequate knowledge in all aspect of the disease, including aetiology, symptoms, transmission risk factors, prevention strategies, and treatment. Ethnicity, gender, higher education, better income, and English proficiency all influenced knowledge (Owiti et al., 2015). The lack of knowledge about viral hepatitis may also constitute a barrier to engagement with care, thereby delaying diagnosis and treatment.

The majority of guidelines propose a model in which immigrants from countries of high prevalence of HBV should be offered screening for viral hepatitis. A more recent study looking at the cost-effectiveness of two different strategies for managing refugees with a positive HBV screen concluded that the 'screen, then vaccinate or initiate management' resulted in positive net benefit, compared to "vaccinate-only strategy" (Jazwa et al., 2015).

In the UK, NICE (National Institute for Health and Care Excellence, 2012) highlighted the need to promote and offer testing for viral hepatitis in "immigration removal centres". The length of stay of immigrants in detention centres varies, but many are held for more than a year, which is sufficient time to screen and initiate treatment if required.

1.6.4 Liver disease in patients with mental disorders

Patients with mental problems tend to have higher incidence of physical diseases in general. Moreover, numerous studies report that psychiatric patients have higher mortality rates than the general population (Salazar-Fraile et al., 1998, Karim et al., 2019). It is also documented

that patients with CLD, compared to other chronic somatic disorders, have a higher prevalence of depression and anxiety disorders (Huang et al., 2017). PWAH are generally more likely to suffer from psychiatric comorbidities (Fazel et al., 2008, Nordentoft and Wandall-Holm, 2003, The Housing Statistical Release, 2019).

One major factor leading to the development of liver disease in mentally ill patients is the high prevalence of alcohol and substance misuse. A study looking at the prevalence of liver disease in those with various mental disorders revealed that patients with schizophrenia had higher overall prevalence of liver disease (22.4%), HCV and alcohol-related liver cirrhosis than a matched control group (Fuller et al., 2011). Similar results were found in those with bipolar disorders in this study. Nevertheless, there was no significant difference between those with mental disorders and the matched control in terms of the presence of non-alcoholic fatty liver disease (NAFLD). The study concluded that the main risk factors for liver disease were alcohol use disorder (OR=3.22), bipolar disorder (OR=2.27), substance use disorder (OR=2.28), and schizophrenia (OR=2.74). A similar study from Spain, also confirmed that patients with schizophrenia and neurosis had a higher risk of death from liver disease (Salazar-Fraile et al., 1998). In addition to the previously reported factors, the latter study attributed the higher rates of death from hepatic disorders among neurosis patients to the excessive use of psychotropic medications.

Severe psychiatric symptoms are associated with high rates of risky sexual behaviour (Lagios and Deane, 2007), a risk factor for viral hepatitis. A literature review demonstrated that severe mental illness was associated with the higher probability of sexual intercourse with high-risk partners (i.e. known HIV-positive, intravenous drugs users, or sex workers) (Campos et al., 2008). Amongst adults with severe mental illness in developed countries, between 2% to 58% had sex with a high-risk partner in the previous 3 to 12 months.

A multicentre study in Brazil (11 public psychiatric hospitals and 15 public mental health outpatient clinics), with increased prevalence of high-risk sexual activity, found that seroprevalence of HBV was observed to be 14.7% (Guimaraes et al., 2009). A systematic review of viral hepatitis among patients with mental disorders found rates of HBV ranging from 2.2% in North America to 9.7% in Asia, while HCV rates varied from 3% in Latin America to 17.4% in North America (Hughes et al., 2016). However, in regions with low prevalence of BBVs such as North America and Europe, patients with severe mental illness have a consistently increased prevalence of HIV, HCV and HBV (Campos et al., 2008). This indicates that even in patients with mental disorders, geographical and cultural differences determine the risk of HBV and HCV transmission.

Additionally, an interesting study on major depression disorders revealed that patients with major depression and NAFLD tend to respond poorly to the standard management with lifestyle modifications including weight loss strategies (Tomeno et al., 2015). In addition, those with major depression have higher liver enzymes and more severe steatosis with higher NAFLD activity scores histologically (Tomeno et al., 2015). This could suggest that depression disorders should be incorporated into lifestyle modification programmes when managing patients with non-viral hepatitis liver disease, particularly NAFLD. Nevertheless, the evidence is limited, and further large-scale studies are required to confirm these findings.

1.6.5 Liver disease in the elderly

Increasing age is an established risk factor for more advanced liver disease (Kim et al., 2015). Many studies report that age is an independent risk factor for progression of hepatic fibrosis, specifically in patients with chronic HCV and ALD (Poynard et al., 2001, Forrest et al., 2005).

Age can influence the incidence of liver cirrhosis and HCC in patients with chronic HCV infection (Thabut et al., 2006). Poynard et al. (2001) demonstrated that liver fibrosis rate increased rapidly in those aged >40 with chronic HCV infection. The relative risk for significant hepatic fibrosis (Metavir stage F2 or higher) is 3.8 times higher for those aged 65 or above vs those younger than 65 (Thabut et al., 2006).

Additionally, the prevalence of NAFLD in the elderly population (above 65 years) is as high as 35.1% (Koehler et al., 2012). Gan et al. (2011) also showed that advanced age is associated with fibrosis progression and disease severity in NAFLD patients. It has also been estimated that around 75% of individuals with diabetes mellitus aged above 60 will have some form of NAFLD (Targher et al., 2007).

Rates of both at-risk and binge alcohol drinking are increased in the elderly. In the UK, among those aged over 60 years, 53% of men and 38% of women were current drinkers and 28% of ALD cases are diagnosed in individuals aged 60 years and above (Breslow and Smothers, 2004, Mangion et al., 1992). This could be due to the raised incidence of social isolation, depression and bereavement in older adults (Kim et al., 2015). Moreover, there is some evidence that older adults with alcohol use disorder are likely to become homeless. HCV prevalence is 0.2% in blood donors compared to 11% in the elderly (Baldo et al., 2000) and HCV-related complications including cirrhosis and HCC are more prevalent in the elderly (Brind et al., 1996).

At first hospitalisation, older adults present with more advanced stages of liver disease, often with decompensated cirrhosis related complications (Frith et al., 2009). In an early study, all elderly individuals with alcohol-related liver disease presented with cirrhosis (100%) vs 55% in those aged 60 years less (Woodhouse and James, 1985). Moreover, those older than 60 years had higher one-year mortality (34% vs 5%) (Potter and James, 1987). Around 1 in 5 of patients

admitted with ALD are aged more than 60 years and have worse outcomes during admission with a median survival of 12.6 months compared to 22.4 months for younger people, though these differences were not statistically significant (Potts et al., 2013). The reasons and mechanisms for the more aggressive liver disease in the elderly remain unknown.

Table 1.2 (below) summarises aetiology and prevalence of liver disease in vulnerable individuals.

Vulnerable group	Link to homelessness	Aetiology of liver disease	Other remarks
Homeless individuals (PWAH)	--	-HCV = 26.5% and 69.1% Chronic HBV = 1-3% HBV exposure (positive anti-HBc) 27%-30% ALD	Higher mortality rates from liver disease (age adjusted). Synergistic effect between HCV and Alcohol leading to rapid progression of liver fibrosis.
People who inject drugs (PWID)	Unstable housing is common among those approaching needle exchange services	HCV Alcohol-related liver disease	- Concomitant alcohol use disorder is common. - Treatment of HCV in this group has the additional benefit of avoiding onward transmission. - Opportunistic screening in needles exchange and OST services is feasible and beneficial.
Prisoners	Two-sided effect: homelessness increases the risk of imprisonment and conversely newly released prisoners are more likely to be homeless	HCV = 5.7% - 15.8% ALD	Higher prevalence of HCC. Higher mortality from liver disease compared to general population.
Immigrants and Refugees	A number of asylum seekers end up being rough sleepers when	HBV = 3.7 – 36.7% depending on country of origin	Lack of knowledge on viral hepatitis and difficulty accessing the healthcare system in the host country are major hurdles.

Vulnerable group	Link to homelessness	Aetiology of liver disease	Other remarks
	their applications are rejected	Positive Schistosoma serology in 44-73% in immigrants/refugees from endemic areas	Opportunistic screening and vaccination for HBV is a good strategy to tackle the burden of liver disease.
Patients with mental disorders	Homelessness and mental health problems frequently co-exist. Psychiatric illness can predispose to homelessness and may often lead to persistent homelessness status	HCV = 3- 17.4% HBV = 2.2 – 9.7% HBV = 14% in Brazilian study of patients with mental health disorders NAFLD	Higher prevalence of liver disease in relation to HCV and NAFLD. Severe psychiatric illness may influence compliance with HCV treatment. NAFLD may be linked to the use of some anti-psychotics.
Elderly people	Older adults with alcohol misuse are likely to become homeless	HCV = 11% ALD NAFLD particularly in those with diabetes and aged > 60	Rapid progression of liver disease. Higher incidence of HCC in elderly with CLD. Higher mortality from liver disease.

Table 1. 2: Aetiology and prevalence of liver disease in vulnerable individuals with high prevalence of homelessness.

HCV = Hepatitis C, HBV = Hepatitis B, NAFLD = Non-alcoholic fatty liver disease, ALD = Alcohol-related liver disease, CLD= Chronic liver disease, HCC = Hepatocellular carcinoma, PWAH = People who are homeless, PWID = People who inject drugs

1.7 The need for dedicated liver services for the homeless

Given the high mortality and morbidity from liver disease and viral hepatitis, there is a great need to develop community services dedicated to screening and managing liver diseases among PWAH and vulnerable adults. Moreover, England aims to be the first country to eliminate HCV within the next 5 years which is earlier than the World Health Organisation (WHO) target of 2030 (Grebely et al., 2017b). Nonetheless, there are still about 89,000 people with HCV in England, the vast majority undiagnosed (Public Health England, 2020). Homeless individuals represent one of the hardest to reach groups due to poor engagement with traditional care models. In addition, the homeless and particularly those who inject drugs remain an important reservoir for the HCV infection. Hence, innovative strategies need to be employed to screen this high-risk group to facilitate their engagement with liver services and pave the way towards eliminating HCV.

In Brighton and Hove (South East England), 876 people have been found rough sleeping in the city over the past two years with 43% were found to have an episode of rough sleeping once (Brighton and Hove City Council, 2014). Since previous research discovered that a tiny proportion (<5%) of vulnerable adults successfully engage with secondary care and hospital referrals (Marufu et al., 2012), near-patient testing, assessment and stratification of liver disease in the community seems to be an appealing approach. Such a strategy is thought to be more acceptable to this cohort of patients (Wilkinson et al., 2009) and may allow earlier intervention and improved care, thereby mitigating health inequalities and avoiding poor health outcomes. A population-based study in the UK described that hospital admission with CLD substantially impaired prognosis [1 and 5 yr. survival probabilities 0.84 (95% CI 0.83-0.86) and 0.66 (95% CI 0.63-0.68) for ambulatory group compared to 0.55 (95% CI 0.53-0.57) and 0.31 (95% CI 0.29-0.33) in those hospitalised] (Ratib et al., 2014). Therefore, an early and

timely diagnosis of CLD in the community is desirable and facilitates timely and appropriate interventions, particularly since homeless individuals have poor overall engagement with both primary and secondary care.

1.8 Enhancing detection of liver disease in the community using non-invasive tools

In order to tackle the rising mortality from liver disease, a multi-level approach has to be adopted. This includes primary preventative measures aiming to reduce the risks of developing CLD by increasing access to OST/needle exchange, reducing alcohol consumption and lifestyle modification to decrease the risk of HCV, ALD and NAFLD, respectively. A typical example of a successful primary intervention was the decrease in liver mortality observed temporarily between 2008 and 2013 following the introduction of an alcohol duty escalator in the UK (Williams et al., 2018), resulting in a drop in alcohol affordability. The mortality from liver disease then began to rise again once this policy was abolished. Another critical intervention is the Minimum Unit Price which was launched in 2018 in Scotland (but not yet in England). This intervention was previously shown to efficiently reduce adverse alcohol-related outcomes in British Columbia and Canada with nearly 9% reduction in alcohol-related hospital admissions and a 32% reduction in alcohol-related mortality (Stockwell et al., 2013, Zhao et al., 2013).

While there are major advancements in managing certain aetiologies of CLD like chronic HCV, such that elimination of the disease is currently a feasible scenario, the intervention measures for NAFLD and ALD are still limited to the traditional lifestyle modifications and alcohol cessation programs, respectively. About 40-50% of patients with ALD will stop drinking after admission with cirrhosis, and evidence from a feasibility study shows that a community diagnosis can be efficient in reducing hazardous drinking (Hazeldine et al., 2015).

Secondary prevention strategies through early detection of liver disease are similarly crucial. Liver disease is predominantly silent in the early stages and patients may not have symptoms and signs until complications appear at advanced stages (Harman et al., 2015), resulting in late diagnosis in a considerable proportion of patients. Hence the need for timely detection of aetiological factors leading to liver disease which are amenable to intervention such as HCV, and identification of those with hepatic fibrosis so measures can be put in place to prevent progression to advanced fibrosis and its complications.

Evidence shows that liver function tests (LFTs) are not reliable to identify patients with progressive or significant fibrosis. Elevated levels of serum alanine transferase (ALT), for instance, may reflect liver inflammation or some degree of fatty infiltration without necessarily indicating the presence of hepatic fibrosis. A large retrospective study looking at outcomes of primary care referrals for abnormal LFTs demonstrated that LFTs had poor sensitivity for predicting CLD and that in the majority no formal diagnosis of liver disease was made within a median of 3.7 years of follow up (Donnan et al., 2009). The study also showed CLD detection rates as low as 3.9% within 5 years of the abnormal LFTs. The rate of diagnosis of CLD following the finding of abnormal transaminases was even lower in the BALLETTS study (1.4%) (Armstrong et al., 2012). According to one study, one-third of patients with HCV will have a normal serum ALT, and the proportion with HBV with normal ALT is probably even higher (Inglesby et al., 1999). Despite this, liver enzymes are still being used as a screening tool in the community to detect liver disease with the majority of referrals for specialist opinion being triggered on the basis of abnormal LFTs (Ratib et al., 2014).

On the other hand, liver biopsy, which is now less used even in secondary care, is not a practical tool for stratifying hepatic fibrosis in the community. Although GPs currently have access to ultrasonography (USG) in the UK, this appears to have a little diagnostic and prognostic value

in detecting early CLD. It also performs poorly in ALD, with high false positives rates (Pavlov et al., 2016). The lack of a perfect community non-invasive tool for detecting early liver disease delays the diagnosis of CLD, many cases with CLD are probably missed in the community using the standard models utilizing algorithms of LFTs and ultrasound. A UK study showed that between 1989 & 1999, half of the individuals with cirrhosis had their initial diagnosis of liver disease only after the first episode of hospitalization with decompensation (Ratib et al., 2014). Moreover, the diagnosis of liver disease following hospitalization carried a worse prognostic value and higher risk of death compared to those diagnosed while ambulatory (HR=2.78, 95% CI 2.53 to 3.06) (Ratib et al., 2014). Considering the high costs of managing patients with advanced liver disease, it would be ideal to establish the diagnosis of liver disease early in the community using simple non-invasive tests.

Recognising these gaps, the Royal College of General Practitioners (RCGP) introduced a programme in 2016 aiming to guide and support General Practitioners (GPs) in identifying and providing care to patients with CLD in the community (Royal College of General Practitioners, 2016). The programme introduced a liver disease toolkit that summarises the management strategies of common liver conditions and the available practical guidelines in the field.

In clinical practice, particularly in hospital settings, imaging modalities such as USG, computed tomography (CT) and magnetic resonance imaging (MRI) are the main methods for detection and diagnosis of advanced liver disease either through the morphological appearance and changes in the liver or through features of portal hypertension such as the presence of splenomegaly and reversal of portal vein flow with collaterals (Berzigotti et al., 2010). The latter feature is also detected indirectly through upper gastrointestinal endoscopy which allows detection of varices and portal hypertensive gastropathy. However, these modalities are expensive and are not available for community screening.

Recently, however, there have been substantial developments in the field of non-invasive assessment of hepatic fibrosis. The three main categories in this respect are serum biomarkers, Ultrasound-based elastography techniques and advanced imaging such as magnetic resonance elastography (MRE) (Papastergiou et al., 2012). Arguably these recent advances in non-invasive methods enable easy and quick recognition of liver fibrosis and reduce the cost burden of CLD on the healthcare system through improved surveillance pathways. Their accuracy and reproducibility allow monitoring of progression or regression of liver fibrosis over time. Nonetheless, the validation of these new techniques in community-based settings is not widely ascertained, and further evaluation of their use, cost-effectiveness, and availability in primary care needs to be undertaken (Harman et al., 2015).

1.8.1 Indirect serum biomarkers for the detection of hepatic fibrosis

Serum biomarkers for liver fibrosis are generally divided into indirect biomarkers, utilising a combination of routine liver function tests and other laboratory data; and direct biomarkers, identifying products of the degradation of the hepatic extracellular which reflect the process of fibrogenesis and fibrinolysis.

A simple aspartate aminotransferase: alanine transferase (AST: ALT) ratio can help determine significant fibrosis as an initial screening test (Park et al., 2000). In one study, AST: ALT ratio of > 0.64 had an AUROC of 0.83 with 93% negative predictive value (McPherson et al., 2010). However, the most commonly used indirect serum biomarkers in clinical practice are the AST: Platelet Ratio Index (APRI) and Fibrosis-4 (FIB-4) tests. The two tests use a combination of AST, ALT, platelet count and age (Wai et al., 2003). They are cost-free and can be easily performed at the bedside (Papastergiou et al., 2012). APRI score is perhaps the most studied indirect biomarker, and with a cut-off value of 0.5 it had 81% sensitivity, but only 50%

specificity, in predicting significant fibrosis (Metavir ≥F2) (Shaheen and Myers, 2007). For cirrhosis (F4), the sensitivity and specificity of an APRI threshold of 1.0 were 76% and 72%. FIB-4 was initially introduced to stratify the degree of fibrosis in patients with chronic HCV/HIV co-infection (Sterling et al., 2006). In a large cohort of patients with HCV monoinfection, FIB-4 test allowed detection of both severe fibrosis (AUROC 0.85) and cirrhosis (AUROC 0.91) (Vallet-Pichard et al., 2007). FIB-4 also demonstrated good reliability in patients with chronic HBV and NAFLD (Mallet et al., 2009, McPherson et al., 2010). A cut-off FIB-4 score of < 1.45 in patients with NAFLD has a negative predictive value of 90% and a sensitivity of 84% for excluding advanced fibrosis. Using a cut-off of >3.25, the positive predictive value (PPV) was 65% and specificity was 68% (Kobayashi et al., 2017, Shah et al., 2009).

A large-scale population community screening programme in Taiwan looked at the performance of both FIB-4 and APRI in the community (Kuo et al., 2019). In this cohort of more than 180,000 participants including HBV, HCV and non-HBV non-HCV cases, both APRI and FIB-4 correlated positively with HCV and hepatocellular carcinoma but not HBV infection. Nonetheless, the study did not investigate the performance of these two indirect biomarkers in diagnosing hepatic fibrosis or cirrhosis in the community.

1.8.2 The Enhanced Liver Fibrosis (ELF) Test is the most validated direct serum biomarker

The Enhanced Liver Fibrosis (ELF) was originally introduced in 2004 as the European Liver Fibrosis test (Rosenberg et al., 2004). It combines three direct serum biomarkers related to the components of the extracellular matrix; hyaluronic acid (HA) and tissue inhibitors of metalloproteinases 1 (TIMP-1) which regulate activities of matrix metalloproteinases (MMPs)

and lastly amino-terminal propeptide of procollagen type III (PIIINP) which is linked to collagen synthesis (Rosenberg et al., 2004, Xie et al., 2014). While all three biomarkers reflect the degree of liver fibrosis, the ELF test is algorithmic incorporation of the markers and is expressed as a score. The age factor was initially incorporated into the ELF algorithmic equation but was subsequently removed for simplification (Kim et al., 2012), and the test was re-introduced as the Enhanced Liver Fibrosis test.

ELF is highly reproducible and is validated in several studies across a wide range of aetiologies of CLD (Zarski et al., 2013, Guha et al., 2008, Yoo et al., 2013). It demonstrated good accuracy in the diagnosis of moderate to severe fibrosis in a group of patients with mixed aetiological factors for CLD that included mostly patients with HCV (Rosenberg et al., 2004). ELF score ≥ 9.8 (which is the manufacturer's recommended cut-off value for significant fibrosis) reliably identifies significant fibrosis in patients with CLD (Fagan et al., 2015). In one meta-analysis of nine studies, ELF score was found to have a pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio values for clinically significant liver fibrosis of 83% (95% CI = 0.80–0.86), 73% (95% CI = 0.69–0.77), 4.00 (95% CI = 2.50–6.39), 0.24 (95% CI = 0.17–0.34), and 16.10 (95% CI = 8.27–31.34), respectively; while for detection of cirrhosis, the values were 80% (95% CI = 0.75–0.85), 71% (95% CI = 0.68–0.74), 3.13 (95% CI = 2.01–4.87), 0.29 (95% CI = 0.19–0.44), and 14.09 (95% CI: 5.43–36.59), respectively (Xie et al., 2014).

ELF score is also a valuable tool in predicting progression to advanced fibrosis and liver-related complications. In a study including 457 patients followed up for a median of 7 years, ELF score predicted liver-related outcomes independent of liver biopsy scores (Parkes et al., 2010). The study also showed that the dynamic changes in ELF test were crucial in predicting outcomes of liver disease as a one-unit change in ELF score was associated with a two-fold increase in

the risk of development of a liver-related outcome. Another study looked at 300 patients with a median follow up 6.1 years for predefined liver-related clinical outcomes as well as evidence of progression to advanced fibrosis (Irvine et al., 2016). The study reported that 19.2% with an ELF score > 9.8 had a liver-related outcome during the follow-up period, in contrast to <1% in those with a score <9.8. Similar to the previous study, a unit rise in the ELF score in this study was found to be associated with 2.53-fold increased risk of a liver-related event. Clear clinical progression to cirrhosis was seen in 55% of those with ELF > 9.8 compared to only 3.5% in those with a score below this cut-off value (Irvine et al., 2016).

ELF test has been extensively validated primarily in HCV and NAFLD. However, a study exploring the role of ELF test in chronic HBV found area under the receiver operating characteristic curves (AUROCs) to predict significant fibrosis (F ≥2), advanced fibrosis (F ≥3), and cirrhosis (F = 4) were 0.901, 0.860, and 0.862 respectively (Kim et al., 2012). More importantly, it showed that for maximum sensitivity and specificity the following cut-offs should be used; 8.5, 9.4, and 10.1 for F ≥2, F ≥3, and F = 4, respectively.

ELF test has also been utilised to refine community referral pathways leading to reduction in unnecessary referrals. One recent study evaluated a community pathway using a stepwise algorithm incorporating FIB-4 score and ELF test. In their large cohort of 3,012 patients, they were able to diagnose five times more patients with advanced fibrosis and cirrhosis compared to the standard pathway adopted by GPs prior to the development 2-step pathway (OR: 0.193; 95% CI 0.111-0.337; p <0.0001) and achieve 88% reduction of referrals to secondary care (OR0.12; 95%CI: 0.042-0.349; p <0.0001), (Srivastava et al., 2019a).

Finally, some biomarkers use a mixture of direct and indirect markers such as the Hepascore which combines hyaluronic acid as a direct product of fibrinogenesis with other indirect blood parameters (Gamma-glutamyl transferase, Alpha2 macroglobulin, bilirubin) and demographic

data including age and sex (Guechot et al., 2010). Although the idea of incorporating direct/indirect biomarkers is theoretically appealing, these combined biomarkers still have not gained wide recognition in clinical practice.

One major criticism of serum biomarkers is that, although they can rule in or rule out cirrhosis, their reliability in distinguishing the intermediate stages of liver fibrosis is insufficient (Lackner et al., 2005). Moreover, indirect biomarkers use routine LFT data and platelet count, which are often affected by acute inflammation and other haematological conditions, respectively. Similarly, the ELF test components, particularly hyaluronic acid, can be influenced by extrahepatic fibrogenesis and severe renal impairment (Gunes Yegin et al., 2019).

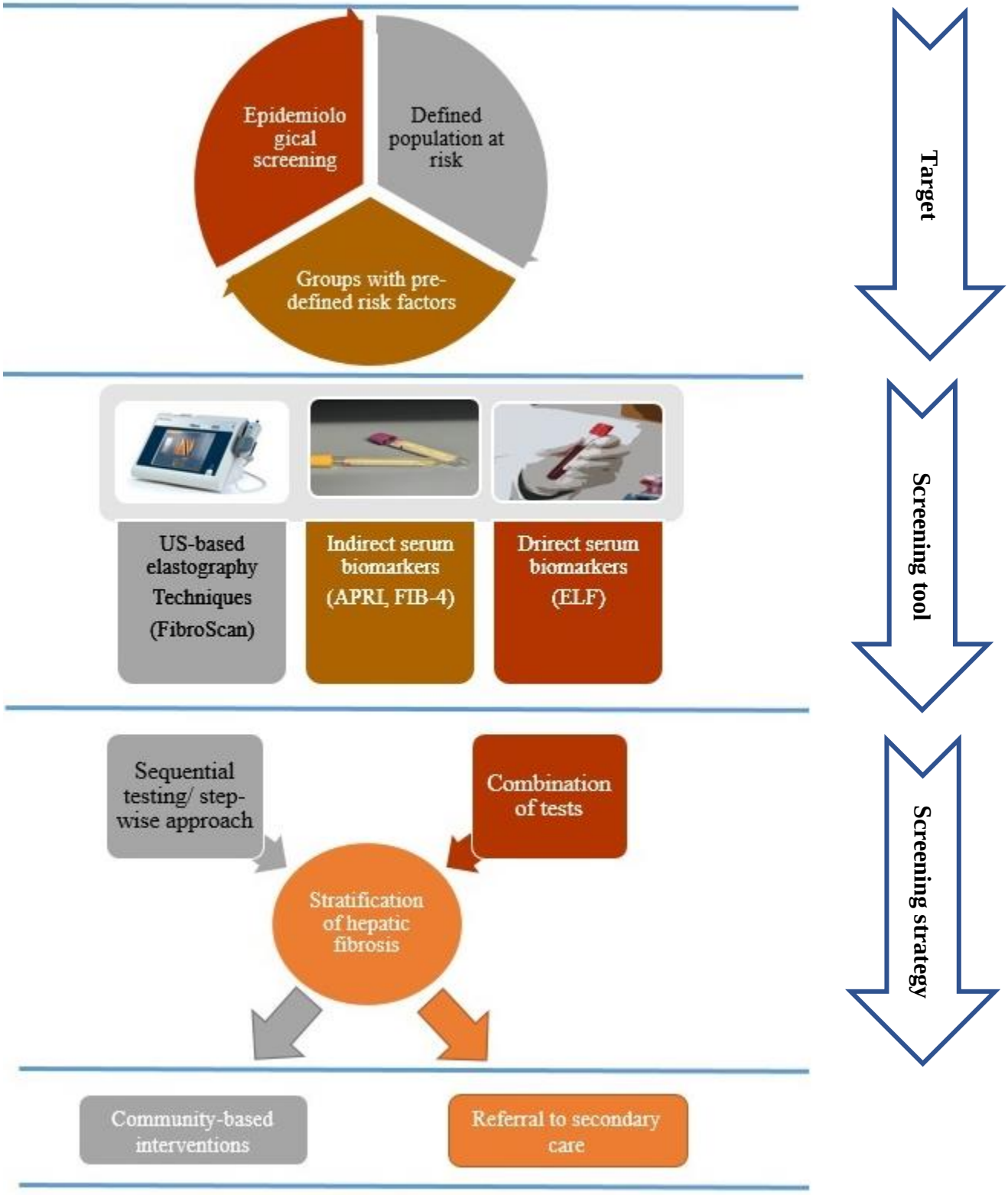


Figure 1. 2: Concepts of screening for liver fibrosis in the community using non-invasive tools.

1.8.3 The evidence for using transient elastography in community screening for liver disease

USG-based elastography techniques have resulted in a paradigm shift in the management of patients with CLD by facilitating the staging of hepatic fibrosis and enabling rapid and accurate assessment. Transient elastography (TE) using the FibroScan (FibroScan® Echosens®, Paris, France) is perhaps the most validated. It is painless, rapid and utilises liver stiffness as a measurement of severity of liver fibrosis through the transmission of low-frequency vibrations which induce an elastic shear wave that propagates within the liver; hence it is often referred to as Vibration-Controlled Transient Elastography (VCTE) (Sandrin et al., 2003). The area assessed through TE is at least 100 times that detected by liver biopsy. It is a widely accepted technique for the detection of all stages of liver fibrosis in individuals with most aetiologies of CLD (Sandrin et al., 2003; Talwalkar et al., 2007) with a sensitivity and specificity around 80-90%. The results are presented in kiloPascals (kPa) ranging from 2.5 to 75 kPa, with 5.5kPa or less being a normal value (5.2kPa for females vs 5.8 kPa for males), (Roulot et al., 2008).

Nonetheless, TE appears to be more useful in diagnosing fibrosis in the two extremes of the spectrum i.e. F4 (cirrhosis) or F0 (no) fibrosis. The FIBROSTIC study showed that TE was superior to serum biomarkers in diagnosing cirrhosis and detecting its early stages (Munteanu et al., 2011). Moreover, by using a pre-test probability of 50%, TE can diagnose cirrhosis in 90% of the cases. A meta-analysis showed that a cut-off value of 13.1kPa could be used to diagnose cirrhosis (Friedrich-Rust et al., 2008). However, the application of a rule in and rule out criteria and using a range instead of single cut-off values also improve the accuracy of TE in the detection of cirrhosis (Berzigotti et al., 2010). TE does not come without limitations. Although the manufacturers have introduced strict criteria for obtaining an accurate FibroScan result involving at least 10 measurements and interquartile over median ratio less than 30% (Foucher et al., 2006), the examination is influenced by many confounding factors. These

variables include but not limited to raised ALT, heavy meals, alcohol excess, ascites and obesity (Yoshioka et al., 2008). The latter barrier can be somewhat overcome by using an XL probe; however, the estimation of fibrosis in obese patients with NAFLD remains a challenge when using the FibroScan (Myers et al., 2012). The FibroScan device comes in portable versions, enabling its utilisation as a practical tool for mass population screening in the community (Myers et al., 2012, Wong et al., 2012).

Several studies have looked at incorporating transient elastography into screening pathways to detect and stratify liver disease in the community. The UK guidelines at present recommend assessment of hepatic fibrosis to determine the severity of liver disease, before commencing treatment, using non-invasive tools either through surrogate markers of fibrosis or liver stiffness measurement, particularly in the context of NAFLD (National Institute for Health and Care Excellence, 2016). In the case of HCV, this approach allows identification of those with advanced fibrosis or cirrhosis who may not only receive a different DAA regimen but may as well require long-term secondary care follow up for HCC surveillance. The literature appears to focus on two screening strategies; population-based screening or more specific and targeted screening based on identifying high-risk groups or vulnerable individuals who have one or more risk factors for developing CLD. The role of non-invasive tests in facilitating engagement with hepatology services has been explored in all these settings, although the data remain inadequate. The advantages and disadvantages of the different screening strategies are summarised in Table 1.3.

Screening strategy	Purpose	Limitations
General population screening	Usually aims to establish epidemiological data such as prevalence of aetiological or risk factors as well as outcomes of disease in the community.	Feasibility challenges. Needs a large sample.
Targeted screening based on predefined risk factors	Used to identify those with significant disease that benefit from treatment such as those with high BMI, alcohol excess.	Relies on definition of risk factors. Different values used to determine best cut-off for screening tools.
Targeted screening for a pre-defined group at risk	Involves screening of a population at risk of liver disease such as homeless individuals, prisoners, substance misusers.	Vulnerable populations are hard to reach and often difficult to engage.

Table 1. 3: The various screening strategies for liver disease using non-invasive tests, their purposes, and limitations.

A large study from Australia looked at predictors of advanced fibrosis and liver-related events among 780 community patients with HCV from 21 primary care centres in comparison to a hospital-based cohort (Bloom et al., 2018). Advanced fibrosis, defined as liver stiffness measurement (LSM) >12.5kPa was observed in 16.5% in the community vs the hospital cohort. The study also demonstrated that the best LSM cut-off for predicting liver-related events in the community setting was 24.0 kPa over a median follow-up of 15.2 months. Moreover, liver-related events occurred in 9.3% of those with an LSM ≥12.5 kPa. Out of the 780 patients, 231 were referred for further evaluation to a tertiary centre; split between 89 with LSM between 8 and 12.5 kPa, and 129 with LSM ≥12.5 kPa. At-risk alcohol consumption, older age, elevated body mass index and ALT were all found to be independent predictors of elevated LSM on multi-variate analysis. Another noteworthy finding was that of those with advanced fibrosis (16.5%) in the community, 8.5% had no laboratory, clinical or imaging features of advanced liver disease.

Another study by Hefner et al. (2016) presented evidence supporting the use of FibroScan in a community clinic treating individuals with liver disease in Southern California. A total of 1341 people were screened between 2013 & 2016. The main reason for referral from primary care to the community centre was HCV (84.7%); other risk factors for CLD being fatty liver (9.2%) and HBV (2.4%). Advanced fibrosis using TE was observed in 50.5% of the HCV patients and 38.5% with NAFLD.

Harman et al. (2015) also adopted this targeted community screening approach by selecting those with hazardous alcohol intake, type 2 diabetes mellitus and persistently raised ALT, in two primary care centres, showing that 98 (26%) had abnormal FibroScan readings. It is important to note that 71 (72%) of those with elevated liver stiffness measurement (>8 kPa) had normal liver enzymes. A similar observation was previously reported by Fracanzani et al.

(2008) in a cohort of patients with biopsy-proven Non-alcoholic steatohepatitis (NASH), of whom 59% had normal ALT.

In a follow-up study, Harris et al. (2019) looked at 533 patients from primary care with the same criteria above and found that 66 (12.4%) had raised LSM (≥ 8.0 kPa). Obesity, in combination with any other risk factors (type 2 diabetes or hazardous alcohol use), further increased the number of patients with an elevated LSM. On multivariate logistic regression analysis, a high body mass index and type 2 diabetes mellitus were significantly associated with an elevated LSM. Moreover, obesity was the only risk factor for clinically significant liver fibrosis in 31% of the patients using this pathway. Prevalence of cirrhosis was 4.8% which is slightly lower than the earlier study (3%) (Harman et al., 2015). The Nottingham group is currently running the Scarred Liver Project which aims to improve the diagnosis and management of CLD by introducing a new liver pathway between primary and secondary care encouraging GPs to follow an algorithm for referring patients, with defined risks factor for chronic liver disease, directly for specialist investigations and input (National Institute for Health and Care Excellence, 2018).

In a more recent study from Scotland, socially deprived individuals with harmful alcohol drinking were identified and consented for FibroScan (Matthews et al., 2019). In this nurse-led model, those who had an LSM of 7.1kPa (significant fibrosis) and above were invited for a clinic consultation. Based on this consultation outcome, onward referrals to a hepatology specialist in secondary care were made. Patients recruited were monitored for compliance for six months. Of the 76 who were finally included, 20 (26%) had significant fibrosis (LSM >7.1kPa); 12 were referred to secondary care, all of whom engaged with the liver services. Although the sample was small, this prospective study showed that a nurse-led outreach clinic

utilising a non-invasive tool such as FibroScan encouraged vulnerable heavy drinkers to engage with liver services.

1.8.4 Challenges of utilising non-invasive liver screening tools in the community and remaining gaps

The current NICE guidelines recommend screening for CLD using FibroScan as a first-line tool in those with harmful alcohol drinking with the view of risk stratification in the community (National Institute for Health and Care Excellence, 2016), with LSM of 14.6 kPa having a 95% specificity for diagnosing cirrhosis; and positive and negative predictive values being 74% and 96% respectively. However, TE is not readily available to all GPs. Moreover, LSM assessment in the UK costs around £50 and considering the number of individuals who currently fulfil the hazardous drinking criteria (estimated to be 4-5% of the population) (Jarvis and Hanratty, 2017), the cost and practicality of implementing the screening service are certainly challenging. In fact, a repeat FibroScan in 3 years-time is still recommended if cirrhosis is ruled out at initial screening reflecting a longitudinal burden and further cost implications of implementing this pathway (National Institute for Health and Care Excellence, 2016). Furthermore, unless dedicated community screening clinics for liver disease are established, this may result in huge overburden of secondary care services with FibroScan referrals.

Nevertheless, if the FibroScan service is shifted to the community, Jarvis and Hanratty (2017) estimate that in order to conduct around 1.125 million scans a year for community liver screening, around 250 FibroScan machines performing 20 scans a day, 5 days a week around the year would be required. Assuming £50 per FibroScan, the community screening cost in the UK may reach £56 million per year for the test alone without taking into account the clinical consultations.

NICE has recently adopted the Enhanced Liver Fibrosis (ELF) test (which costs £108) as a screening test in the community for NAFLD (National Institute for Health and Care Excellence, 2016). ELF is not a point of care test and additionally is not easily accessible to primary care providers. A large number of tests will have to be performed to achieve adequate screening, given that NAFLD prevalence could be as high as 30% in western countries (Dyson et al., 2014). In addition to all of this, liver disease is still not recognized as a priority by Clinical Commissioning Groups with no or limited incentives provided to GPs for keeping a register of patients with CLD (Jarvis and Hanratty, 2017).

In view of these challenges, studies have explored the cost-effectiveness of screening pathway in the community. Srivastava et al. (2019b) compared the costs of 5 different pathways for detection of NAFLD in the community; a standard care pathway, FIB-4 for all patients followed by ELF test for patients with indeterminate FIB-4 results, FIB-4 followed by FibroScan for indeterminate FIB-4, ELF alone, and FibroScan alone. The cost-analysis indicated that for advanced fibrosis the costs were £25,543, £8932, £9083, £9487 and £10,351 respectively. These outcomes suggest that a two-tier approach using two serum biomarkers can improve resource utilisation. However, more studies are required before any firm recommendations can be made.

Nevertheless, targeting individuals with defined risk factors and vulnerable adults appears to be the best approach for community screening. The main challenge that remains is formulating strict criteria to define high-risk groups and establish cut-off values for triggering a referral to secondary care.

Many liver community screening models for homeless individuals have been proposed and trialled. These models range from services set-up in dedicated community centres catering for homeless and vulnerable adults to more proactive strategies such as utilising peers in

recruitment and screening. However, there is still no consensus as to which model serves this population better and what screening tools should be utilised in these models to achieve the highest level of cost-effectiveness, engagement and linkage to care. The advantages and disadvantages of each of these models are summarised below (Table 1.4). A description of the various studies looking into the detection of liver disease and HCV is detailed in Chapter 3 (systematic review).

Type of model	Advantages	Disadvantages
Hostel/Shelter based	- Provides near patient service. - Provides easy and access to patients. - Utilises hostel staff and key workers to maximise recruitment.	- No great opportunity for on-site integrated services. - Requires significant resource mobilization if the service is to be offered in several hostels.
Street/Road-based and campaigning	- Allows screening of a large number of individuals in a short period of time. - Can be utilised to raise awareness of the targeted group about liver disease	- Difficult to follow patients up after screening. - Usually implemented as a single isolated event with limited sustainability.
Community services based in drug and alcohol misuse services	- Allow for opportunistic screening. - Fibrosis assessment using FibroScan can be offered onsite. - Opportunity for integrated treatment through social, drug and alcohol support which can offer holistic management resulting in better compliance and outcomes.	- Relatively small numbers can be recruited. - Limited active case finding activity as the service is commonly confined only to patients who are engaging with these centers. - Subject to resource limitations.
Remote consultations	- Involves iver specialist input in the management of patients through remote consultations. - Engagement of primary care practitioners with liver care.	- Requires close collaboration between specialists and community workers. - Many individuals were lost to follow up in the study which adopted this approach
Peer support models And mobile services	- Use of peers to aid active case finding.	- Requires good training of the peers.

	- Multi-centre approach - Peers can be trained to undertake rapid testing such as saliva rapid testing for HCV. - In some models, peers were trained to perform FibroScan. - Homeless people may be willing to engage more with peers.	- Relies on commitment and acceptability of the peer worker.
Dedicated Primary care/community Centers for homeless and vulnerable adults	- Can cover a large homeless population. - Opportunity for multidisciplinary approach through education, counselling and screening for other health problems. - Allow for engagement of primary care physicians in the liver screening and treatment process.	- Homeless adults frequently do not engage with their primary care physicians. - Primary care physicians may not be ready or willing to accept the burden of screening and treatment of HCV cases in the community.
Multi-site approach	- Targets homeless population at multiple sites. - Maximises the number of individuals covered.	- Feasibility of running the service in multiple sites may be challenging on the long term.
Models offering accommodation and housing first	Based on the idea that homeless individuals are more likely to be compliant and engaged if they have stable housing.	- Assessment and treatment of liver disease is often subject to delays as accommodation is awaited. - Small numbers can be accommodated in these models.

Table 1. 4: Community models for screening for liver disease in homeless individuals and their advantages and disadvantages.

1.9 Senescence markers in liver fibrosis: the role of serum cytokeratin 18 (CK-18), matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs)

Serum apoptotic cytokeratin 18 (CK-18) and matrix metalloproteinase 2 (MMP-2) are two hepatic senescence markers considered non-invasive biomarkers of hepatic fibrosis.

CK-18 is a substrate of caspases during apoptosis, an essential intermediate filament protein in hepatic cells (Caulin et al., 1997, MacFarlane et al., 2000). Studies have shown that the level of peripheral CK-18 is associated with the degree of hepatocyte apoptosis, and severity of fibrosis and inflammation in chronic HCV and NAFLD (Yilmaz, 2009b, Kwok et al., 2014, He et al., 2017). There are two types of antigens related to CK-18, M30 antigen (a neoepitope in CK-18) and M65 (cytosolic pool of CK-18); both can distinguish between advanced and early-stages fibrosis (Yilmaz, 2009a). Of note, the role of CK-18 as a serum biomarker in liver disease has been explored primarily in NAFLD. In a meta-analysis of 11 studies, including 822 patients (389 had histological diagnosis of NASH), the performance of M30 and M65 was found to be similar (Kwok et al., 2014). M30 is a more commonly used test, and in a subgroup of six studies, a cut-off level of 121.6–338.0 U/L had a 60–88% sensitivity and 66–97% specificity for NASH, AUROC being 0.70–0.87 (Kwok et al., 2014). In a later meta-analysis by He et al. (2017) (25 studies), pooled sensitivity and specificity for serum CK-18 markers for diagnosing NASH were as follows: CK-18 (M30):0.75 and 0.77; CK-18 (M65): 0.71 and 0.77, respectively.

One study from Egypt looked at the level of CK-18 M30 in patients with chronic HCV (Saeed et al., 2017) revealing significant differences between patients and healthy controls (HC) ($p<0.001$). Moreover, there was a significant difference in CK-18 M30 levels ($p=0.02$) in patients with mild fibrosis and advanced fibrosis. Another study found significantly higher serum levels total CK-18 and CK-18 fragments in patients with cirrhosis and HCC who were

undergoing surgery vs patients with non-cirrhotic liver disease: total CK-18: 262.9 ± 130.0 U/L vs 158.7 ± 44.5 U/L, P=0.038); CK-18 fragments: 145.1±69.6 U/L vs 81.6 ± 15.2 U/L, P=0.005), respectively. However, the levels in the cirrhotic group fell dramatically to near preoperative levels at postoperative day 5.

The CANONIC [CLIF Acute-on-Chronic Liver Failure (ACLF) in Cirrhosis] study group compared the levels of CK-18 and Keratin-18 between patients with acute decompensation and ACLF, HCs and stable patients with cirrhosis. They found that the concentrations of CK-18 and K18 increased, specifically, the CK-18: K18 ratio decreased with increasing severity of the acute decompensation and ACLF (Macdonald et al., 2018).

MMPs are a family of over 24 zinc-dependent endopeptidases and considered the main lytic enzymes of the hepatic extracellular matrix. They have a major role in the tissue remodelling and repair during physiological and pathological states (Kessenbrock et al., 2010, Duarte et al., 2015).

Almost all MMPs play some role in liver fibrosis, fibrinolysis, carcinogenesis and regeneration. However, the main MMPs expressed in humans, which were described in relation to the pathogenesis of liver fibrosis are MMP-1 (collagenases), MMP-2 (gelatinase A) and MMP-9 (gelatinase B). MMP-2 specifically decreases natural collagen types and denatures interstitial collagens (Kessenbrock et al., 2010, Duarte et al., 2015). MMP-2 is secreted from hepatic stellate cells and has a high diagnostic accuracy of up to 92% for detecting hepatic fibrosis (Kessenbrock et al., 2010, Duarte et al., 2015).

On the other hand, tissue inhibitors of metalloproteinases (TIMPs) are a group of physiological inhibitors (TIMP 1–4) responsible for regulating proteolytic activities of MMPs in tissues (Duarte et al., 2015). TIMP-1 overexpression attenuates the clearance of fibrotic matrix material leading to extensive accumulation and abundance of extracellular matrix (ECM)

(Yoshiji et al., 2002). In a study from 1999, plasma TIMP-1 levels measured in 43 patients with chronic HCV had significant correlation with histological activity index (r = 0.45), portal inflammation (r = 0.48), periportal necrosis (r = 0.34) and focal necrosis (r = 0.38) (Walsh et al., 1999). However, plasma MMP-2 or serum ALT were not related to fibrosis or histological activity index. Subsequent to this, a study involving cirrhotic and non-cirrhotic HCV patients and healthy controls revealed a great potential of circulating MMP-2 in detecting cirrhosis with a sensitivity of 74%-83%, a specificity of 96%-100%, respectively, and diagnostic efficiency of 92% (Boeker et al., 2002). Furthermore, in ALD, MMP-2 alongside MMP-8, and MMP-9 were shown to be potential serum markers for both hepatic fibrosis and the assessment of disease severity (Prystupa et al., 2015).

Using combined levels of MMP-2 and CK-18, in a study of 189 patients with chronic HBV vs health controls, significantly higher levels were found in the former (308 [1–762] vs 168 [67–287], p=0.001), (Sumer et al., 2013). Likewise, serum MMP-2 levels were demonstrated to be statistically higher in the HBV group, 3.0 (1.1–6.8) vs 2.0 (1.2–3.4), p=0.001. Additionally, higher values of both CK-18 and MMP-2 were seen in patients with cirrhosis and their concentrations appeared to correlate well with the stage of fibrosis (as assessed using the modified Knodell scoring system), AST and ALT levels (Sumer et al., 2013).

Although these senescence markers, discussed above, have been utilized in secondary care settings for years, there is limited data on their role in a community screening setting.

1.10 The role of T-helper 17 (Th17) cells and its peripheral cytokine levels in liver fibrosis

T-helper 17 cells (Th17) are a subset of differentiated CD4 T-helper cells characterized by the ability to produce Interleukin 17 (IL-17). Their central cytokines include IL-17A, IL-17F, IL-21 and IL-22 but they also produce IL-26, tumour necrosis factor (TNF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) (Stockinger and Veldhoen, 2007, Hartigan-O'Connor et al., 2011, Dong, 2008). Th17 cells are pro-inflammatory cells with predominantly effector function. They tend to differentiate from naive T-helper cells, in response to a variety of stimuli, facilitated by pro-inflammatory cytokines such as IL-1β, IL-6, IL-21, IL-23, and TGF-β, IL-21, which appear to enhance the amplification of the process of Th17 activation via signal transducer and activator of transcription 3 (STAT3) in an autocrine process (Stockinger and Veldhoen, 2007, Dong, 2008, Ivanov et al., 2009). Activation of STAT-3, in turn, leads to the induction of expression of relevant receptors, particularly retinoic acid receptor-related orphan receptor gamma T (RORγt) (Chen et al., 2007).

The two most important Th17 cytokines concerning hepatic injury and regeneration are IL-17 and IL-22 (Lafdil et al., 2009, Yasumi et al., 2007). IL-22 tends to ameliorate liver fibrosis, and IL-17 exacerbates it. IL-22 mainly targets epithelial cells and hepatocytes through the binding to IL-22 receptor, while IL-17 targets a wide range of cells including Kuppfer cells hepatocytes, stellate cells, biliary epithelial cells and sinusoidal endothelial cells by binding to IL-17R that is expressed ubiquitously (Lafdil et al., 2009, Yasumi et al., 2007).

Among the IL-17 family, Interleukins 17A and 17F are considered the major Th17 cytokines that drive inflammation (Jin and Dong, 2013, Zambrano-Zaragoza et al., 2014). These cytokines, although sharing structural similarity, appear to have different biological functions. After being secreted, IL-17A plays a crucial role in angiogenesis, inflammation, and neutrophil

recruitment. Interleukin-17A has been identified as a driver of hepatic stellate cell activation and a key player in the fibrogenesis process (Lafdil et al., 2009). Moreover, the concentrations of IL-17 were found to be markedly raised in patients with acute liver injury serving as a marker of severity in these patients (Yasumi et al., 2007).

Several studies have described the role of Th17 and its cytokines in the pathogenesis of autoimmune, fibroproliferative and inflammatory diseases. Th17 is also a key player in the development and progression of liver disease both in animal and human models (Hammerich et al., 2011), but much of the evidence focuses on chronic HBV. Table 1.5 summarises some of the studies looking at the role of Th17 in CLD.

Th17 has been linked to the severity of chronic viral hepatitis and in particular chronic HBV as higher proportions of Th17 cells were found peripherally in patients with the infection compared to healthy individuals (1.53% vs 0.92%, $p < 0.05$) in one study by Ge et al. (2010). The increase in Th17 percentage was more pronounced in those with chronic active hepatitis. Another study produced similar findings and demonstrated that both peripheral serum levels of IL-17 and intra-hepatic IL-17 were significantly elevated in patients with chronic HBV. This study which included 96 patients showed higher percentages of Th17 in patients with ACLF secondary to HBV (Zhang et al., 2010). Moreover, in a larger study involving 173 patients, IL-17 mRNA and proteins levels were increased in HBV-related samples (Du et al., 2013). Sun et al. (2012) showed that intrahepatic IL-17 correlated positively with progression to cirrhosis in chronic HBV as well as the stage of fibrosis. Moreover, peripheral Th17 cells increased with disease severity as determined by Child-Pugh classifications.

The involvement of Th17/IL-17 axis in HCV infection has not been extensively explored. However, it is plausible to speculate that IL-17 may plays a role in stimulating liver inflammation during HCV infection, in a similar way to HBV (Paquissi, 2017). Compared with

healthy individuals, patients with chronic HCV had higher proportions of Th17 cells both circulating (1.56% vs 0.96%) and infiltrating the liver (16.08% vs 0.82%/hpf), and also higher serum IL-17 levels (84.86 vs 60.52 pg/mL), (Chang et al., 2012).

Nonetheless, the role of IL-17 in hepatic fibrosis is not limited to viral hepatitis. Th17/IL-17 axis is responsible for disease pathophysiology in other forms of CLD such as obstructive cholestasis, autoimmune liver disease, primary biliary cholangitis (PBC) (Harada et al., 2009, Rong et al., 2009), drug-induced liver injury (Yasumi et al., 2007, Wang et al., 2016), hepato-splenic schistosomiasis (Mbow et al., 2013) and ALD (Lemmers et al., 2009). In this latter study, plasma levels of IL-17 were compared between patients with ALD, chronic HCV and autoimmune hepatitis vs healthy controls, revealing higher plasma levels of IL-17 in the ALD group. The higher percentages of Th17 cells infiltrating the hepatocytes conferred a prognostic value as it correlated with the model for end-stage liver disease (MELD) score and modified discriminant function in those with cirrhosis and alcoholic hepatitis, respectively (Lemmers et al., 2009).

Recently, studies established an association between Th17 and NAFLD (assessed with FibroScan). In a study comparing 70 patients with NAFLD and 26 healthy controls, those with NAFLD, divided into raised FibroScan reading and high BMI subgroups, had 2.2 and 2.3-fold increase in IL-22 levels in serum, respectively, compared to the healthy controls (Su et al., 2018). The same applied to levels of IL-17A which were significantly raised by 5.6 and 5.8-fold in the FibroScan and BMI subgroups, respectively. Median proportions of T-helper 22 cells in the NAFLD group were greater than those in healthy controls (3.85% vs 0.86%; $p< 0.001$). Comparable results were obtained for Th17 cells (6.36% vs 0.9%; $p < 0.001$). Moreover, there was a significant correlation of LSM with Th17 and Th22 proportions and moderate correlation with peripheral plasma concentrations of IL-17A and IL-22. These

findings suggest that Th17 and Th22 and their cytokines have a key role in the inflammatory process in patients with NAFLD and may influence fibrosis progression in this cohort of patients. Such a relationship between Th17 cytokine profile and progression of hepatic fibrosis was similarly seen in HBV patients (Sun et al., 2012).

IL-22, which is secreted by Th17, prevents hepatocyte apoptosis and some in vivo studies described its overexpression in cases of reduced hepatic fibrosis (Kong et al., 2012). The same protective effect was observed upon treatment with recombinant IL-22. IL-22 also hinders fibrosis and development of portal hypertension (Pan et al., 2014). Moreover, it appears to be involved in recovering the liver tissue and regeneration following organ damage (Feng et al., 2012).

Based on the discussion above, it is unsurprising that some investigators highlighted the potential role of the Th17 axis as a therapeutic target for hindering or reversal of hepatic fibrosis and other fibroproliferative disorders (Zhang et al., 2017). Gao and Waisman (2012) suggested that recombinant IL-22 protein or IL-17 inhibitors should be trialled for the treatment of liver failure and injury.

In addition to Th17-specific cytokines, tumour necrosis factor (TNF) and interferon-Gamma (IFN-γ) are pro-inflammatory cytokines produced primarily as part of the T-helper 1 (Th1) response and mediate cytotoxic hepatocyte injury in viral hepatitis by promoting apoptosis and immune cell activation (Xia and Protzer, 2017). TNF is a pleiotropic cytokine released by several cells and exerts an antiviral effect both independently and in combination with IFN-γ (Laidlaw et al., 2017). IFN-γ promotes progression of chronic HCV infection and correlates positively with aggressive disease (Napoli 1996). TNF is significantly involved in the inflammatory process in ALD, and in the context of severe alcoholic hepatitis acts as a mediator

of disruption of both portal and systematic haemodynamic circulations (Tilg et al., 2006, Mookerjee et al., 2003).

IL-10 is a prototypic anti-inflammatory cytokine and has been shown to control the activity and immune response of both Th1 and Th17 (Huber et al., 2011). It is secreted predominantly by T-regulatory cells but can also be produced by Th17. IL-10 can influence the production of TGF-β secretion; the latter is responsible for the activation of Th17 (Hammerich et al., 2011). Although it has no evident antiviral activity, IL-10 can normalise serum ALT levels, improve histological features, and reduce hepatic fibrosis in a large proportion of patients receiving treatment for HCV (Nelson et al., 2000). In CLD, IL-10 generally has a protective function preventing liver injury and fibrogenesis (Hammerich and Tacke, 2014). This is similar to IL-22, which also protects against fibrosis by inhibiting the activation of hepatic stellate cells, thereby reducing collagen production (Pan et al., 2014). Together with other pro-inflammatory cytokines including TGF-β, IL-6 is responsible for activating Th17. IL-6 is markedly increased in acute liver injury, but it promotes the development of HCC on the long-term. A similar relationship was described between IL-22 and HCC by Jiang et al. (2011).

Study	Study groups	main outcome	Other outcomes
Sun et al., 2012	HBV (chronic infection/Cirrhotic) patients (n=78) vs healthy control (n=12)	Increased plasma levels in HBV Cirrhosis patients	Circulating Th17 proportions were higher in HBV patients. Positive intrahepatic IL-17 correlated positively with fibrotic staging and progression from HBV to cirrhosis.
Lemmers et al., 2009	ALD (n=76) Vs HCV (n=16), Autoimmune (n=18) vs healthy control (n=10)	IL-17 levels were: ALD [55.9 (0–265.9) pg/mL; n = 33] vs HC [0 (0–76.3) pg/mL; n = 10], Vs. HCV [0 (0–82.5) pg/L; n = 16] ($p < 0.001$)	IL-17 secreting cells infiltrating liver tissue had prognostic value and correlated with MELD and discriminant factor for AH.
Su et al., 2018	NAFLD (n=70) vs health control (n=26)	IL-17A levels were significantly raised by 5.6 and 5.8 in those with high LSM and high BMI, respectively	IL-22 was higher by 2.2 -2.3-fold in the same subgroups. Positive correlation was seen between the liver stiffness values and the percentages of Th17 and Th22.
Zhang et al., 2010	HBV (n=66) vs ACLF (n=23) vs Healthy controls (n=30)	IL-17 increased in HBV and ACLF patients compared with HCs.	Increased levels of IL-23p19, and IL-1β in the HBV group. IL-22 was not increased.
Chang et al., 2012	HCV (n=53) vs Healthy controls (n=23)	Serum IL-17 levels were significantly higher in HCV subjects than in normal controls	Increased proportions of both circulating and liver infiltrating Th17 cells in HCV patients.

		(84.86 ± 29.45 pg/mL vs. 60.52 ± 14.80 pg/mL, p<0.001)	
Rong et al., 2009	PBC (n = 36) vs HBV (n=28) vs Healthy controls (n=28)	IL-17A was elevated markedly PBC patients compared with both HBV and HCs groups (25 ± 10·7 vs. 16 ± 8·8 vs 12 ± 6·4 pg/mL, respectively, p =0·001)	L-1β, IL-6 and IL-23 were significantly raised in patients with PBC compared with HCs. IL-23 was the only pro-Th17 cytokine with higher level in PBC patients compared with those with HBV.

Table 1. 5: Studies exploring the role of peripheral and hepatic Th17 cytokines in patients with liver disease.

HCV = Hepatitis C, HBV = Hepatitis B, NAFLD = Non-alcoholic fatty liver disease, ALD = Alcohol-related liver disease, CLD= Chronic liver disease, PBC= Primary biliary cirrhosis, HC= Healthy controls, MELD= Model for end stage liver disease, ACLF = Acute on Chronic Liver Failure, AH= Alcoholic Hepatitis.

CHAPTER 2: Local community liver services for vulnerable adults and PWID in Brighton: from project ITTREAT (integrated community-based test – stage – treat) to VALID (Vulnerable Adults LIver Disease) study

The VALID (Vulnerable Adults LIver Disease) project, which is the subject of this thesis has been established based on our prior experience in setting up an integrated community service for PWIDS (ITTREAT). This section describes how ITTREAT was established and is based on a manuscript published by the author of this thesis (Hashim et al., 2018).

2.1 Introduction & rationale

Having identified a clear unmet need to link PWID into care by developing a community HCV service model, we engaged with various stakeholders [substance misuse service (SMS), psychiatrists, patient groups (Hepatitis C Trust, British Liver Trust), Brighton and Hove Commissioners, and Pharma].

The aim was to set up a unique "one-stop" HCV community clinic that provided all components of care (BBV screening, stratification of hepatic fibrosis, nurse-led HCV treatment under Hepatologist supervision, hepatitis B vaccination, OST and social and psychiatric input) at one site. In view of the complex needs of PWID, our philosophy was that an integrated and multidisciplinary model based on a substance misuse service had the best chance of success. We selected this model rather than one based in primary care due to:

- Our prior established links with the SMS enabling us to engage PWID in an environment they were comfortable in
- A recent meta-analysis identifying “treatment of addiction during HCV therapy” as a factor associated with higher treatment completion (Dimova et al., 2013)
- A historical reluctance by GPs in England to be involved in antiviral prescription.

In 2013, funding was obtained for two years (National Gilead Fellowship and Brighton and Hove Commissioners) to set up our community hepatitis C service at the SMS in Brighton (Sussex Partnership Trust). In 2015 additional funding from the same sources extended our work for two years (until Dec 2017). The funding allowed for the appointment of a band 7-community hepatitis nurse and a health economics and qualitative researcher, mobile FibroScan purchase and data collection (clinical, qualitative, patient reported and health economic outcomes).

2.2 Prerequisites for a successful HCV community service as per the local experience

In our view the following were prerequisites for a successful HCV community service:

- An integrated and multidisciplinary approach with provision of all components of the service at one site, preferably a SMS.
- An experienced community hepatitis nurse additionally trained in substance misuse and passionate about working with this client group to provide holistic care.
- Easy access to nurse (mobile phone) and close supervision by a Hepatologist.
- Flexible clinic appointments in contrast to the inflexible, non-personalised and stigmatised environment in secondary care.
- Community FibroScan for non-invasive staging of hepatic fibrosis.

- Presence of onsite psychiatrist.
- Ongoing alcohol and drug use not a bar to HCV treatment.
- Personalised strategies for drug delivery (e.g. home delivery).
- Provision of peer advocates (buddies) to support clients throughout their treatment journey.
- Good engagement between key workers, drug and alcohol team, psychiatrist, peer advocates and hepatitis nurse.
- Non-judgemental approach.

2.3 ITTREAT service set-up

The liver service for PWID in Brighton involved training of the hepatitis nurse (MOS) who worked under the supervision of a consultant hepatologist (SV), identification of a lead psychiatrist at the SMS (HW), and detailed discussions with managers at SMS to address logistic issues including clinic space. The service was publicised by the ongoing engagement with stakeholders, MOS engaging with SMS staff and the use of posters. In addition, both MOS and SV attended the monthly Substance Misuse Board, chaired by the Commissioners and usually well attended by various stakeholders.

In summary, setting up the community HCV service encompassed establishing the need for a community HCV service, engaging with stakeholders, developing a team, obtaining the funding, and interim analysis of clinical outcomes in 3 years.

2.4 Delivery logistics and barriers to success

Though the need for community service was greatly appreciated, set up was associated with a variety of issues that included:

- Scepticism “it ain’t going to work”
- Concerns about treating those with ongoing drug and alcohol use “can’t be trusted with expensive drugs”
- Misconceptions about treatment efficacy and reinfection risks in PWID.
- Logistic issues especially lack of clinical space. Not infrequently clinical space had to be shared with the consultant psychiatrist. A change in providers in 2015 (Surrey and Borders) meant relocating the service to new premises. This heightened the issues of availability of clinical rooms, and there were ongoing negotiations with management and clinical staff to resolve this problem.
- Concerns that interactions between the community hepatitis nurse, psychiatrist, and key workers would be incongruent.
- Remote access to hospital pathology and radiology database - this was resolved with the use of a laptop and remote modem.
- Ongoing need to train the staff at the SMS in BBV testing and providing them with the latest HCV treatment updates. This required not only regular training of the substance misuse teams but also reaching out to the wider community to include volunteers, peer mentors, those running Narcotics/Alcohol Anonymous meetings, homeless hostel workers, rehabilitation units’ staff and GPs. We are now in fact part of the GP rotation-teaching programme and provide update sessions to GPs on a regular basis highlighting the changes in HCV treatment and the criteria for referral to our service. In the past

PWID would have been denied HCV treatment and so it is essential to dispel this antiquated myth amongst the medical and the wider community.

- Restrictive access to DAA due to prohibitive costs. The Early Access Programme enabled treatment of those with decompensated cirrhosis due to a high probability of death and or irreversible damage within a year (Interim Clinical Commissioning Policy Statement, 2014). NHS England then extended treatment to cirrhotics (Clinical Commissioning Policy Statement, 2015) and subsequently to those with advanced fibrosis (LSM > 9.5 kPa). There are, however, exceptional criteria to include those with extra hepatic disease and PWID (as window of opportunity). Treatment can only be dispensed through nationally selected operational delivery networks (ODNs) (n=22), of which we are one. Each patient is discussed at a weekly multidisciplinary meeting. Each genotype had a first-choice regimen and all second-choice drugs (which in fact maybe more appropriate) needed "buddy ODN" approval. There are severe financial penalties for the ODN if guidelines are breached. Each ODN has been provided with a run rate based on the regional prevalence of HCV and again, there are financial penalties for exceeding this. While each ODN could treat a subset of patients (10-20%) under the exceptional criteria, this remained highly scrutinised. It was therefore frustrating that despite effective antivirals and engaged SMS clients who often only have a small window of opportunity, we were still unable to offer treatment to a substantial number of PWID. This was in sharp contrast to countries like Australia where there was unrestricted access to DAA (including for re-infection), and primary care physicians were encouraged to take on prescribing and treatment as already stated (The Kirby Institute, 2016).
- Need for upfront funding for service set up – this has somewhat been negated by the establishment of ODN and availability of CQUIN funds.

2.5 Service evaluation

We aimed to evaluate this community-based HCV service through collection of the following data:

1. Clinical: demographics, drug and alcohol use, uptake of DBST, HBV vaccination and HCV treatment as well as treatment outcomes.
2. Qualitative component: Conduction of interviews with SMS attendees and two focus groups with staff members.
3. Patient reported outcomes using validated questionnaires:
    a. Liver related quality of life (QOL) - Short-form Liver Disease Quality of Life (SF-LDQOL) (LDQOL); (Kanwal et al., 2008).
    b. Non-disease specific health related outcomes - SF-12v2, which is a shortened form (12 items) of the SF-36v2 Health Survey (SF-36).

4. Assessment of quality adjusted life years (QALY) using EQ-5D-5L (EQ-5D-5L survey) and perform a health economics (HE) assessment (cost per cure).

The outcomes of project ITTREAT are summarised in Chapter 3 (systematic review).

2.6 From project ITTREAT to introducing VALID (Vulnerable Adults LIver Disease) study

There is limited published evidence on community based integrated HCV treatment models in England. Without scientific evidence it will be challenging for local commissioners to develop effective local commissioning business cases. With this conundrum in mind, we have drafted a successful business case for a community based integrated model of care. This has ensured the permanency of the community hepatitis nurse once research funding runs out.

Based upon the success of Project ITTREAT our team established the VALID (Vulnerable Adults LIver Disease) project. This is a similar integrated community liver service dedicated to PWAH which was established at two homeless hostels and offers non-invasive assessment of hepatic fibrosis (FibroScan) followed by targeted treatment for chronic liver disease including for BBV (Hashim et al., 2019). The methodology and outcomes of VALID study are discussed in detail in Chapters 4, 5, 6 & 7.

Linking PWIDs and PWAH into care is essential if HCV infection is to be eliminated by 2030 as set out in the WHO strategy. These individuals have, however, consistently failed to access traditional models of secondary care. The advent of DAA provides an unprecedented opportunity to address the national HCV burden. Our integrated and multidisciplinary community models of care (Project ITTREAT, VALID Study) have been successful in engaging such individuals with outcomes comparable with secondary care, despite the complex nature of the cohort. Provision of all aspects of the care at one site, a dedicated and highly motivated team and the excellent communication between them and substance misuse staff, other community services, and stakeholders is the key to the success of this service.

CHAPTER 3: Community models for detection and treatment of Hepatitis C virus and liver disease amongst people who are homeless: A systematic review.

3.1 Introduction

People who are homeless (PWAH) are a disenfranchised cohort with inadequate access to and engagement with health services. They thus remain an important HCV reservoir impeding World Health organization action plan for HCV elimination by 2030. One of the top recommendations of the UK Lancet report was the need to develop community services for the screening of high-risk individuals (William et al., 2014), and ensuring early detection of CLD amongst vulnerable groups. Moreover, with the introduction of the DAAs and their established efficacy (Vermehren et al., 2018), there is currently a trend toward shifting HCV treatment to the community, particularly for vulnerable populations who may not have robust access to secondary care. The latter issue was referenced in the HCV in England Report (2020) (Public Health England, 2020), highlighting that only a small proportion of HCV care is community-based compared to 78.5% still being delivered in secondary care.

Evidence is scarce regarding the evaluation of liver disease among PWAH in the community. While Hanlon et al. (2018) presented a systematic review looking at community interventions to improve management of chronic conditions, CLD among this group was not explicitly addressed.

In this chapter, we conducted a systematic review exploring community screening models designed to aid the detection, evaluation and treatment of HCV and hepatic fibrosis amongst PWAH.

3.2 Methods

This systematic review aimed to identify and describe currently available evidence on community models for detecting and treating HCV and liver disease amongst PWAH. Ethical approval was not required; hence no protocol was designed. The PICOS (participants, interventions, comparators, outcomes, and study design) structure was used as described by PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses (Liberati et al., 2009).

Participants

PWAH, defined as rough sleepers including living in the streets or those in unstable housing (sheltered or temporary/unstable accommodation)

Intervention

Interventions provided by the community model of care to include:

- Alcohol and substance use assessment.
- Intervention for Alcohol Use Disorder (AUD) and injecting drug use (IDU).
- Blood-borne virus (BBV) screening and prevalence.
- Assessment of liver fibrosis.
- HCV treatment.
- Health-related quality of life assessment (HRQoL).
- Health economic assessment.

Comparisons

Not relevant as no known comparison studies.

Outcomes

These included:

- Demographic data.
- The country and type of study.
- Type of community model including site and details of service provider.
- Prevalence of IDU and AUD and method of assessment.
- Interventions for IDU and AUD and outcomes.
- Method of BBV assessment and HCV seroprevalence.
- Method of hepatic fibrosis assessment and prevalence of ≥F2 and F4 fibrosis (Metavir).
- HCV treatment: outcomes (sustained virological response, SVR), treatment regimen and completion rates.
- HRQoL after successful HCV treatment.
- Costs of community-based liver care for PWAH.

Study design

Randomised controlled trials (RCT), cross-sectional, prospective, retrospective cohort studies, case series and conference proceedings were included.

Search strategy

A systematic electronic search was performed using MEDLINE/PubMed, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Google Scholar and the Cochrane Database of Systematic Reviews. Platforms used to access the databases were the

Healthcare Databases Advanced Search (HDAS). The initial search was undertaken by AH in December 2017 (Table 3.1).

The search themes related to PWAH, HCV and liver disease. Due to paucity of published data all levels of evidence were considered. The following combinations keywords were used: homeless AND "liver disease", homeless AND "hepatic disease", homeless AND "liver disorder", homeless AND "hepatic disorder", homeless* AND liver, homeless* AND “liver fibrosis” AND HCV, homeless* AND "Hepatitis C". MeSH terms used were: Homeless person, Homelessness, Liver disease, Hepatitis C with the following search combinations: Homeless person* AND liver disease, Homeless person* AND Hepatitis C, Homeless person* AND "liver disease", Homeless person* AND "Hepatitis C”. In addition, the “explode term” function was used to expand the search using the combination of the MeSH terms: Liver disease and Homelessness/ OR Homeless person.

Hand searching of reference lists in relevant manuscripts was performed. Online portals for major Hepatology journals including Hepatology and the Journal of Hepatology were also searched for relevant publications and conference abstracts. The search was updated on 16.11.19 and then 13.10.20 using the same methodology and search strategies to cover all articles until December 2019. Articles were selected using the original exclusion and inclusion criteria (see below).

Eligibility criteria

Inclusion criteria

- To ensure that we were as inclusive as possible we selected studies in which the number of PWAH were at least 30% of the total study population.
- Studies, which specifically discussed community-based interventions, related to HCV and liver disease in PWAH, including those addressing AUD and IDU. Studies that did not include HCV-related liver disease were excluded.

Exclusion criteria

- Studies, which looked at data, extracted from previously recorded national or local databases.
- Studies which focused primarily on alcohol and substance use and mental health issues in PWAH with no reference to liver disease.
- Studies which looked at general health conditions in PWAH without addressing liver disease
- Non-community-based models (i.e. studies exploring secondary care interventions, admissions to hospital, accident and emergency attendance)
- Non-English literature

Study selection

AH reviewed titles and abstracts of identified manuscripts for relevance and screened full texts applying exclusion criteria. LMa independently reviewed a selection and if required, further screening was conducted by SV.

Quality assessment

The Newcastle-Ottawa Scale (NOS) (Wells et al., 2014), developed to assess the quality of non-randomised studies including cohort studies, was used to assess those meeting eligibility criteria.

Data extraction

Data was extracted in tables by AH and this was reviewed by LMa and SV.

Statistical analysis

Studies identified for full analysis were heterogeneous in design, therefore a descriptive approach was undertaken.

3.3 Results

The database search returned 1717 results. Articles identified through other sources were n=3. A screen for duplicate results performed "using HDAS duplicate removal feature" resulted in 334 being removed with 123 assessed for eligibility. Of these 81 were excluded, 42 meeting full inclusion criteria for final analysis (Fig 3.1). These included 29 as full manuscripts and 13 as conference abstracts.

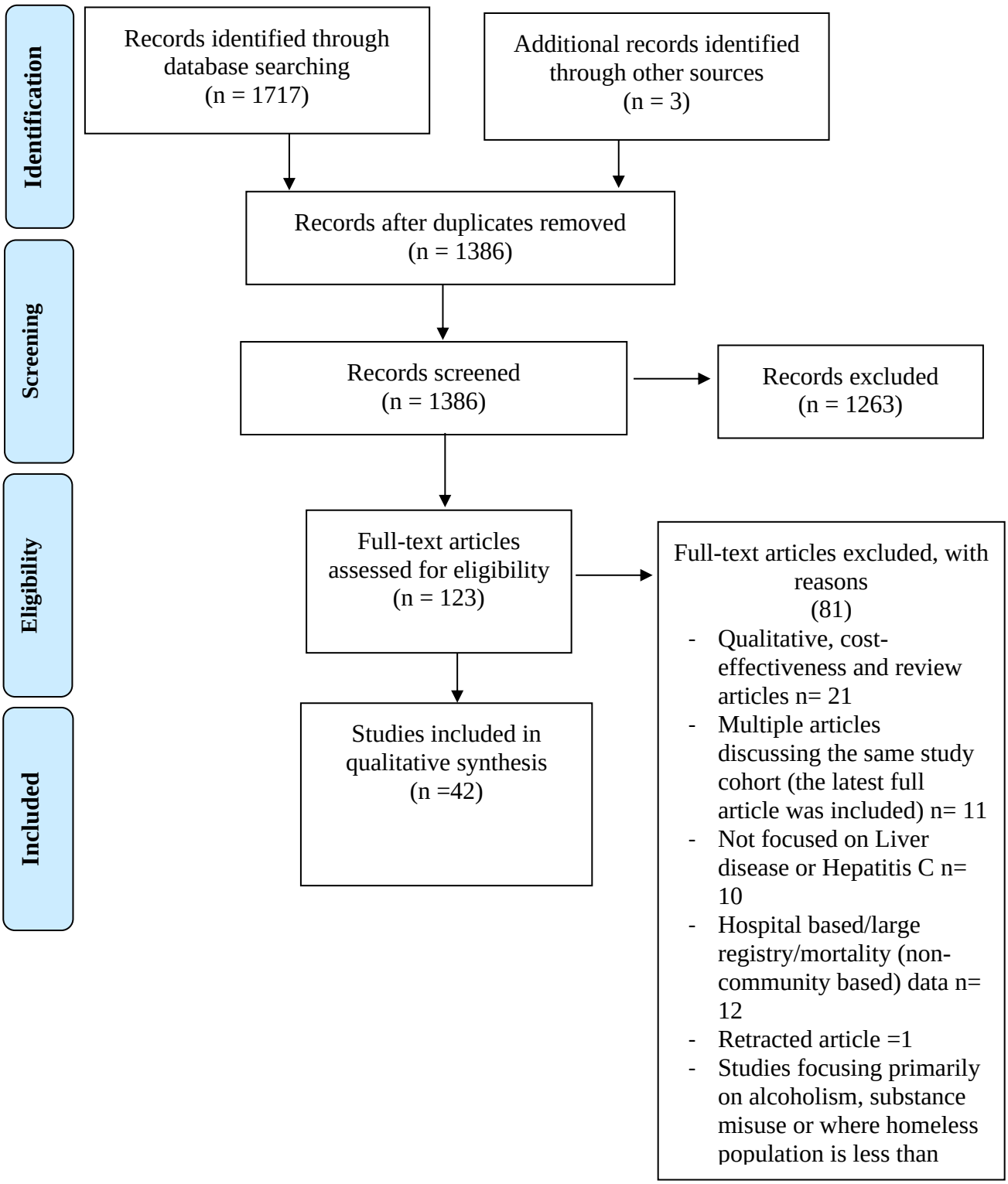


Figure 3. 1: PRISMA flow diagram.

The country and type of study (Table 3.2)

Of the 42 studies, 29 were North American (Page et al., 2017, Ho et al., 2015, Boyce et al., 2009, Strehlow et al., 2012, Desai et al., 2003, Nyamathi et al., 2013, Beste and Stein, 2008, Stein et al., 2012, Beiser et al., 2019, Hodges et al., 2019, Bakr et al., 2019, Ho et al., 2011, Benitez and Fernando, 2019, Khalili et al., 2019, Klinkenberg et al., 2003, Edlin et al., 2013, Heaney et al., 2016) or from the United Kingdom (O'Sullivan et al., 2020, Aisyah et al., 2018, Crowley et al., 2017, Lambert et al., 2019, Stagg et al., 2019, Selvapatt et al., 2015, Hashim et al., 2019, Buchanan and Ord, 2019, Surey et al., 2016, Macbeth et al., 2018, Mckenna et al., 2019, Candfield et al., 2018). There were only two RCTs (Ho et al., 2015, Stagg et al., 2019), 21 being prospective cohort (O'Sullivan et al., 2020, Read et al., 2017, Foucher et al., 2009, Hashim et al., 2019, Newman et al., 2013, Lambert et al., 2019, Ho et al., 2011, Bajis et al., 2019, Beiser et al., 2019, Heaney et al., 2019, Hodges et al., 2019, Macbeth et al., 2018, Benitez and Fernando, 2019, Mckenna et al., 2019, Candfield et al., 2018, Barror et al., 2019, Khalili et al., 2019, Edlin et al., 2013, Colson et al., 2011, Amiri et al., 2011, Klinkenberg et al., 2003), 14 crossectional (Aisyah et al., 2018, Page et al., 2017, Selvapatt et al., 2015, Surey et al., 2016, Crowley et al., 2017, Boyce et al., 2009, Strehlow et al., 2012, Doosti-Irani et al., 2017, Ferreira et al., 2017, Nyamathi et al., 2013, Heaney et al., 2016, Stein et al., 2012, Nikoo et al., 2019, Sahajian et al., 2007) and five retrospective studies (Andric et al., 2017, Desai et al., 2003, Beste and Stein, 2008, Buchanan and Ord, 2019, Bakr et al., 2019).

Quality

The reported methodological quality in the majority of studies was poor. The NOS, converting scores to the Agency for Healthcare Research and Quality standards of good, fair and poor,

rated 40 studies as poor as none scored points in the comparison domain. The RCT by Ho et al., 2015 and Stagg et al., 2019 scored 9 and 8 respectively (good rating).

Demographic data (Table 3.2)

In the 42 studies, the sample size ranged from 6-2097 (total n= 13,976). Prevalence of homeless varied from 30%-100%. Total number of homeless individuals as a proportion of the total study sample was provided in all but two studies (Foucher et al., 2009, Khalili et al., 2019), this being 69% (8221/11973). Nineteen studies included only PWAH (Page et al., 2017, Selvapatt et al., 2015, Surey et al., 2016, Boyce et al., 2009, Strehlow et al., 2012, Doosti-Irani et al., 2017, Ferreira et al., 2017, Desai et al., 2003, Ho et al., 2011, Heaney et al., 2016, Stein et al., 2012, Nikoo et al., 2019, Hodges et al., 2019, Macbeth et al., 2018, Mckenna et al., 2019, Bakr et al., 2019, Colson et al., 2011, Amiri et al., 2014, Klinkenberg et al., 2003) (n= 5078). Definition of homelessness was provided in 29 studies (O'Sullivan 2020, Page et al., 2017, Read et al., 2017, Andric et al., 2017, Hashim et al., 2019, Ho et al., 2015, Crowley et al., 2017, Newman et al., 2013, Strehlow et al., 2012, Doosti-Irani et al., 2017, Sahijian et al., 2007, Lambert et al., 2019, Nyamathi et al., 2013, Beste and Stein, 2008, Stein et al., 2012, Bajis et al., 2019, Beisier et al., 2019, Harney et al., 2019, Stagg et al., 2019, Nikoo et al., 2019, Benitez and Fernando et al., 2019, Buchanan and Ord, 2019, Candfield et al., 2018, Barror et al., 2019, Bakr et al., 2019, Edlin et al., 2013, Colson et al., 2011, Amiri et al., 2014, Klinkenberg et al., 2003) (Table 3.2).

Age ranged from 31-55 years and was reported in all but eight studies (Andric et al., 2017-Selvapatt et al., 2015, Surey et al., 2016, Ho et al., 2011, Heaney et al., 2016, Benitez and Fernando, 2019, Buchanan and Ord, 2019, Mckenna et al., 2019). This was a predominantly young cohort with only one study reporting mean and/or median age $\geq$ 50 yrs (Ho et al., 2015). Gender was reported in all but nine studies (Andric et al., 2017, Selvapatt et al., 2015, Surey et

al., 2016, Ho et al., 2011, Heaney et al., 2016, Nikoo et al., 2019, Benitez and Fernando, 2019, Buchanan and Ord, 2019, Mckenna et al., 2019). Of the remaining 33, four included predominantly women (Page et al., 2017, Boyce et al., 2009, Sahajian et al., 2007, Harney et al., 2019), with 29 studies included predominantly men, of which eight studies included $\geq$ 90% men (Aysiah et al., 2018, Ho et al., 2015, Doosti-Irani et al., 2017, Ferreira et al., 2017, Boyce et al., 2009, Newman et al., 2013, Strehlow et al., 2012, Doosti-Irani et al., 2017, Ferreira et al., 2017, Desai et al., 2003, Sahajian et al., 2007, Lambert et al., 2019, Naymathi et al., 2013, Bakr et al., 2019, Colson et al., 2011). In the 30 that reported actual number of males (Aysiah et al., 2018, O'Sullivan et al., 2020, Page et al., 2017, Read et al., 2017, Foucher et al., 2009, Hashim et al., 2019, Ho et al., 2015, Crowley et al., 2017, Boyce et al., 2009, Newman et al., 2013, Strehlow et al., 2012, Doosti-Irani et al., 2017, Ferreira et al., 2017, Desai et al., 2003, Sahajian et al., 2007, Lambert et al., 2019, Naymathi et al., 2013, Beste and Stein, 2008, Bajis et al., 2019, Beiser et al., 2019, Harney et al., 2019, Stagg et al., 2019, Hodges et al., 2019, Macbeth et al., 2019, Candfield et al., 2019, Barror et al., 2019, Bakr et al., 2019, Edlin et al., 2013, Colson et al., 2011, Amiri et al., 2014) prevalence of men was 78% (8650/11024).

Site of community model provider details and services offered (Table 3.2)

The community model was partly or entirely based at homeless sites (dedicated community centres, hostels, shelters, primary care, streets) in all but five studies (O'Sullivan et al., 2020, Crowley et al., 2017, Doosti-Irani et al., 2017, Naymathi et al., 2013, Buchannan and Ord 2019, Edlin et al., 2013). In these latter five studies, care was provided at drug and alcohol treatment centres/needle exchange centres. Details of providers were not reported in 9 studies (Boyce et al., 2009, Doosti-Irani et al., 2017, Ferreira et al., 2017, Desai et al., 2003, Heaney et al., 2016, Nikoo et al., 2019, Candfield et al., 2019, Khalili et al., 2019, Colson et al., 2011), service

providers being multidisciplinary in 22 studies (O'Sullivan et al., 2020, Aysiah et al., 2018, Andric et al., 2017, Selvapatt et al., 2015, Surey et al., 2016, Ho et al., 2015, Newman et al., 2013, Strehlow et al., 2012, Lambert et al., 2019, Ho et al., 2011, Beste and Stein, 2008, Bajis et al., 2019, Beiser et al., 2019, Hodges et al., 2019, Benitez and Fernando, 2019, Buchanan and Ord, 2019 Mckenna et al., 2019, Barror et al., 2019, Bakr et al., 2019, Edlin et al., 2013, Amiri et al., 2014, Klinkenberg et al., 2003).

All but six studies provided BBV screening (Andric et al., 2017, Crowley et al., 2017, Newman et al., 2013, Ho et al., 2011, Hodges et al., 2019, Bakr et al., 2019). Twenty-one studies provided HCV treatment (O'Sullivan 2020, Read et al., 2017, Andric et al., 2017, Selvapatt et al., 2015, Foucher et al., 2009, Hashim et al., 2019, Ho et al., 2015, Newman et al., 2013, Ho et al., 2011, Bajis et al., 2019, Beiser et al., 2019, Harney et al., 2019, Stagg et al., 2019, Hodges et al., 2019, Macbeth et al., 2019, Benitez and Fernando, 2019, Buchanan and Ord, 2019, Mckenna et al., 2019, Candfield et al., 2019, Khalili et al., 2019, Edlin et al., 2013). Twenty-five studies provided data on both alcohol and substance assessment (O'Sullivan et al., 2020, Aysiah et al., 2018, Page et al., 2017, Read et al., 2017, Foucher et al., 2009, Hashim et al., 2019, Surey et al., 2016, Ho et al., 2015, Crowley et al., 2017, Strehlow et al., 2012, Ferreira et al., 2017, Desai et al., 2003, Sahajian et al., 2007, Lambert et al., 2019, Naymathi et al., 2013, Beste and Stein, 2008, Heaney et al., 2019, Stein et al., 2012, Bajis et al., 2019, Beiser et al., 2019, Stagg et al., 2019, Buchannan and Ord et al., 2019, Candfield et al., 2019, Colson et al., 2011, Klinkenberg et al., 2003), 11 on substance use (Andric et al., 2017, Boyce et al., 2009-Newman et al., 2013, Doosti-Irani et al., 2017, Harney et al., 2019, Nikoo et al., 2019, Macbeth et al., 2019, Khalili et al., 2019, Bakr et al., 2019, Edlin et al., 2013, Amiri et al., 2014), with the remaining six providing no data on alcohol or substance use (Selvapatt et al., 2015, Ho et al., 2011, Hodges et al., 2019, Benitez and Fernando, 2019, Mckenna et al., 2019, Barror et al., 2019). Alcohol and substance use were mostly self-reported or assessed by a

questionnaire, with only four studies using validated tools [The Alcohol Use Disorders Identification Test (AUDIT/AUDIT-C), Drake/Carey scale] (Hashim et al., 2019, Ho et al., 2015, Bajis et al., 2019, Klinkenberg et al., 2003). Only eight studies (n= 2491) provided a service to include all of the following: BBV screen, assessment of alcohol/ substance use/liver fibrosis and HCV treatment (O'Sullivan et al., 2020, Read et al., 2017, Foucher et al., 2009, Hashim et al., 2019, Ho et al., 2015, Bajis et al., 2019, Beiser et al., 2019, Candfield et al., 2019).

AUD data (Table 3.3)

Definition of AUD was very variable which made direct comparison difficult. Twenty-three studies (O'Sullivan et al., 2020, Aysiah et al., 2018, Page et al., 2017, Read et al., 2017, Foucher et al., 2009, Hashim et al., 2019, Ho et al., 2015, Crowley et al., 2017, Strehlow et al., 2012, Desai et al., 2003, Sahajian et al., 2007, Lambert et al., 2019, Naymathi et al., 2013, Beste and Stein, 2008, Heaney et al., 2016, Stein et al., 2012, Bajis et al., 2019, Beiser et al., 2019, Stagg et al., 2019, Buchannan and Ord et al., 2019, Candfield et al., 2019, Colson et al., 2011, Klinkenberg et al., 2003) provided data on AUD (referred in studies as > 4 drinks/day, AUDITC $\geq$20, AUDIT C $\geq$ 4, alcohol instability, problem alcohol use, lifetime alcohol abuse, alcoholism, problematic alcohol use, current alcohol dependence, alcohol abuse, high-risk alcohol use, alcohol use disorder, alcohol related concern, heavy alcohol use, drinking > 21 units/week, excessive alcohol use, Drake/Carey scale). The prevalence of AUD varied from 4-97%. Of these 23, 18 (O'Sullivan et al., 2020, Aysiah et al., 2018, Page et al., 2017, Read et al., 2017, Hashim et al., 2019, Ho et al., 2015, Crowley et al., 2017, Strehlow et al., 2012, Desai et al., 2003, Sahajian et al., 2007, Lambert et al., 2019, Naymathi et al., 2013, Beste and Stein, 2008, Bajis et al., 2019, Beiser et al., 2019, Stagg et al., 2019, Buchannan and Ord et al., 2019, Candfield et al., 2019) provided actual numbers with AUD, prevalence being 34%

(2035/5955). Of these 18 studies, three included only PWAH (Page et al., 2017, Strehlow et al., 2012, Desai et al., 2003), prevalence of AUD being 54% (572/1051). No study provided any interventions for AUD or specifically addressed alcohol-related liver disease (ALD).

IDU data (Table 3.3)

IDU data was provided in all but 13 studies (Selvapatt et al., 2015, Ho et al., 2015, Crowley et al., 2017, Desai et al., 2003, Ho et al., 2011, Hodges et al., 2019, Benitez and Fernando, 2019, Mckenna et al., 2019, Candfield et al., 2019, Bakr et al., 2019, Edlin et al., 2013, Amiri et al., 2014, Klinkenberg et al., 2003), prevalence varying from 7-74%. In 12 studies that reported IDU ever/lifetime use (O'Sullivan et al., 2020, Read et al., 2017, Strehlow et al., 2012-Doosti-Irani et al., 2017, Desai et al., 2003, Naymathi et al., 2013, Bajis et al., 2019, Stein et al., 2012, Beiser et al., 2019, Barror et al., 2019, Khalili et al., 2019, Colson et al., 2011) this ranged from 3 - 100%. Fourteen studies provided actual numbers with IDU within the last year (O'Sullivan et al., 2020, Aysiah et al., 2018, Read et al., 2017, Andric et al., 2017, Hashim et al., 2019-Surey et al., 2016, Newman et al., 2013, Lambert et al., 2019, Beste and Stein, 2008, Bajis et al., 2019, Harney et al., 2019, Stagg et al., 2019, Nikoo et al., 2019, Macbeth et al., 2019), prevalence being 23% (787/3496). Of these 14 studies, three included only PWAH (Surey et al., 2016, Nikoo et al., 2019, Macbeth et al., 2019) prevalence of IDU within the last year being 21% (126/595). Only three studies provided OST/harm reduction counselling/motivational counselling (Surey et al., 2016, Crowley et al., 2017, Edlin et al., 2013) with two providing mental health input (Ho et al., 2015, Edlin et al., 2013).

BBV assessment and prevalence (Table 3.3)

Method for assessment of HCV was reported in 23 studies and this included venous blood in 14 (Aysiah et al., 2018, Page et al., 2017, Read et al., 2017, Boyce et al., 2009, Strehlow et al., 2012, Doosti-Irani et al., 2017, Desai et al., 2003, Lambert et al., 2019, Sahajian et al., 2007, Naymathi et al., 2013, Beste and Stein, 2008, Stein et al., 2012, Colson et al., 2011, Klinkenberg et al., 2003) oral swabs in three (Selvapatt et al., 2015, Stagg et al., 2019, Barror et al., 2019), finger prick tests in three (Hashim et al., 2019, Ferreira et al., 2017, Bajis et al., 2019), multiple testing to include venous blood/finger prick/oral swab in three studies (O'Sullivan et al., 2020, Lambert et al., 2019, Barror et al., 2019), with one study used point of care HCV RNA testing (Bajis et al., 2019).

Fourteen studies only included patients with HCV so had 100% HCV seroprevalence (Read et al., 2017, Andric et al., 2017, Ho et al., 2015, Crowley et al., 2017, Newman et al., 2013, Ho et al., 2011, Beste and Stein, 2008, Beiser et al., 2019, Hodges et al., 2019, Macbeth et al., 2019, Buchannan and Ord et al., 2019, Mckenna et al., 2019, Candfield et al., 2019, Bakr et al., 2019) and three only reported data on HCV RNA prevalence (Bajis et al., 2019, Harney et al., 2019, Edlin et al., 2013). Of the remaining 25 studies, HCV seroprevalence varied from 2.5-58%. Of these 25, 21 reported actual number with a positive HCV serology (O'Sullivan et al., 2020, Aisyah et al., 2018, Page et al., 2017, Selvapatt et al., 2015, Hashim et al., 2019, Surey et al., 2016, Boyce et al., 2009, Strehlow et al., 2012, Doosti-Irani et al., 2017, Ferreira et al., 2017, Desai et al., 2003, Sahajian et al., 2007, Lambert et al., 2019, Stagg et al., 2019, Nikoo et al., 2019, Macbeth et al., 2019-Benitez and Fernando, 2019, Barror et al., 2019, Khalili et al., 2019, Edlin et al., 2013, Klinkenberg et al., 2003), prevalence being 19% (3098/16500). Of these 21 studies, 13 included only PWAH (Aisyah et al., 2018, Page et al.,

2017, Selvapatt et al., 2015, Surey et al., 2016, Boyce et al., 2009, Newman et al., 2013, Strehlow et al., 2012, Doosti-Irani et al., 2017, Ferreira et al., 2017, Desai et al., 2003, Nikoo et al., 2019, Macbeth et al., 2019, Colson et al., 2011, Klinkenberg et al., 2003), HCV seroprevalence being 26% (1033/3937). Nine studies provided data on HCV RNA prevalence (O'Sullivan 2020, Selvapatt et al., 2015, Hashim et al., 2019, Bajis et al., 2019, Harney et al., 2019, Stagg et al., 2019, Barror et al., 2019, Edlin et al., 2013, Colson et al., 2011) (included one study with only PWAH -Colson et al., 2011), this being 939/3708 (25%). Twenty studies provided additional data on other BBV prevalence to include HIV and HBV (Table 3.3).

Hepatic fibrosis assessment and prevalence (Table 3.4)

Fourteen studies performed assessment of hepatic fibrosis (O'Sullivan 2020, Read et al., 2017, Foucher et al., 2009, Hashim et al., 2019, Ho et al., 2015, Crowley et al., 2017, Bajis et al., 2019-Beiser et al., 2019, Hodges et al., 2019, Macbeth et al., 2019, Mckenna et al., 2019, Candfield et al., 2019, Barror et al., 2019, Bakr et al., 2019). The method was transient elastography (TE) in nine studies (O'Sullivan et al., 2020, Read et al., 2017, Foucher et al., 2009, Hashim et al., 2019, Crowley et al., 2017, Bajis et al., 2019, Hodges et al., 2019, Macbeth et al., 2019, Barror et al., 2019), liver biopsy in one (Ho et al., 2015) multiple methods (FIB-4, APRI, TE, serum biomarkers and clinical) in two studies (Beiser et al., 2019, Bakr et al., 2019) and not reported in two (Mckenna et al., 2019, Candfield et al., 2019). Seven studies provided data on $\geq$ F2 fibrosis (Aisyah et al., 2018, Read et al., 2017, Hashim et al., 2019, Crowley et al., 2017, Bajis et al., 2019, Beiser et al., 2019, Hodges et al., 2019) which was 37% (479/1285). Prevalence of cirrhosis (F4 fibrosis) was available in 11 studies (O'Sullivan et al., 2020, Read et al., 2017, Hashim et al., 2019, Crowley et al., 2017, Bajis et al., 2019, Beiser et al., 2019, Hodges et al., 2019, Macbeth et al., 2019, Mckenna et al., 2019, Candfield et al., 2019, Bakr et al., 2019), being 17% (243/1405). Of these, four studies included only PWAH (Hodges et al.,

2019, Macbeth et al., 2019, Mckenna et al., 2019, Bakr et al., 2019), prevalence of cirrhosis being 17% (25/151).

HCV treatment and outcomes (Table 3.4)

Twenty-two studies provided data on HCV treatment of which 14 were predominantly or completely direct-acting antiviral (DAA)-based (O'Sullivan 2020, Read et al., 2017, Andric et al., 2017, Hashim et al., 2019, Bajis et al., 2019, Beiser et al., 2019, Harney et al., 2019, Hodges et al., 2019, Macbeth et al., 2019, Benitez and Fernando, 2019, Mckenna et al., 2019, Candfield et al., 2019, Khalili et al., 2019), six pegylated interferon-based (Selvapatt et al., 2015, Foucher et al., 2009, Ho et al., 2015, Newman et al., 2013, Ho et al., 2011, Edlin et al., 2013) and two (Stagg et al., 2019, Khalili et al., 2019) provided no further details. SVR rates were variably reported as intention to treat (ITT), modified ITT (mITT) or not specified. In the six pegylated interferon-based studies (Selvapatt et al., 2015, Foucher et al., 2009, Ho et al., 2015, Newman et al., 2013, Ho et al., 2011, Edlin et al., 2013) SVR varied from 0- 71%. As these drugs are no longer used, no further analysis was done.

In the 14 DAA-based studies, a total of 750 were treated, 636 achieving SVR (85%). Six studies provided ITT SVR (O'Sullivan et al 2020, Read et al., 2017, Hashim et al., 2019, Beiser et al., 2019, Hodges et al., 2019, Bakr et al., 2019), this being 86% (505/584). Only two studies that included only PWAH (Hodges et al., 2019, Bakr et al., 2019) provided ITT SVR, this being 84/91 (92%). Treatment completion rates with DAA was available in 9 studies (O'Sullivan et al., 2020, Read et al., 2017, Hashim et al., 2019, Bajis et al., 2019-Beiser et al., 2019, Hodges et al., 2019-Benitez and Fernando, 2019, Mckenna et al., 2019, Candfield et al., 2019), this being 96% (691/723). These included three studies (Hodges et al., 2019, Macbeth et al., 2019, Mckenna et al., 2019) with only PWAH, treatment completion being 109/112 (97%).

In Ho et al. (2015) RCT the integrated care group (received input from mental health provider) were more likely to receive HCV treatment (31.9% vs. 18.8%, p=0.005) and achieve SVR (15.9% vs. 7.7%; OR 2.26; 95% CI, 1.15-4.44; P = .018). Similarly, in the RCT by Stagg et al. (2019), those receiving peer support vs standard care, successful engagement with hepatitis services was achieved by 36.5% vs 18.4% (95% CI 1.0-35.2%, p = 0.04), respectively.

Only one study performed HRQoL and health economic assessment (O'Sullivan et al., 2020). This prospective cohort study reported that both generic (SF-12 v2 physical and mental health domains p<0.001; EQ-5D-5L composite profile score, p= 0.009 and visual analogue scale, p<0.001) and liver-specific (SFLDQoL, p<= 0.011) HRQoL improved significantly at end of HCV treatment in those with SVR. This was achieved at modest costs: cost (British pounds 2018) per HCV case detected £171and mean cost per HCV cure (excluding medication) £702 $\pm$ 188 (O'Sullivan et al., 2020).

Databases	Date initial search performed	Date repeat search performed	Date repeat search performed	Date repeat search performed
PubMed (HDAS) (1946 to date of search)	December 2017	June 2018	17.11.19	13.10.20
Embase (HDAS) (1974 to date of search)	December 2017	June 2018	17.11.19	13.10.20
CINAHL (HDAS) (1981 to date of search)	--	June 2018	17.11.19	13.10.20
Medline, PubMed (HDAS) (1946 to date of search)				13.10.20

Table 3. 1: Databases used in the search.

Study, Country	Type of study	Sample size	Homeless n/ %, definition	Age (yrs)	Male	Where model based	Services offered	Service provider
Page et al., 2017 (USA) Full manuscript	Cross sectional	246	100%, homeless and unstable housed	48 (42-54)*	0%	Multi-site based at homeless shelters, low-cost single room occupancy hotels,	BBV screen, alcohol /substance use/ mental health assessment, free meals	Mobile outreach team - unspecified
Read et al., 2017 (Australia) Full manuscript	Prospective cohort	72	n=20/67 (30%), homeless in last 6 months	45 (25-69)**	n=48/72 (67%)	Dedicated community centre for homeless/ vulnerable adults	BBV screen, alcohol /substance use/ fibrosis assessment, HCV treatment	Primary care nurses
Andric et al., 2017 (Australia) Abstract	Retrospective cohort	57	n=31/57 (54%), homeless/ temporary accommodation	_	_	Primary care practices with remote with tertiary centres	HCV treatment, substance use assessment	Multidisciplinary (Primary care, specialists)
Selvapatt et al., 2015 (UK) Abstract	Cross sectional	95	100%	_	_	Dedicated community centre for homeless	BBV screen, counselling, HCV treatment (occurred in secondary care)	Multidisciplinary (specialist, hepatitis nurse)
Foucher et al., 2009 (France) Abstract	Prospective cohort	575	30% homeless	31	n= 430/575 (75%)	Street-based	BBV screen, alcohol /substance use/ fibrosis assessment, HCV treatment	Outreach worker

Study, Country	Type of study	Sample size	Homeless n/ %, definition	Age (yrs)	Male	Where model based	Services offered	Service provider
Hashim et al., 2018 (UK) Abstract	Prospective cohort	127	n=96/127 (76%), rough sleepers/ temporary accommodation	47.6±9	n=97/127 (76%)	Homeless hostel-based	BBV screen, alcohol /substance use/ fibrosis assessment, HCV treatment	Research team (Hepatology trainee, hepatologist)
Surey et al., 2017 (UK) Abstract	Cross-sectional	379	100%	_	_	Homeless hostels/day centres (EARTH study)	BBV screen, substance use assessment, harm reduction counselling	Multidisciplinary (Peer outreach worker, liver specialist)
Ho et al., 2015 (USA) Full manuscript	RCT	363 (182 IC vs. 181 UC	n=179/363 (51%), self-reported within 5 years of recruitment	55.3±5.5 vs. 55.5±5.8	n=355/363 (98%)	Dedicated community centre (Veterans affairs clinic)	BBV screen, depression/ alcohol/ substance use/fibrosis assessment, HCV treatment	Multidisciplinary (Gastro/ID specialists, nurses, with mental health provider (active arm)
Crowley et al., 2017 (Ireland) Full manuscript	Cross sectional	68	n=26/68 (38%), unstable housing	39.0 (35.2-44.0)*	n=50/68 (74%)	Addiction centre	Alcohol/substance use/fibrosis assessment, OST	Research assistant
Boyce et al., 2009 (USA)	Cross sectional	59	100%	Average age 22 vs.	n=19/59 (32%)	Shelter-based	BBV screen, substance use assessment	_

Study, Country	Type of study	Sample size	Homeless n/ %, definition	Age (yrs)	Male	Where model based	Services offered	Service provider
Full manuscript				38 (HCV +ve vs. -ve)				
Newman et al., 2013 (Canada) Full manuscript	Prospective cohort	34	n= 9/34 (33%), unstable housing	42 (21-67)**	n=20 /34 (59%)	Homeless/ vulnerable adults centre	Substance use assessment, HCV treatment	Multidisciplinary (GP, psychiatrist, nurse, counsellor)
Strehlow et al., 2012 (USA) Full manuscript	Cross sectional	387	100%, "literal homelessness" (where previous night spent)	<45 n=205/387 (53%), ≥ 45 n=182/387 (48%)	n=282/387 (73%)	Homeless and vulnerable adults centre	BBV screen, alcohol/substance use assessment, face-to-face interviews, pre/ post-test counselling	Multidisciplinary (Specialist clinicians, researchers)
Aisyah et al., 2018 (UK) Full manuscript	Cross sectional	1207	n=491/1207 (41%)	30-49 yrs n=976 (81%) ≥ 50 yrs n=228 (19%)	n=1093/1207 (90%)	Find & Treat service Multi-site model (hostels, prisons, addiction centres)	BBV/TB screen, alcohol/substance use assessment	Multidisciplinary (Specialist outreach team)

Study, Country	Type of study	Sample size	Homeless n/ %, definition	Age (yrs)	Male	Where model based	Services offered	Service provider
Doosti-irani et al. (2017) (Iran) Full manuscript	Cross sectional	307	100%, continuously/ discontinuously homeless last month/for at least 10 days	35.86 ±9.6	100%	Addiction centres	BBV screen, substance use assessment	_
Ferreira et al., 2017 (Brazil) Full manuscript	Cross sectional	481	100%	36 (29 –45)*	100%	Homeless/vulnerable adult centres	BBV screen, substance /alcohol use assessment	_
Desai et al., 2003 (USA) Full manuscript	Retrospective	418	100%	≥ 50 yrs (17.2%)	n=413/418 (98%)	Homeless hostels Domiciliary Care for Homeless Veterans (DCHV)	BBV screen, alcohol /substance use assessment	-
Sahajian et al., 2007 (France) Full manuscript	Cross sectional	988	n=481/988 (49%), sheltered/ third-party housing	18-49 n=790/988 (80%) >50 n=186/	n=486/988 (49%)	Homeless and vulnerable adults primary care centres	BBV screen, alcohol /substance use assessment	GP

Study, Country	Type of study	Sample size	Homeless n/ %, definition	Age (yrs)	Male	Where model based	Services offered	Service provider
				488 (19%)				
Lambert et al., 2019 (Ireland) Full manuscript	Prospective cohort	597	n=177/247 (72%), using homeless services/ hostels	36 (29-43)*	n=438/597 (73%)	Homeless primary care centres (Safetynet clinics)	BBV screen, alcohol /substance use assessment, referral to secondary care	Multidisciplinary (Research assistant, nurse)
Nyamathi et al., 2013 (USA) Full manuscript	Cross-sectional	157	n=124/157 (80%), homeless for 3 months/lived on street	41.9±10.1	100%	Addiction centres	BBV screen, alcohol /substance use assessment	Research nurse
Ho et al., 2011 (USA) Abstract	Prospective cohort	28	100%	_	_	Homeless primary care centre	HCV treatment	Multidisciplinary (GP, psychologist)
Beste and Stein, 2008 (USA) Full manuscript	Retrospective cohort	121	n=85/121 (70%), shelter/ street based	43.3±9.2	n=82/121 (68%)	Homeless primary care centre	BBV screen, alcohol /substance use assessment	Multidisciplinary (GP, nurses)
Heaney et al., 2016	Cross sectional	186	100%	_	_	Shelter-based	BBV screen, alcohol /substance use assessment	_

Study, Country	Type of study	Sample size	Homeless n/ %, definition	Age (yrs)	Male	Where model based	Services offered	Service provider
(USA) Abstract								
Stein et al., 2012 (USA) Full manuscript	Cross sectional	534	100%, if previous night spent on streets/shelter	45.96± 10.3	79%	Homeless hostel /streets (41 sites) Free Meal programme	BBV screen, alcohol /substance use assessment (Gelberg-Andersen Behavioral Model for Vulnerable Populations)	Research team
Bajis et al., 2019 (Australia) Full manuscript	Prospective cohort	202	n=116/199 (58%), unstable housing	48±12.1	n=163/199 (82%)	Homelessness community centre over eight liver health campaign days (LiveRLife Campaign)	BBV screen, alcohol /substance use/ fibrosis assessment, HCV treatment, $20 voucher	Multidisciplinary (GP, nurses)
Beiser et al., 2019 (USA) Full manuscript	Prospective cohort	510	n=179/300 (60%), homeless/ unstable housing	45.6±10.5 vs. 49.8 ±11.1 treated vs. untreated	n= 347/510 (68%)	Homeless and vulnerable adults centres	BBV screen, alcohol /substance use/fibrosis assessment, HCV treatment	Multidisciplinary (Non-clinician care coordinator, nurse and GP)
Harney et al., 2019 (Australia) Full	Prospective cohort	67	n=18/39 (46%), rough sleeping	45 (23–74) (HCV RNA	n=18/39 (46%)	Homeless primary care centre	BBV screen, substance use assessment, HCV treatment	Hepatitis nurse

Study, Country	Type of study	Sample size	Homeless n/ %, definition	Age (yrs)	Male	Where model based	Services offered	Service provider
manuscript				positive)				
Stagg et al., 2019 (UK) Full manuscript	RCT	364	n=200/364 (55%) currently homeless	43 (35-48)*	n=278/364 (76%)	Outreach services for problematic drug use and homeless	BBV screen, alcohol/ substance use assessment/ HCV treatment – randomised: peer or no peer support	Peer advocate
Nikoo et al., 2019 (Canada) Full manuscript	Cross-sectional (part of RCT)	497	100% (no fixed abode for > 7 nights. All had at least one mental health disorder)	18-44 yrs n=317/497 (64%), >44 yrs n=180/497 90 (36%)	_	Homeless shelters/outreach	BBV screening, substance use assessment	_
Hodges et al., 2019 (USA) Full manuscript	Prospective cohort	102	100%	45±14	n=65/102 (64%)	Integrated care (homeless and vulnerable adults health care centre)	Fibrosis assessment, HCV treatment	Multidisciplinary (nurses, doctors, medical assistants, behavioral health workers, case managers)
Macbeth et al., 2018 (UK) Full manuscript	Prospective cohort	30	100%	Mean 41 yrs	n=20/30 (67%)	Homeless primary care centre	BBV screen/substance use assessment/fibrosis assessment, HCV treatment	Nurse led

Study, Country	Type of study	Sample size	Homeless n/ %, definition	Age (yrs)	Male	Where model based	Services offered	Service provider
Benitez et al., 2019 (USA) Abstract	Prospective cohort	408	n=22/28 (79%) receiving HCV treatment experiencing homelessness	_	_	Multi-site (homeless hostels and Homeless primary care centre)	BBV screen, HCV treatment	Multidisciplinary (Primary care physician, dedicated care coordinator)
Buchanan et al., 2019 (UK) Abstract	Retrospective cohort	48	n=31/48 (65%), no fixed abode	_	_	HCV outreach treatment clinic in needle exchange centre	BBV screen, alcohol /substance use assessment, HCV treatment	Multidisciplinary (HCV outreach team and harm minimising services)
Mckenna et al., 2019 (UK) Abstract	Prospective cohort	6	100%	_	_	Homeless shelter	BBV screen, fibrosis assessment, HCV treatment	Multidisciplinary (community nurse, hepatologists)
Candfield et al., 2019 (UK) Abstract	Prospective cohort	71	n= 51/71 (72%), homeless/living in hostels	47 (26-63)	n=52/71 (73%),	Multi-site (homeless primary care and addiction centres)	BBV screen, alcohol/substance use/fibrosis assessment, HCV treatment	_
Barror et al., 2019 (European) Full manuscript	Prospective cohort	2079	n=799/2079 (39%) ever being homeless	41.3 (32–50)*	n=1783/2079 (86%)	Multisite (prison, addiction and alcohol services, homeless sites)	BBV screen, fibrosis assessment (done in both community and secondary care)	Multidisciplinary (Doctors, nurses, peers, GP, research teams)

Study, Country	Type of study	Sample size	Homeless n/ %, definition	Age (yrs)	Male	Where model based	Services offered	Service provider
O'Sullivan et al., 2020 (UK) Full manuscript	Prospective cohort	573	n= 289/573 (50%), unstable housing/rough sleepers	40.5±10	n=462/573 (81%)	Addiction centre-based	BBV screen, alcohol /substance use/ fibrosis assessment, HCV treatment, QoL/ health economics	Multidisciplinary (Hepatitis nurse, hepatologist, psychiatrist)
Khalili et al., 2019 (USA), Abstract	Prospective cohort	479	Chronic homeless 47% vs. 43% (HCV vs. no HCV) (p=0.09)	53.5 (median)	67.8%	Homeless shelters	BBV screen, substance use assessment, HCV treatment, financial incentive	-
Bakr et al., 2019 (USA), Full manuscript	Retrospective cohort	24	100% (recently homeless)	58.5 ± 8.6	100%	Veterans health administration	Substance use and fibrosis assessment, HCV treatment	Multidisciplinary (ID physician, GP, pharmacist)
Edlin et al., 2013 (USA), Abstract	Prospective cohort	43	n=31/43 (72%), homeless in last 6 months	37 (18-62)**	n=32/43 (74%)	Community-based needle exchange programmes	BBV screen, substance use assessment, psychiatric care (motivational enhancement therapy), HCV treatment	Multidisciplinary (Case manager, staff from needle exchange, tertiary physicians)

Study, Country	Type of study	Sample size	Homeless n/ %, definition	Age (yrs)	Male	Where model based	Services offered	Service provider
Colson et al., 2011 (France), Abstract	Prospective cohort	190	100% (homeless people)	41 ± 14	n=182/190 (96%)	-	BBV screen, alcohol/substance use assessment	-
Amiri et al., 2014 (Iran), Full manuscript	Prospective cohort	593	100% (Homeless in prior month	41 (median)	n=513/593 (87%)	Homeless centres	BBV screen, substance use assessment	Multidisciplinary (Research team)
Klinkenberg et al., 2003 (USA), Full manuscript	Prospective (recruited as part of a RCT)	204	100% (Currently homeless - staying in shelter/street)	39.8 (mean)	77.9%	Hospitals, social service agencies, shelter, soup kitchen, streets	BBV screen, substance/alcohol use/mental health assessment, financial incentive	Multidisciplinary Research staff, outreach team

Table 3. 2: Demographics, type of study and services offered.

RCT= randomised controlled trial, HCV= hepatitis C virus, BBV= blood-borne virus, TB= tuberculosis, OST= opioid substitution treatment, QoL= quality of life, Gastro= gastroenterology, ID= infectious diseases, GP= general practitioner, IC= integrated care, UC= usual care. Age shown as median (IQR)*, median (range)** or mean ± SD (Standard Deviation)

Study	IDU prevalence, definition, how assessed	Alcohol use prevalence, definition, how assessed	HCV seroprevalence, how assessed	HBV/HIV prevalence	Liver fibrosis, how assessed and stage
Page et el 2017	n= 47/246 (19%), self-reported	n=50/246 (20%), heavy drinking, self-reported	n=113/246 (46%), venous blood	HIV/HCV n= 58/246 (24%)	_
Read et al., 2017	n= 53/72 (74%) IDU current/last six months, 100% ever IDU	n=12/56 (21%), > 4 standard drinks in one session in last month	100%, venous blood	HIV n=8/72 (11%), HBV n=0	TE n=72 F0/FI n= 51(71%), F2 n=10 (14%), F3 n=4 (6%), F4 n=7 (10%)
Andric et al. 2017	n=25/57 (44%), current active IDU	_	100%	_	_
Selvapatt et al., 2015	_	_	n=6/95 (6%), oral swab, n=5/6 (80%) HCV PCR positive	HIV/HCV n=1/95 (1%)	_
Foucher et al., 2009	n=271/575 (47%) IDU, questionnaire	On average 67 units/week questionnaire	34% HCV infection	HIV=3% HBV=1%	TE Median/ LSM 5.3 kPa (2.2-75 kPa)
Hashim et al., 2018	n=68/127 (54%), current IDU, self-reported	n=63/127 (50%), AUDIT score ≥ 20	n=59 /125(47%), finger prick, 49/125 (39%) HCV RNA positive	HBV n=0 HIV n=3 (2%)	TE n=127 ≥F2 n=33 (26%), F4 n=21 (17%)
Surey et al., 2017	n=22/68 (32%) with HCV recent IDU, interviews	_	n=68/379 (18%), oral swab	_	_

Study	IDU prevalence, definition, how assessed	Alcohol use prevalence, definition, how assessed	HCV seroprevalence, how assessed	HBV/HIV prevalence	Liver fibrosis, how assessed and stage
Ho et al., 2015	n=172/363 (47%), active drug use (within 1 year), questionnaire	96/363 (26%), AUDIT-C score ≥ 4 (high risk drinking)	100%	HIV/HCV n=42/363 (12%)	Liver biopsy n=28/124 (23%) advanced fibrosis (Metavir F3-F4) Excluded ALD
Crowley et al., 2017	n=48/68 (71%), self-reported drug/ alcohol instability	N=48/68 (71%), self-reported drug/alcohol instability	100%	--	TE n=68 LSM≥8.5, n=22 (32%), LSM≥12.5, n=12 (20%)
Boyce et al., 2009	n=4/40 (10%) IDU, questionnaire	_	n=3/40 (8%), venous blood	HBV n=1/40 (3%)	_
Newman et al., 2013	n=12/34 (35%) IDU last six months, semi structured interview	_	100%	_	_
Strehlow et al., 2012	n=110/387 (28%), IDU ever, interviews	n=116/387 (30%) hazardous, drinking (four or more drinks on any day last 30 days), interviews	N=120/387 (31%), venous blood	_	_
Aisyah et al., 2018	n=75/1158 (7%) active IDU , n=27/448 (6%) PWAH active IDU	n=408/1207 (34%), problem alcohol use	n=98/1207 (8%), venous blood overall, n=65/491 (13%) homeless	HCV±HBV n= 57/98 (58%) HCV/HIV n= 3/98 (3%)	_
Doosti-irani et al., 2017	39% ever IDU	_	n=96/307 (31%) 95% CI 26.31-36.71, venous blood	HIV n=20/307 (7%), HBV n=3/307 (1%), HIV/HCV (6%)	_

Study	IDU prevalence, definition, how assessed	Alcohol use prevalence, definition, how assessed	HCV seroprevalence, how assessed	HBV/HIV prevalence	Liver fibrosis, how assessed and stage
Ferreira et al., 2017	n=42/481 (9%) (IDU yes), interviews	n=358/478 (75%) alcohol use yes, interviews	n=12/481 (2.5%), 95% CI 1.4 - 4.3%, finger prick,	--	_
Desai et al., 2003	n=295/418 (71%), lifetime drug abuse	n=406/418 (97%), lifetime alcohol abuse,	N=184/418 (44%), venous blood	--	_
Sahajian et al., 2007	n=16/942 (2%) IDU, questionnaire	n=33/941 (4%) alcoholism, questionnaire	n=44/944 (5%), 95% CI 3.4–6.1, venous	HIV n=4/941 (<1%) HBV n=27/941 (<1%)	_
Lambert et al., 2019	N=84/157 (54%) current IDU, self-reported on questionnaire	n= 72/193 (37%), problematic alcohol use, self-reported on questionnaire	n=199/538 (37%), rapid oral swab/venous 46 referred to secondary care, two completed HCV treatment	_	
Nyamathi et al., 2013	n=53/157 (34%), lifetime IDU, Drug History form	n=61/157 (40%), lifetime ≥ 4 drinks/day, Drug History form	25%, venous blood	_	_
Ho et al., 2011	_	_	100%	--	_
Beste and Stein, 2008	n=11/121 (9%), active IDU	n=19/121 (16%), current alcohol dependence/abuse	100%, venous blood	HBV n=11/121 (9%)	_

Study	IDU prevalence, definition, how assessed	Alcohol use prevalence, definition, how assessed	HCV seroprevalence, how assessed	HBV/HIV prevalence	Liver fibrosis, how assessed and stage
Heaney et al., 2016	22% IDU	35%, alcohol abuse	n=41/186 (22%)	HIV/HCV n=1/41 (2%)	_
Stein et al., 2012	21% lifetime IDU, interviews	29%, dependency diagnosis DSM -1V, interviews	28%, venous blood	HBV 31%	_
Bajis et al., 2019	n=54/199 (27%) IDU in last 6 months, n=98/199 (49%) ever IDU, survey	n=75/199 (38%) high-risk alcohol consumption (AUDIT-C)	Finger prick, n=47/202 (23%) PCR, fingerpick point of care Xpert® + venous blood	_	TE n=186 F0/F1 n=136 (73%), F2 n=29 (21%), F3 n=9 (5%), F4 n=12 (6%)
Beiser et al., 2019	n=289/510 (57%) opioid use disorder, n=414/510 (81%) IDU ever	n=185/510 (36%) alcohol use disorder	100%, venous blood	HIV n=61/300 (20%)	FIB-4, TE, serum biomarkers, clinical, n=510 F0/F1 n=288 (56%), F2/F3 n=77 (15%), F4 n=93 (18%)
Harney et al., 2019	n=19/39 (49%) IDU within last 3 months	_	n=39/52 (75%) PCR positive, venous blood	_	_
Stagg et al., 2019	n=82/364 (23%) current IDU	n=216/364 (59%), alcohol related concerns	n=136/364 (37%), oral swab, n=101/136 (76%) HCV PCR positive	HBV n= 3/364 (1%) HIV n=3/364 (1%)	_
Nikoo et al., 2019	n=98/497 (20%) IDU last month	_	n=139/447 (28%)	_	_
Hodges et al., 2019	_	_	100%	_	TE n=102 F0 n=41 (40%), F1 n=15

Study	IDU prevalence, definition, how assessed	Alcohol use prevalence, definition, how assessed	HCV seroprevalence, how assessed	HBV/HIV prevalence	Liver fibrosis, how assessed and stage
					(15%), F2=18 (18%), F3 n=12 (12%), F4 n=16(16%)
Macbeth et al., 2018	n=6/30 (20%) IDU last six months	_	100%	_	TE+ clinical Cirrhosis n=2/30 (7%)
Benitez et al., 2019	_	_	n=408/6760 (6%)	_	_
Buchanan et al., 2019	73% IDU at time of HCV assessment	n=12/54 (22%) alcohol dependent	100%	_	_
Mckenna et al., 2019	_	_	100%	_	Cirrhosis n=3/6 (50%)
Candfield et al., 2019	n=53/71(75%) on OST	n=29/71 (41%), heavy drinking (35U women, 50U men)	100%	HIV n=5/71 (7%)	Cirrhosis n=20/71 (28%)
Barror et al., 2019	n=927/2079 (45%) ever IDU	_	n=769 /2079 (37%), oral swab /finger prick /venous n=397/2079 (19%) PCR positive, 316/397 (80%) linked to care	_	TE/Fibromax n=312, data NA
*O'Sullivan et al., 2020	n=411 (72%) IDU ever, n=178 (31%) IDU current at time of	n=505 (88%) alcohol ever, n=134 (23%) currently > 21 units/week, self-reported	n=323/558 (58%), finger prick/venous blood	_	TE (n=219) F0-F1 n=115 (53%),F2-F3 n=51 (22%) F4 n=53 (24 %)

Study	IDU prevalence, definition, how assessed	Alcohol use prevalence, definition, how assessed	HCV seroprevalence, how assessed	HBV/HIV prevalence	Liver fibrosis, how assessed and stage
	HCV treatment, self-reported		n=259/558 (46%) RNA positive		
Khalili et al., 2019	HCV vs. no HCV)(p<0.0001) IDU history 66% vs. 14% SUD treatment 66% vs. 36% self-reported on questionnaire	_	n=94/479 (20%), HCV rapid testing of whom 63% HCV RNA positive	HBV 14%, HIV 4%	_
Bakr et al., 2019	Polysubstance use n=22/24 (92%), self-reported	_	100%	_	Fibrosis assessment by imaging/FIB-4/APRI Cirrhosis n=4/13 (31%)
Edlin et al., 2013	n=33/43 (77%) used heroin and n=26/43 (60%) cocaine in last 30 days	_	n=34/43 (79%) HCV RNA positive	_	_
Colson et al., 2011	n=6/190 (3%) past or current IDU	66% excessive alcohol	n=9/190 (5%) (1 HIV/HCV coinfected), venous blood, of whom n=8 HCV RNA positive	HIV n=2/190 (1%) HBV n=8/190 (4%)	
Amiri et al., 2014	27.5% lifetime history of drug use, self-reported on questionnaires	_	23.3% (95% CI 20.0%-26.9%), venous blood	HIV 3.4% (95% CI 2.1%-5.1%) HBV 2.58% (95% CI 1.5%-41.1%)	_

Study	IDU prevalence, definition, how assessed	Alcohol use prevalence, definition, how assessed	HCV seroprevalence, how assessed	HBV/HIV prevalence	Liver fibrosis, how assessed and stage
Klinkenberg et al., 2003	62.8% substance abuse disorder, 46.9% substance dependence, 10% both, assessed using Drake/Carey scales	Severity of alcohol use at baseline in n=114 tested for HCV 3.21 $\pm$ .97	n=34/114 (30%), venous blood	HIV n=11/172 (6%)	

Table 3. 3: Injecting drug use and alcohol use data and blood-borne virus and liver fibrosis prevalence.

ALD= alcohol-related liver disease, IDU= injecting drug use, OST= opioid substitution treatment, PCR = polymerase chain reaction ** median (range).

Study	Number with HCV treated	SVR	Treatment regimen	Treatment completion	Regimen
Read et al., 2017	n=72	ITT n=59/72 (82%), mITT n= 59/65 (92%)	DAA	n=69/72 (96%) completed treatment, n=7 SVR data awaited, n=3 did not attend for EOTR, n=1 overdose death, n=2 LTFU, n=25/72 (35%) received adherence support	LDV/SOF n=38, SOF/DCV n=28, ABBVIE 3D±RBV n= n=6, n=6 no data
Andric et al., 2017	n=55	n=30/46 (65%), n=9 treatment ongoing/ SVR awaited	DAA	Completion data NA, n=16/46 LTFU	_
Selvapatt et al., 2015	n=1	0%	IFN-based treated in secondary care	n=1 commenced treatment with PEG/RBV but virological breakthrough week 12 so stopped	PEG/RBV
Foucher et al., 2009	n=27	n=9/19 (47%)	IFN-based	Completion data NA n=4 relapse, n=6 treatment failure, n=8 treatment on going	_
Hashim et al., 2018	n=29	ITT n=24/29 (83%)	DAA	n=27/29 (93%) completed treatment, n=2 not completed, of whom one did not achieve SVR	Abbvie 3D±RBV n=5, SOF/LDVRBV n=4, ELB/GRZ n=4, SOF/VEL, n= 11, GLE/PIB n=5
Ho et al., 2015	32% Integrated Care (IC) vs. 19% usual care (UC)	n=29/182 (16%) IC vs. 14/181 (8%) UC (OR 2.26, 95% CI 1.13–4.52, p=.022)	IFN-based	Treatment completion 70.3+33.1% IC, 61.7±36.5% UC Compliance defined as at least 80% of planned treatment	PEG /RBV and DAA + PEG/RBV DAAs boceprevir or telaprevir

Study	Number with HCV treated	SVR	Treatment regimen	Treatment completion	Regimen
Newman et al., 2013	n=14	n=8/14 (57%)	IFN-based	n=10/14 (71%) completed treatment, in n=4 stopped early due to illness, relapse and NR	PEG/RBV
Ho et al., 2011	n=28	ITT n=18/28 (64%)	IFN-based	n=24/28 (86%) completed treatment, 4 stopped treatment due to side effects	--
Bajis et al., 2019	n=23	n=15 /15 (100%)	DAA	n=15/15 (100%) completed treatment, n=8 no available treatment outcome	LDV/SOF n=12, SOF/DCV n=7, SOF/VEL n=1, NA n=3
Beiser et al., 2019	n=300	ITT n=255/300 (85%)	DAA	n=285/300 (95%) completed ,15 did not complete treatment, n=17 treatment failure, n=14 missing data	LDV/SOF±RBV n=239, VEL/SOF± n=31, DCV/SOF±RBV n=13, SOF/RBV n=9, SIM/SOF n=5, EBR/ GZR n= 2, SOF/PEG/ RBV n = 1
Harney et al., 2019	n=24	n=13/16(81%)	DAA	Completion data NA n=1moved out of area, n=2 died 8 = No SVR data	_
Hodges et al., 2019	n=78	ITT 71/78 (92%)	DAA	n=77/78 (99%) completed treatment, n=3 treatment failure, LTFU n= 4	LDV/SOF+RBV n=67, SOF/VEL n=28, GRZ/ELB n=7
Macbeth et al., 2018	n=30	n=19/23 (83%) n=7 SVR data pending	DAA predominantly	n=28/30 (93%) completed treatment, n=4 no SVR	ELB/GZR± RBV 37%, SOF/VEL 34%, ABBVIE 3D± RBV 13%, LDV/SOF± RBV 13%, SOF/PEG/RBV 3%
Benitez et al. 2019	n=28	n=18/21 (86%)	DAA	n=21/22 (95%) completed, n=3 LTFU	_
Buchannan et al., 2019	n=37	n=18/20 (90%) n=17 SVR data pending	DAA	Completion data NA, n=2 did not achieve SVR,	_

Study	Number with HCV treated	SVR	Treatment regimen	Treatment completion	Regimen
Mckenna et al., 2019	n=6	n=1/1 SVR, awaited in rest	DAA	n=4/4 (100%) completed treatment, ongoing n=2	_
Candfield et al., 2019	n=48	17/24 (71%)	DAA	n=43/48 (90%) completed treatment	_
O'Sullivan et al., 2020	n=125	ITT n=109/125 (87%) ITT SVR with DAA n= 83/92 (90%) mITT with DAA n=83/87 (95%)	Predominantly DAA INF based n=33/125 (26%), DAA n=92/125 (74%)	Treatment completion n=122/125 (98%) n=9 did not achieve DAA-based SV: n=5 LTFU, n=4 RR	PEG/RBV n=16, PEG/RBV+ DAA n=17, DAA n= 94:Abbive 3D n=24, LDV/SOF±RBV n=31, DAC/SOF+RBV n=2, SOF +RBV n=2, ELB/GRZ+RBV n=5, SOF/VEL± RBV n=13, GLE/PIB n=5
Khalili et al., 2019	28% treated but no details provided	_	_	_	_
Bakr et al., 2019	n=13	ITT SVR 13/13 (100%)	DAA	_	LDV/SOF n=7, SOF/VEL n=3, GLE/PIB n=2, ELB/GRZ n=1
Edlin et al., 2013	n=21 (14 chronic and 7 acute HCV)	ITT SVR n=15/21 (71%)	IFN-based	_	PEG/RBV

Table 3. 4: HCV treatment regimens and outcomes.

SOF= sofosbuvir, LDV= ledipasvir, ABBVIE 3D= ombitasvir/paritaprevir/ritonavir + dasabuvir, DCV= daclatasvir, RBV= ribavirin, PEG= pegylated interferon, VEL= velpatasvir, SIM= simeprevir, EBR/GZR= elbasvir/grazoprevir, LTFU= loss to follow up, EOTR= end of treatment response, RR= responder relapse, TE= transient elastrography

3.4 Discussion

The quality of evidence assessing the effectiveness of liver-related interventions in PWAH remains poor, with only 2 studies reporting RCTs' results. In these RCTs (Ho et al., 2015, Stagg et al., 2019), mental health providers and peer support significantly increased linkage to care. Nonetheless, in Stagg et al. RCT engaging homeless adults with HCV treatment was still suboptimal. Despite the high prevalence of AUD (34%) amongst PWAH, none of the studies specifically addressed ALD or discussed interventions for AUD. Moreover, the definition of AUD was not unified, limiting the ability to perform a valid and accurate comparison between the various models. There was a high HCV seroprevalence amongst PWAH (26%), and this high HCV burden was observed across the different community models. The review also confirms that the burden of other BBVs (particularly HBV and HIV) remains relatively low compared to HCV. The vast majority of the studies were from western populations with only a few studies from middle-income countries (mainly Iran) where the burden of HCV burden is considerably high (Mohd Hanafiah et al., 2013).

In almost 90% of the studies, the model of care was based at a homeless site, endorsing the importance of engaging with these vulnerable individuals in an environment they are comfortable with. Qualitative studies (Phillips et al., 2020) and a recent systematic review (Bajis et al., 2017) confirm this, indicating that a trusting client-provider relationship and integrated services are the key to successful linkage to care. Beiser et al. (2017) also described that the majority of PWAH preferred to receive their HCV treatment in a primary care setting compared to a liver-specialist setting. Qualitative studies were not included in this review, but the findings suggest a need for further systematic reviews looking specifically into enablers and predictors of engagement with services among PWAH. In the current review, less than a third of the studies provided any form of an integrated service or multidisciplinary approach.

However, recruitment sites varied from community dedicated centres for PWAH to services provided at substance misuse centres to more proactive models such as mobile, street-based services and opportunistic screening through meal programmes.

Although the cut-off values for diagnosing advanced fibrosis and cirrhosis varied across the different studies the prevalence of cirrhosis was still high. This observation is likely to be due to the synergistic effect between HCV and AUD. A recent international study reported AUD to be present in 28-50% of individuals with decompensated cirrhosis due to HCV, ongoing alcohol use being an independent predictor of more advanced liver disease (Alavi et al., 2018). There has been a significant reduction in addiction services funding in England from over the past few years (Rhodes, 2018) which coincided with 55% increase in alcohol/substance use-related deaths in PWAH (Office of National Statistics, 2018). While HCV can be easily treated with DAAs with SVR rates reaching more than 90%, AUD among PWAH remains a significant risk factor for progression of CLD even when HCV cure is achieved. Alcohol use could also reduce benefits from successful antiviral treatment at a patient and population level (Alavi et al., 2018). It may also contribute to poor compliance with DAA therapy and an almost six times higher liver-related morbidity compared to the general population (Innes et al., 2017).

This review did have limitations. Almost all studies were of poor quality, with about 30% only available in abstract form or conference proceedings. Additionally, there was significant heterogeneity in defining homelessness, reporting of AUD and substance misuse disorder and fibrosis assessment, thus making direct comparisons between studies practically challenging.

3.5 Conclusion

This systematic review highlights the significant burden from liver disease, including HCV and increased hepatic fibrosis, AUD and IDU in PWAH. Despite this, the quality of evidence assessing the effectiveness of interventions in PWAH remains poor, though where good quality evidence exists, community-based interventions can increase linkage to care and HCV treatment outcomes. These data endorse the need for a well-designed national study evaluating community-based interventions to improve liver disease outcomes amongst PWAH.

CHAPTER 4: Methodology of VALID study

4.1 Project aims and outcome measures

The overall goal of the study was to set up a community liver service for vulnerable/PWAH adults with an aim to assess, stratify and treat CLD in this group. The concept of this service was based on our prior success in setting up a comprehensive community HCV service at a drug and alcohol centre in Brighton (Chapter 2) as well as national recommendations published in the Lancet liver report (Williams et al., 2018) which encompass; strengthening the early detection and treatment of liver disease by improving the level of expertise and facilities in primary care and developing support services in the community setting for screening of high-risk patients.

The primary objective was:

Assessment of clinically significant hepatic fibrosis (CSHF) (liver stiffness measurement $\geq$8kPa).

Secondary objectives were to assess:

1. Service uptake.
2. Prevalence of HCV, alcohol use disorder (AUDIT questionnaire and alcohol breath test) and substance misuse (self-reported) and current injecting drug use.
3. Independent predictors of clinically significant hepatic fibrosis (LSM $\geq$ 8kPa)
4. Nutritional status and its relation to chronic liver disease.

5. ELF and APRI test, hepatocyte senescence biomarkers and cytokine profile (Th17 panel) in PWAH.
6. HCV treatment outcomes.

Outcome measures

The primary outcome measure was the percentage of PWAH with clinically significant chronic liver disease (liver stiffness measurement ≥ 8kPa) in the community.

Secondary outcome measures amongst PWAH included percentage accepting the service, having a positive HCV antibody, having alcohol dependence, having IDU, having CSHF as detected by ELF test and APRI, and correlation, if any, between LSM and ELF/APRI and cytokines and hepatic senescence biomarkers.

4.2 Study design

Prospective cohort study.

4.3 Study period

October 2015 to August 2018.

4.4 Study acronym

The study was named: VALID (Vulnerable Adults LIver Disease) study.

4.5 Setting up the VALID study hostel-based clinics

While the initial aim was to set the service up at two dedicated homeless GP practices, two affiliated homeless hostels were also included in order to increase and improve access to the service. A hostel-based clinic ensured that homeless individuals were screened and provided care in an environment they felt more comfortable with. Moreover, it allowed direct and active involvement of key workers and hostel staff who had the relevant experience in dealing with this group of patients including their special needs thus facilitating their engagement with the liver services.

4.6 The concept of secondary prevention and early detection

The theoretical idea behind the methodological approach of setting up community liver screening services is based on the concept of secondary prevention which focuses on early detection of diseases when the chances of obtaining positive health outcomes are higher (Kisling and Das, 2020). This contrasts with primary prevention which aims rather to avoid the occurrence or the manifestations of the disease, usually through changing socio-economic factors and undertaking lifestyle modifications (Patterson and Chambers, 1995).

Secondary prevention requires reorientation of health services in the community to develop care models that promote identification of early asymptomatic cases and restoration of normal health by applying prompt and effective interventions (Patterson and Chambers, 1995). This can be undertaken in groups through institutional-based/population-based mass screening programmes or individual case-finding approach (Speechley et al., 2017). The latter can be further classified into active and passive case finding strategies (Figure 4.1).

The disease process takes place in several phases. In general, the preclinical phase is the period during the natural course of a disease that occurs between the onset of the biological process and the occurrence of clinical symptoms; and patients are usually asymptomatic (Herman et

al., 2002). Within this phase, the disease might still be detectable, “the detectable pre-clinical phase”, and this represents the ideal time or window for screening and prevention of chronic diseases. Once the symptoms appear, the clinical phase begins.

The clinical course of CLD constitutes a good model for the application of secondary prevention strategies for various reasons. Hepatic fibrosis is mostly asymptomatic with symptoms manifesting towards the end of the disease spectrum when complications ensue. Therefore, screening those who have significant fibrosis (but not necessarily have the clinical manifestations) is crucial. The long duration of progression of CLD from early stages to advanced disease also provides a great window of opportunity for early detection. Moreover, the ultimate goal of screening in these settings is to detect liver fibrosis at the early stages to prevent unwanted outcomes, i.e., development to cirrhosis and its complications. With interventions currently being available for many risk factors for CLD such as alcohol cessation, DAA treatment and lifestyle modifications, progression to cirrhosis secondary to ALD, chronic HCV and NAFLD, respectively, can be hindered. In many cases, reversal of the liver fibrosis and regression can be achieved (Hsu et al., 2019, Glass et al., 2015).

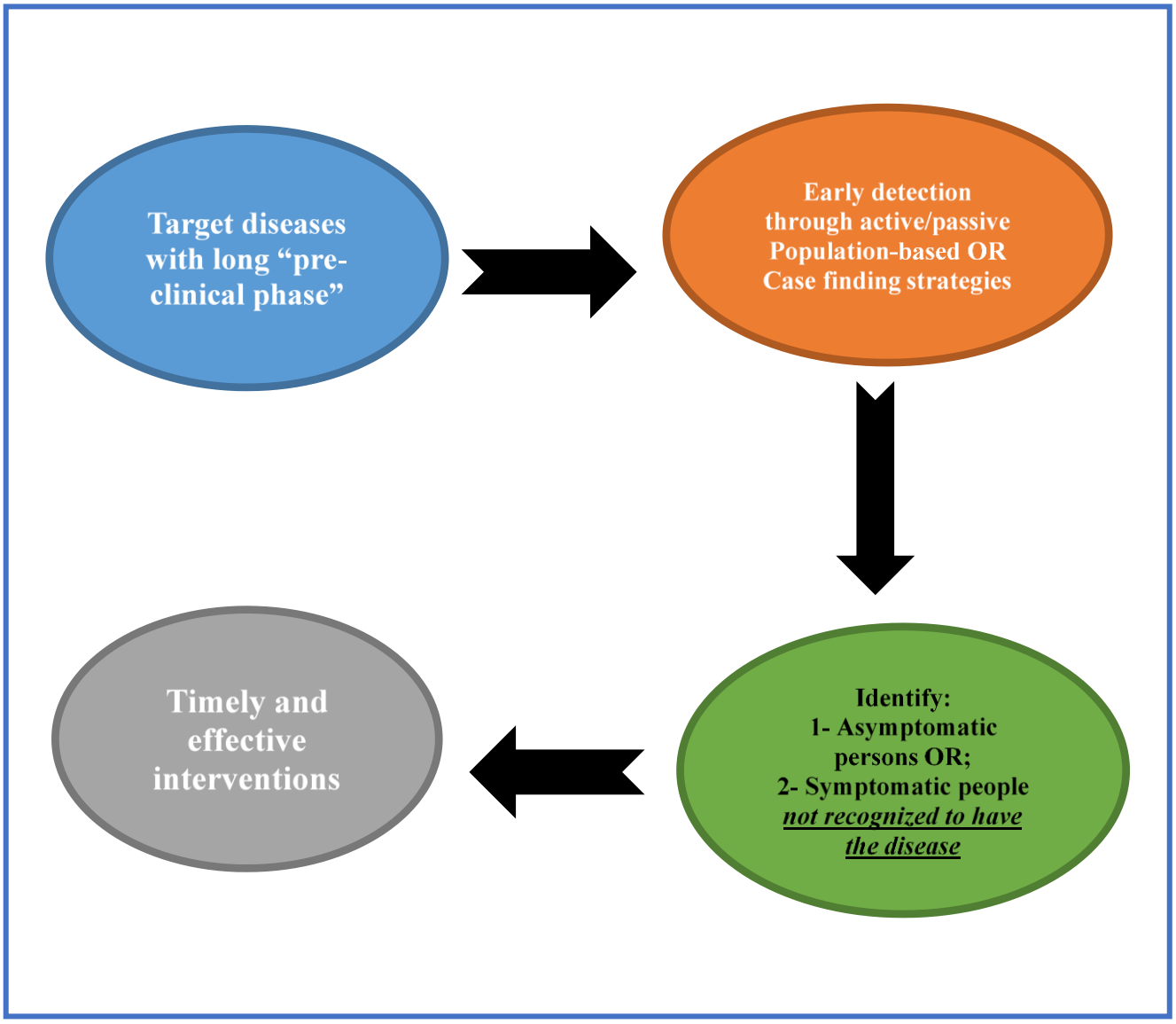


Figure 4. 1: The principles of secondary prevention and early detection of diseases in the community.

4.7 Recruitment sites

The Vulnerable Adults Liver Disease (VALID) project was based at Arch healthcare service [previously known as Brighton Homeless Healthcare (BHH) and its affiliated Glenwood lodge homeless hostel as well as a second homeless GP practice (Brighton Health and Wellbeing Centre, BHWC) and its affiliated St Patrick's homeless hostel in Hove. The main recruitment site was Glenwood Lodge. The Arch healthcare service is one of the few national GP practices dedicated solely for PWAH including street homeless, sofa surfers, temporarily housed and the traveller community.

4.8 Service set up

Setting up the hostel-based services required the following:

- Engaging with various stakeholders including commissioners, primary care physicians, hostel staff, outreach services, drug and alcohol services etc
- A space for clinical consultation room was identified and set up as per the NHS standards with all the necessary equipment, including a couch, washing sink, medical waste bins, sharps bins, phlebotomy equipment, alcohol wipes etc.
- Considering the nature of the consultation, safety measures such as a security alarm system were installed with a panic button attached to the doctor's desk and linked to the hostel management office and the nearby police station.
- The clinical consultation notes were transferred immediately to the affiliated GP surgeries and were either documented directly on the GP electronic system (System One) or scanned and uploaded into the records.

4.9 Eligibility criteria

Inclusion criteria:

1. Consecutive adults aged > 18 years attending the two specified primary care practices and their affiliated homeless hostels who are deemed vulnerable or homeless by their GPs. Initially, the service was offered to individuals aged ≥ 50 years (as per the requirement of the funder). As illustrated in Chapter 1, homeless individuals age prematurely and the average age at death of PWAH varies between 42 & 52 years (Hassanally and Asaria, 2018, Office of National Statistics, 2018, Aldridge et al., 2019, Roncarati et al., 2018). According to personal communications with the team at Brighton Homeless Healthcare, the average age of death in Brighton is 47 years (Tim Worthley, personal communication, Feb 2016). Given these observations and following negotiations with the funder/obtaining funding from additional sources, in July 2016 (after 8 months of the initial recruitment- end of October 2015) the recruitment age was amended to include those aged ≥ 40 years, and in July 2017 to include all eligible vulnerable adults aged ≥ 18 years. This allowed the exploration of CLD in a larger population and facilitated the comparison between the older (≥ 50 years) vs. the younger vulnerable individuals.
2. Those who are willing and able to give informed consent.

Exclusion criteria:

Those who are unwilling or unable to give informed consent. These individuals were still offered the service, but their data was not collected.

4.10 Recruitment process to the VALID study

The recruitment to the service began at the end of October 2015. A poster was developed explaining the recruitment process, inclusion criteria, the medical services provided during the VALID liver screening appointment, and the clinics' time and dates. The poster was displayed at all recruitment sites. It was also distributed to the nearby hostels, pubs (Wetherspoon pubs), and other local services that cater to PWAH and vulnerable individuals such as the rough sleeping team and charity sites offering free meals and temporary shelters.

The two General Practice (GP) surgeries involved in the study were also asked to advertise for the service via their usual standard of care. In one GP surgery, mobile texts were sent to registered patients who fulfilled the inclusion criteria. In the other GP practice, small leaflets (showing the overall aim of the service and eligibility) were left for interested clients to collect from reception after their primary consultation or appointments. Doctors and nurses in the surgeries were encouraged to discuss the benefits of the VALID clinic service during their consultation with the patients. The diagram below (Figure 4.2) summarises the recruitment process to the VALID study clinic.

One of the hostel managers from Glenwood Lodge was later trained and assisted in visiting other hostels in Brighton to provide education about CLD in vulnerable adults as well as to increase awareness of the VALID study. The hostel manager was trained to use face-to-face meetings (both on an individual and group level) and distribute study posters to facilitate the recruitment process in an attempt to publicize the service and encourage additional individuals to attend the recruitment sites for enrollment and screening. He received training in undertaking dry blood-borne viruses testing at a later stage through finger-prick testing and Dried Blood Sample Testing (DBST).

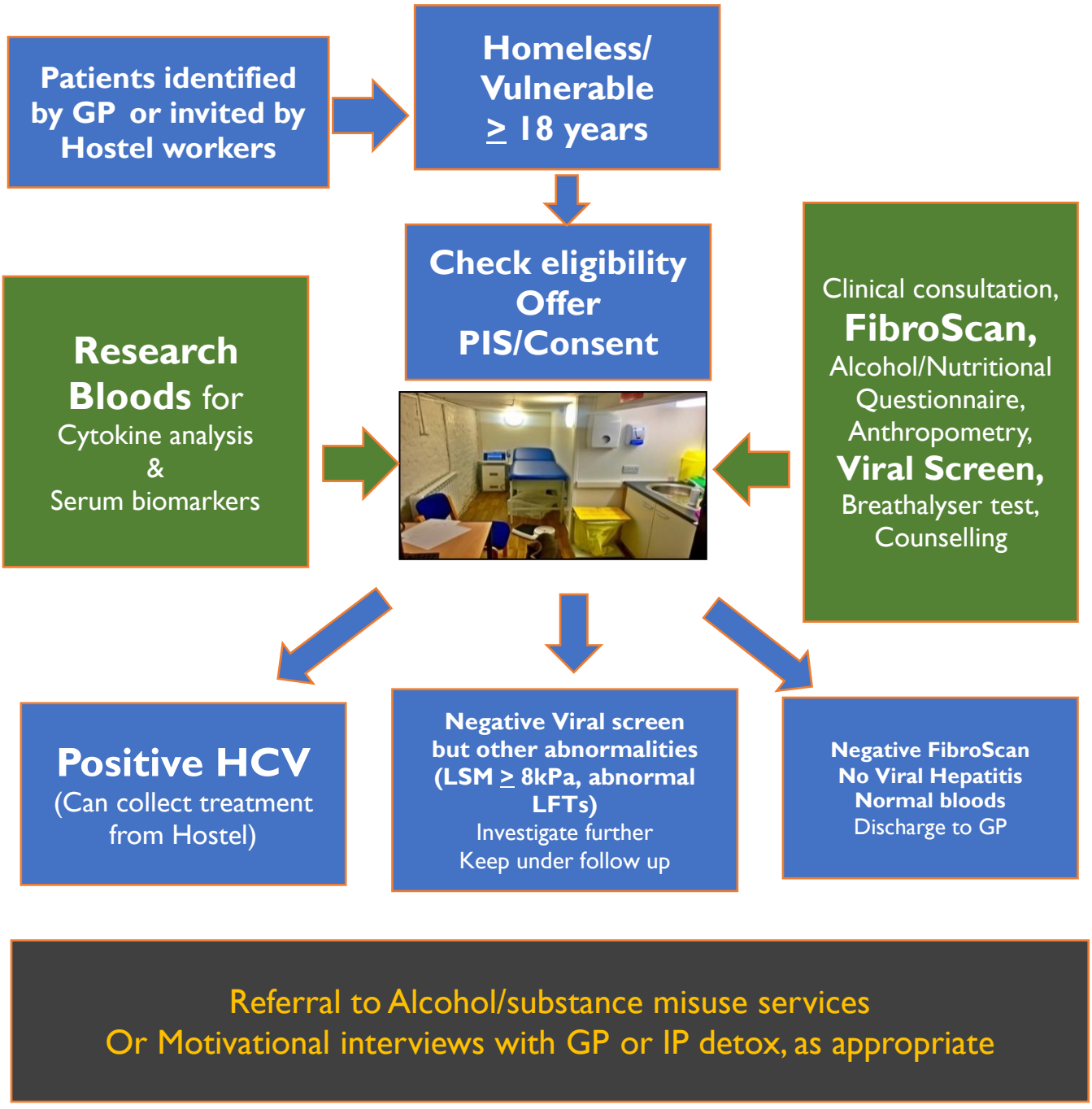


Figure 4. 2: VALID study recruitment pathway.

4.11 Components of the service

Eligible individuals who were willing to participate were approached by the Hepatology Research Fellow (AH) and provided with a Patient Information Sheet. The Hepatology Research Fellow briefly discussed the study, and if interested clients were willing to participate, written informed consent was obtained for both data collection and research blood samples.

Each participant was offered the following standard of care procedures as part of the community service:

I. History and physical examination:

This was conducted to elucidate the basic socio-demographic factors, alcohol and substance misuse history, social history, presence of significant comorbidities, and homelessness status.

II. Routine blood sampling including full blood count, Renal and Liver biochemistry as well as micronutrients as well. BBVs screening was undertaken using venous blood, in addition to DBST.

Routine blood samples were obtained to check for blood-borne viruses (HCV, HBV and HIV) and Hepatitis B immunity status. The following techniques were used using Abbott ARCHITECT chemiluminescent microparticle immunoassay (CMIA) system (Jonas et al., 2005). When a small sample was obtained, screening for HCV was prioritised.

Hepatitis C antibody was analysed qualitatively using the ARCHITECT System chemiluminescent microparticle immunoassay (CMIA) from serum samples. The ARCHITECT Anti-HCV detects antibodies to structural and non-structural proteins of

HCV. Samples testing positive for Hepatitis C antibody were checked for viral load (HCV PCR) and genotype. The viral load was quantitatively determined using the Abbott Real-Time HCV assay, an in vitro reverse transcriptionpolymerase chain reaction (RT-PCR) assay to quantitate HCV RNA. Hepatitis B surface antigen, Hepatitis B core antibody and Hepatitis B surface antibody were similarly analysed in serum samples using chemiluminescent microparticle immunoassay with flexible assay protocols, known as the Chemiflex. Hepatitis B Surface Antibody (HBsAb) levels were determined using a pre-generated ARCHITECT HBsAb calibration curve. Patients testing negative for HCV Ab were deemed not to have chronic HCV (i.e. HCV PCR negative).

Similarly, HIV Ag/Ab combo was analysed using CMIA, which detects HIV p24 antigen and antibodies to HIV-1.

Positivity of sample for all qualitative tests above was established by comparing the chemiluminescent signal in the reaction to the cut-off signal determined from an active calibration. When the signal in the sample more than or equal to the cut-off signal, the sample was considered positive.

The DBST allowed assessment of HCV antibody (if positive reflex HCV qualitative RNA), hepatitis B surface antigen, hepatitis B core antibody and HIV antibody using the following assays: Biorad hepatitis C antibody (ELISA), Murex hepatitis B surface antigen (ELISA), Biorad hepatitis B core total antibody (ELISA), Roche Cobas CAP CT HCV RNA (TAQ PCR BIORAD) and Gen Screen HIV Ultra (ELISA), (Alere Toxicology, 2020).

III. FibroScan examination (Echosens, Paris, France, FS 502 Touch) (Figure 4.2):

This was performed by AH after undergoing appropriate training as mandated by Echosens. Participants were asked to lie on comfortably on their back with their right hand behind their head. The ultrasound transducer M probe was be applied to the right lower chest after selecting the ideal intercostal space. The device transmits low-frequency vibrations (2.5-3.5 MHz) and calculates liver stiffness measurement (LSM). A successful FibroScan examination was defined as 10 shots and an interquartile range to median ratio of $\leq$0.30. Liver stiffness measurements expressed as the median value of the total measurements in kilo Pascals (kPa). Based on previous studies, LSM of $\geq$ 8kPa was defined as clinically significant hepatic fibrosis (Talwalker et al., 2007). Cirrhosis was defined as liver stiffness measurement of $\geq$ 13kPa (Freidrick-rust et al., 2008).

IV. Alcohol and substance misuse assessment:

The Alcohol Use Disorders Identification Test (AUDIT) questionnaire (Babor, 2001) was used to identify participants with any current alcohol misuse. A score of 20 or more was taken as an indicator of alcohol dependence. Participants were also asked to state their substance misuse history and alcohol intake. The latter was determined by calculating the number of alcohol units consumed per week.

Each participant was also offered an alcohol breath test analysis using the AlcoDigital LifeGuard breathalyzer device (Alcodigital, 2013, Berger, 2002).

V. Assessment of nutritional status:

As per standard of care, this included measurement of body mass index (BMI), waist/hip ratio, mid-arm and waist circumference as well as an assessment of micronutrients (serum calcium, magnesium and phosphate). A standard measuring tape

was used to record the mid-arm circumference (all participants had mid-arm circumference checked on the left arm unless there was difficulty). Waist and Hip circumferences were measured using the same tape and the waist: hip ratio was subsequently calculated. Those who were identified to need nutritional support were referred to their GPs, as is the current standard of care.

VI. Research samples:

About four tablespoons of blood were taken for research purposes from consecutive participants attending/returning to the VALID study clinic. As far as possible, this was done at the same time as the routine clinical blood samples. Research samples were used to test for:

- T-helper -17 cytokine MSD panel (IFN-γ, IL-1β, IL-6, IL-10, IL-17A, IL-17E/IL-25, IL-17F, IL-21, IL-22, TNF)
- Enhanced Liver Fibrosis score (ELF test)
- Senescence markers including TIMP-1, MMP-2 and CK-18 M30

VII. DAA based HCV treatment:

In England, HCV treatment is administrated via 22 national centres known as Operational Delivery Networks (ODNs). The DAA regimen is determined and funded by the National Health Service England after approval at a regional ODN liver multidisciplinary meeting. All those with positive HCV RNA were deemed treatment eligible (irrespective of ongoing drug and alcohol use), unless not stable enough to engage with treatment. HCV treatment was delivered at the homeless sites by AH under SV supervision. Those with negative HCV Ab and LSM < 8 kPa were discharged back to the GP. Those with an LSM $\geq$ 8 kPa with or without a positive HCV RNA were seen back in the community clinic and offered targeted treatment/advice.

Where necessary, hostel managers and key workers were asked to facilitate the delivery of HCV medications to participants and inform the team if there had been any concerns regarding the collection of the medications.

Figure 4. 3: The portable FibroScan® 402 model which was used in the VALID study.

4.12 Important definitions

- Liver stiffness values:

  In this study, a liver stiffness (LSM) value of ≥ 8.0 kPa was considered as clinically significant hepatic fibrosis (CSHF). An LSM of 8.0 kPa or greater has been previously shown to accurately determine the presence of significant hepatic fibrosis in community screening (Roulot et al., 2011, Talwalkar et al., 2007). Cirrhosis was defined as LSM ≥ 13kPa. The latter cut-off value was based on a metanalysis by Friedrich-Rust et al. (2008).

- Homelessness and unstable housing:

  A homeless adult was defined as any individual who was living in the streets, in a hostel or sheltered accommodation, sofa surfing, temporary or supported accommodation, at the time of recruitment.

- Vulnerable adult:

  Those who are homeless, have current or past history of alcohol or substance use disorder or those with current or past history of significant mental illnesses.

- Alcohol intake:

  The following definitions were applied:

  Drinking alcohol > recommended = 14 units/week or more

  Harmful drinking = drinking alcohol ≥ 35 units for females and ≥ 50 units for males (National Institute for Health and Care Excellence, 2013).

Alcohol dependence = AUDIT questionnaire score of ≥ 20

- Major comorbidity:

  A major comorbidity was defined as the presence of significant chronic illnesses other than liver disease such as chronic lung disease, cardiac problems, and complicated diabetes mellitus. Controlled hypertension was not included.

- AST: Platelet Ratio Index (APRI) Score:

  APRI cut-off values were determined based on a meta-analysis of 40 studies by Lin et al. (2011).

  CSHF was defined using APRI score cut-off of > 1.5, < 2.0

  Cirrhosis was defined using APRI score cut-off of ≥ 2.0

- ELF Score:

  CSHF was defined using a cut-off score of ≥ 9.8

  Cirrhosis was defined using a cut-off score of ≥ 10.51

  These cut-off values were selected based on previous evidence and a recent systematic review and meta-analysis by Vali et al. (2020).

4.13 Sample size

Based on our prior work (O'Sullivan et al., 2020) we estimated that a) 35% will have CSHF (LSM ≥ 8 kPa); b) 40% HCV seroprevalence. The number of patients we aimed to recruit was 300. Of this, we expected 100 patients would be aged ≥50 years allowing us to construct a 95% confidence interval (CI) width ±10% (CI 40% to 60%) around an estimated prevalence of CLD of 50% in this group while recruiting 200 non-elderly patients would allow us to calculate a

95%CI width ±6% (24% to 37%) around a prevalence of CLD of 30% in this group. A total of n=300 would allow us to construct a 95%CI of approximate width ±5% (CI 32% to 43%) around the combined prevalence of CSHF of 37% in the 2 groups. A sample size of 300 would suffice for fitting a logistic regression model with 11 independent variables.

4.14 Ethical considerations and funding

Ethical approval for the study and all substantial amendments were obtained from the Health Research Authority National Research Ethics Services Committee South Central-Hampshire B (REC ref no 15/SC/0112). All participants gave written informed consent after being provided with a patient information sheet. This study was funded by a research grant from the Dunhill Medical Trust (R369/0714), Kent Surrey and Sussex Deanery and the National Gilead Fellowship.

4.15 Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS) v.26. Data are summarised using counts, means $\pm$standard deviations (for normally distributed variables), medians (interquartile ranges [IQR]) for skewed variables, or frequencies and percentages for categorial variables. Mann Whitney and chi-square tests were utilised for continuous and categorical variables, respectively. Statistical significance was set at $p < 0.05$ with the determination of 95% Confidence Interval (CI) when appropriate. Logistic regression analysis was used to model the relationship between the binary dependent outcomes (No vs Yes) (HCV RNA positive vs negative, CSHF vs no CSHF, cirrhosis vs no cirrhosis) and key independent factors. A multifactorial logistic regression model was then derived to look at the relationship between the key factors and the dependent outcome. To build the model, the statistically

significant key factors ($p<0.1$) from the unifactorial analyses were added to the null model using forward selection where the factor with the highest significant p-value, based on the likelihood ratio test, was added next. Factors were removed from the model if $p > 0.05$.

Only cytokines with more than one third (33%) of the population having detectable levels were included in the analysis in Chapter 5. Undetectable cytokine values were assigned half the lower detection limit of the assay. The detection limit of each assay was 0.5 pg/ml for IL-10, 2 pg/ml for IL-17A, 0.5 pg/ml for IL-22, 4 pg/ml for IFN- γ, 1 pg/ml for TNF, 1 pg/ml for IL-6. Where necessary, further analysis of cytokines results was performed after removal of outliers via the robust regression and outlier removal (ROUT) method using GraphPad Prism version 8 (Motulsky and Brown, 2006).

4.16 Processing, storage and analysis of research blood samples

The research blood samples were collected by AH and transported to the Clinical Investigations Research Unit (CIRU) laboratory based at the Royal Sussex County Hospital, Brighton on the same day. The storage process was undertaken by the CIRU staff; however, when samples arrived out of hours, AH (who underwent prior training) performed the processing and storage procedures.

4.16.1 Storage and processing of research blood samples

Serum samples were collected into 2x 5ml gold top vacuette serum separator tube (SST) with clot activators. EDTA Plasma Samples were collected into 3x4ml purple top vacuette, K3EDTA Plasma tube.

Serum samples were allowed to clot at room temperature for a minimum of 30mins and a maximum of 2 hours before centrifugation. They were then centrifuged at 1500g/3500rpm for 15mins at room temperature. Following centrifugation, using a non-sterile pasture pipette, approximately 1ml (or more if available) of serum was transferred each, into 4x2ml non-sterile cryovials.

Plasma EDTA samples and cell pellet were processed and frozen within 4 hours of collection. Plasma samples were centrifuged 2x 4ml EDTA tubes at 1500g/3500rpm for 15mins at room temperature while 1x4ml EDTA tube was reserved for aliquoting as Whole Blood. From 1 x 4ml EDTA Tube, 2 x 2ml Cryovial were aliquoted with 1.5-1.8ml ml of Whole blood. After centrifugation of the other 2 x 4ml EDTA samples, using a non-sterile pasture pipette, approximately 1ml (or more if available) of plasma was transferred each into 4x2ml non-sterile cryovials.

After processing as above, all samples were stored in the -80 freezer and documented on a sample log. Full details of the storage and processing protocol are provided in Appendix 2.

4.16.2 Analysis of T-helper 17 (Th17) cytokines

Cytokine analysis was performed on serum samples by scientists at Cambridge Biomedical Research Centre (Keith Burling and his team) under the research fellow's observation (AH).

The U-PLEX Th17 Combo 2 (human) by Mesoscale Discovery (MSD) was used to analyse the common Th17 cytokines (Mesoscale Discovery). The assay involves 10 cytokines considered to be key in the Th17 response pathway:

IFN-γ, IL-1β, IL-6, IL-10, IL-17A, IL-17E/IL-25, IL-17F, IL-21, IL-22, TNF

The technique based on multi-plex analysis has the ability and advantage to independently and quantitatively assay multiple analytes simultaneously in a single experiment using a small volume of sample and is, therefore, not time-consuming (Elshal and McCoy, 2006).

In the U-plex analyses, biotinylated capture reagents are joined with U-PLEX Linkers. The U-PLEX Linkers self-assemble onto specific spots on the U-PLEX plate. After the binding of the analytes to the capture reagents, the detection antibodies conjugated with electrochemiluminescent labels (MSD GOLD SULFO-TAG) then bind to the analytes, completing the sandwich immunoassay (Wallowitz et al., 2016).

Once the sandwich immunoassay is finished, the plate is placed into an the MSD instrument and analyte concentration in the sample is measured.

In addition to antibodies, U-PLEX is designed to be used with other readily available biotin-conjugated reagents, including peptides, proteins, and nucleic acids.

The samples were analysed by staff at Cambridge Biomedical Research Center. The following analysis steps were used as per the manufacturer's instructions[2]:

Step 1: Washing and adding sample

- Washed the plate three times with at least 150 μL/well of 1X MSD wash Buffer.
- Added 50 μL of prepared samples, calibrators, or controls per well. Sealed the plate with an adhesive plate and incubated it at room temperature with shaking for two hours.

[2] The steps provided for the analysis of Th17 panel were extracted from the MSD cytokine analysis protocols manual (Mesoscale Discovery)

Step 2: Washing and detection of antibody solution

- Washed the plate three times with at least 150 μL/well of 1x MSD Wash Buffer.
- Added 25 μL of detection antibody solution to each well. Sealed the plate with an adhesive plate seal and incubated at room temperature with shaking for 2 hours.

Step 3: Washing and reading

- Washed the plate three times with at least 150 μL/well of 1x MSD Wash Buffer.
- Added 150 μL of 2x Read Buffer T to each well.
- Analysed the plate on an MSD instrument.

4.16.3 Analysis of senescence markers[3]

Senescence markers were analysed by the team at the Nottingham Biomedical Research Unit according to the protocols below.

Serum samples were thawed from the master tube, and aliquots were refrozen at -80 for use. Aliquots made for samples 1-121 (97 samples) were: 20μl (10 for Luminex); 130μl (50 for M30); 300μl (ELF); 200μl (DNA/RNA); and residual.

Cytokeratin -18 M30 (CK-18 M30) processing and analysis

CK-18 M30 (caspase-cleaved fragments) antigen levels were determined in serum using the M30-Apoptosense ELISA kits, 10011 lot PE-XS1258 (Peviva) from Bioaxxes. The following steps were undertaken:

[3] Protocols for analysis of the senescence markers were provided by Jane Grove from the Nottingham Biomedical Research Unit.

Duplicate samples of 25µl of the sample were used. Then 120µl aliquots were thawed on a 96-well plate. Wash buffer was prepared and Hi control – 671U/L = +/-100 expected was used. The same standard set for both plates was used, and pooled conjugates were made to ensure minimal inter-plate variation. In each plate, 25µl of the sample was put in duplicate. Then 75µl of conjugate was added and the plates were sealed and incubated 4 hours on bench (in room temp. 28C). The plate was washed 5 times in 250µl of wash buffer using a multichannel pipette. Following this, the blot was dried thoroughly, and 200µl tetramethylbenzidine was added using P200 Gilson and incubated for 19 min at 32C, then 50µl stop was added in the same order. The plate was read on Multiskan FC plate reader A450nm and re-read after 5 minutes with no major changes. Blank values were subtracted, and outlier data were discarded.

Replicate means, standard deviation and coefficient of variance were calculated. Any data where %CV>20% was discarded. The lower limit of detection was calculated, a standard curve was generated using A-G with a log fit curve, and a standard plot curve was created using excel. CK-18 M30 high control was checked to be in the acceptable range 571-771U/L. The lower limit of detection concentrations was calculated, and data values were inserted, as necessary. Inter-plate assay variability was calculated using Hi control data = 1.1% (%CV).

TIMP-1 & MMP-2 processing and analysis

These were analysed by the team at the Nottingham Biomedical Research Unit according to the protocols below.

Levels of TIMP-1 and MMP-2 were quantified by Luminex using a Human Premixed multi-analyte kit (R&D Systems). Data were then acquired on a validated and calibrated Bio-Plex 200 system (Bio-Rad) and analysed with Bio-Plex Manager 6.0 software with a detection target

of 50 beads per region and a standard curve was fitted using five-parameter logistic regression. All samples were assayed in duplicate, and freeze-thaw cycles were limited to 2 for all measurements.

TIMP-1 is also part of the ELF panel (this was determined additionally commercially by iQur). R&D systems Human Premixed multi-analyte kit was used [cat number LXSAHM-02]. The method followed as described in kit. Data were acquired on a validated and calibrated Bio-Plex 200 system (Bio-Rad) and analysed with Bio-Plex Manager 6.1 software (Bio-Rad) with detection target of 50 beads per region, Low RP1 target for CAL2 calibration, and recommended doublet discriminator gates. Any points with %CV <25% were excluded from the standard curve, and those with accuracy outside of 80-120% of expected were excluded starting from the lowest standard. The analysis software was then used to fit a curve to this set of reliable standards data using five-parameter logistic regression with default automated weighting (all fitted to ≥6 points).

Samples and standards were assayed in duplicate, limiting the Freeze-thawing of serum samples to a maximum of 2 cycles, with most samples only freeze-thawed once.

A standard curve was prepared for analytes of MMP-2 and TIMP-1 using solutions provided of MMP-2 (78430pg/ml) TIMP-1 (10670 pg/ml) 3-fold dilution. Serum samples were diluted 1/50 as recommended by the manufacturer kit. This was achieved by mixing 4µl of the sample with 196µl of diluent reagent RD6-52 provided. Plates were washed using a handheld microplate magnet. Instrument settings were: 50µl sample volume; Bio-Plex.

MagPlex Beads (Magnetic); Doublet Discriminant or gates were set at 8000 and 23000. Magnetic Pro Assay panel was inputted with MMP-2 as region 20 and TIMP-1 as region 76, low RPI target was selected, 50 beads/microparticles were analysed per region, and MFI was recorded.

The instrument was validated 18 days before use (within 30 days recommended) and calibrated on the same day just before the assay was run. All samples were assessed on the same day on 2 plates set up using a single batch of reagents to minimise intra-plate variability. Intra-plate variability was calculated as 9% by comparing standards 2, 3, and 4 on the two plates. Room temperature incubations were at 28C. Standard curves were plotted automatically by software Bioplex Manager 6.1 using a 5-parameter logistic curve (log-log plot).

4.16.4 Enhanced Liver Fibrosis test (ELF) analysis

Serum samples were sent to be tested for ELF test using the Siemens Healthineers Enhanced Liver Fibrosis (ELF) Test (iQur Ltd) and were analysed as per the manufacturer protocol. Samples were shipped to the company for analysis. The ELF score was generated using the following algorithmic equation combining quantitative measurements of hyaluronic acid (HA), amino-terminal propeptide of type III procollagen (PIIINP), and tissue inhibitor of metalloproteinase 1 (TIMP-1):

ELF score equation = 2.278 + 0.851 ln(CHA) + 0.751 ln(CP3NP) + 0.394 ln(CTIMP1).

CHAPTER 5: VALID study clinical results

5.1 Baseline demographic and clinical data

During the study period, 131 individuals were approached, of whom 127 (97%) were willing to participate. Of the remaining four, three declined to provide a blood sample and one was not registered with any of the two recruiting primary care practices.

The study group was a predominantly heterosexual Caucasian cohort with a mean age of 47 +/- 9.4, 76% being males, and 76% (96) being homeless or living in unstable housing. There was a high prevalence of current IDU (36, 28%), hazardous drinking (48%) with 49.6% experiencing alcohol dependence at the time of enrolment (AUDIT-C questionnaire $\geq$ 20). Mental health problems were reported by 92 (72.4%) of whom 59/92 (64%) were receiving treatment (Table 5.1). The majority of homeless individuals in the study were living in hostels (62.2%). Major comorbidities were observed in 23 individuals (18.1%) while 104 (81.9%) were current smokers.

Blood results are summarised in Table (5.1). Of the 101 patient who had micronutrients data available, 16.8% had micronutrient deficiency as evidenced by serum phosphate, calcium & magnesium below the normal range. The average BMI of this study group was 24.3 ((SD = 4.2). Mean mid-arm circumference was 29.42 cm (SD = 4) while the mean waist:hip ratio was 0.93 (SD = 0.08).

Variable	
Age (yrs) Age ≥50	47±9.4 60 (47%)
Ethnicity Caucasian	 122 (96%)
Males	97 (76%)
Recruitment Site Homeless hostel 1 Primary care practice 1 Homeless hostel 2 Primary care practice 2	 88 (69%) 13 (10%) 3 (2.4%) 23 (18%)
Homeless Residence at the time of recruitment Hostel Own/rented Supported/temporary accommodation Street homeless	96 (76%) 79 (62%) 31 (24%) 15 (12%) 2 (2%)
Median alcohol units /week Alcohol > weekly recommended (>14 units) Hazardous alcohol intake (≥ 35 units for females, ≥ 50 for males/week)	40 (IQR: 98) 83 (65%) 61 (48%)
Breathalyzer reading (µg/dL) (n=110) Detectable Alcohol on Breathalyzer (n= 110)	1± 25 29 (26%)
AUDIT questionnaire score (0-40) AUDIT questionnaire ≥ 20 (alcohol dependence)	17 ± 13.8 63 (50%)
Major comorbidities*	23 (18%)
Smoking Current Ex-Smoker Never	 104 (82%) 13 (10%) 10 (8%)
Injecting drug use (UDU) Current Daily Weekly Less than weekly Missing Past Never	 36 (28%) 15 (12%) 15 (12%) 5 (4%) 1 (1%) 32 (25%) 59 (47%)
Non-IDU Current Past Never	 59 (47%) 29 (23%) 39 (31%)
Ever had mental health diagnosis On treatment for mental health problems	92 (72%) 59 (47%)
Sexual Orientation Heterosexual Homosexual Bisexual Transgender	 115 (91%) 4 (3%) 7 (6%) 1 (1%)

Variable	
Bilirubin (μmol/L)	9 ±8
ALT (iu/L)	49 ±62
AST (iu/L)(n=106)	58 ±62
Albumin (g/L)	45 ±4
Platelet count (10^9/L)	245 ±97
INR (n=114)	1 ±0.1
Magnesium (n=98)	0.86 ±0.08
Calcium (n=101)	2.24 ±0.08
Phosphate (n=99)	1.07 ±0.19
Any micronutrient deficiency (n=101)	17 (17%)
Hepatic fibrosis	
Median LSM (kPa)	5.4 (4.3-8.0)
Clinically significant hepatic fibrosis (LSM ≥ 8kPa)	33 (26%)
Cirrhosis (LSM ≥ 13kPa)	21 (17%)
ELF score (n=101)	9.1 ±1.4
ELF ≥ 9.8	28 (26%)
ELF ≥ 10.51	14 (13%)
APRI score (n =106)	0.4 (0.25-0.97)
APRI ≥ 1.5-2	18 (17%)
APRI >2	16 (15%)
Anthropometric measurements	
BMI (kg/m^2)	24.3 ±4.2
Mid-Arm circumference (cms)	29.42 ±4
Waist: Hip ratio	0.93 ±0.08
Blood-borne virus screening	
HIV antibody positive (n=125)	3 (2%)
HBsAg positive (n=125)	0%
HBcAb positive (n=124)	21 (17%)
HBsAb ≥ 100 IU/L (n=114)	24 (21%)
HBsAb ≥ 10 IU/L (n=114)	45 (39%)
HCV antibody positive (n=125)	59 (47%)
HCV RNA positive	49 (39%)
Genotype	
1a	21 (43%)
1b	1 (2%)
3	24 (49%)
2b	1 (2%)
Could not be determined	2 (4%)

Table 5. 1: Baseline demographic and clinical data in the study cohort (n=127).

Brackets () indicate number with data available
Normal values: bilirubin (0-21 μmol/L), ALT (0-41 iu/L), AST (0-32iu/L) albumin (35-52g/L), INR (0.8-1.2), platelets (150-450x10^9/L), Magnesium (0.66-1.07mmol/L), Phosphate (0.81-1.45mmol/L), Calcium (2.15-2.5) mmol/L
*Major comorbidities: defined as the presence of significant chronic illnesses other than liver disease such as chronic lung/cardiac disease and complicated diabetes mellitus. Controlled hypertension was not included.

One in four patients (26%) had clinically significant hepatic fibrosis (CSHF, LSM ≥ 8kpa) whereas 17% fulfilled the defined criteria for cirrhosis using FibroScan (LSM ≥ 13kPa) (Table 5.1). ELF score was performed in 101 patients with a mean score of 9.1 (SD= 1.4). A similar proportion of patients had CSHF as detected by ELF test (26%). Only 106 out of 127 patients had their AST available, and this was mainly due to difficult blood sampling and sample hemolysis in a cohort with a high prevalence of IDU. In those who had data available to calculate APRI (n=106), only 17% of them had CSHF (Table 5.1) according to the APRI fibrosis staging criteria illustrated in Chapter 4.

The prevalence of HCV antibody in this cohort was 47.2%, of which 83 % had a positive HCV RNA indicating HCV viremia (49 patients, 39.2% of the total population) (Table 5.1). The two main genotypes were 1a and 3a. None of the patients had chronic HBV; however, 21 (17%) had positive HBcAb indicating past HBV infection. Three patients were positive for HIV, but they were already known to the HIV service. One patient had HIV/HCV infection. Only 21% (24/114) had evidence of protective HBsAb levels (HBsAb ≥ 100 IU/L).

5.2 Comparison of basic demographic and clinical characteristics between homeless and non-homeless individuals

Compared to non-homeless individuals, homeless people were more likely to be of male gender (78/96, 81% vs 19/31 61%, p=0.023), be younger (45.7 + 9.4 vs 53.5 + 6.6, p<0.001) and less likely to be aged > 50 years [38/96 (40%) vs 22/31 (71%), p=0.002]. Moreover, those who were homeless had higher prevalence of current IDU [36/96 (38%) vs. 0/32 (0%), p<0.001]; current non-IDU [51/96 (53%) vs. 8/31 (25%), p=0.005]; active smoking [87/96 (91%) vs. 17/31 (55%), p< 0.001] (Table 5.2). Alcohol dependence (AUDIT score ≥ 20) was more prevalent amongst the non-homeless compared to the homeless [42/96 (44%) vs. 21/31 (68%),

p=0.02]; the latter, however, were more likely to have a detectable breathalyzer at the time of the consultation [28/88 (32%) vs. 1/22 (5%), p=0.02]. Finally, homeless individuals had significantly higher prevalence of chronic HCV [44/96 (47%) vs. 5/31 (16%), p=0.002]. There were no statistical differences between homeless vs non-homeless in the prevalence of CSHF [26/96 (27%) vs .7/31 (23%), p=0.619]. Similar to CSHF, there were no statistically significant differences in the prevalence of cirrhosis between homeless vs hon-homeless [16/96 (17%) vs. 5/31 (16%), p=0.944].

Variable	Homeless (n=96)	Non-Homeless (n=31)	P value
Age (yrs)	45.7±9.4	53.5±6.6	<0.001
Age ≥50	38 (39.6%)	22 (71%)	0.002
Ethnicity-Caucasian	91 (94.8%)	31 (100%)	0.43
Males	78 (81.3%)	19 (61.3%)	0.023
Alcohol units /week	76 ±98	91.6±89.5	0.411
AUDIT-C questionnaire score (0-40)	15.9±14.3	20.5±11.7	0.074
AUDIT-C questionnaire ≥ 20 (alcohol dependence)	42 (43.8%)	36 (67.7%)	0.02
Detectable breathalyzer test	28/88 (32%)	1/22 (5%)	0.009
Major comorbidities	16 (16.7%)	7 (22.6%)	0.46
Current Smoking	87 (90.6%)	17 (54.8%)	<0.001
Current Injecting drug use	36 (37.5%)	0 (0%)	<0.001
Current Non injecting drug use	51 (53.1%)	8 (25.8%)	0.008
Ever had mental health diagnosis	70 (72.9%)	22 (71%)	0.83
CSHF	26 (27.1%)	7 (22.6%)	0.619
Cirrhosis	16 (16.7%)	5 (16.1%)	0.944
HCV RNA positive (n=125)	44 (46.8%)	5 (16.1%)	0.002

Table 5. 2 : Basic demographic and clinical characteristics of homeless vs non-homeless study participants.

5.3 Clinical predictors of clinically significant hepatic fibrosis (CSHF)

Table 5.3 shows the socio-demographic and clinical factors associated with CSHF with table 5.4 showing the unifactorial and multifactorial regression analysis of clinical predictors of CSHF. Alcohol misuse disorder was significantly associated with clinically significant hepatic fibrosis (defined as LSM $\geq$ 8kPa) (Table 5.3). Median total alcohol units/week, hazardous alcohol intake and alcohol dependence as detected by AUDIT questionnaire $\geq$ 20 were all significantly higher among those with CSHF. Moreover, 43% of participants with CSHF vs 21% of those without CSHF had detectable breathalyzer test at the time of enrolment (p=0.022). The prevalence of positive HCV RNA was higher among those with CSHF (52% vs 35%), but the difference was not statistically significant. In addition, patients with CSHF had a higher mean waist/hip ratio than those without CSHF.

Regarding age, 15 (46%) participants with CSHF were aged $\geq$ 50 whereas 45 (48%) without CSHF where in the same age group (p=0.811) (Table 5.3). Independent predictors of CSHF were total alcohol unit/week OR 1.01, 95% CI: 1.01-1.02, p= 0.002 and positive HCV RNA (OR: 2.93, 95% CI: 1.12 – 7.66, p=0.029) (Table 5.4).

Of the n=33 with CSHF, n= 7 were HCV antibody positive, n= 12 had alcohol dependence (AUDIT score $\geq$20), n= 12 had both risk factors and n= 2 had neither risk factor.

	Clinically significant hepatic fibrosis (n=33)	**No clinically significant hepatic fibrosis (n=94)**	**P value**
Age $\geq$ 50	16 (48%)	44 (47%)	0.868
Male Gender	28 (85%)	69 (73%)	0.183
Alcohol units /week	100 (213)	30 (91)	0.001
Alcohol > recommended	26 (79%)	57 (61%)	0.059
Hazardous Alcohol intake	23 (70%)	38 (40%)	0.004
Alcohol Audit questionnaire score	22.2 $\pm$ 14	15.2 $\pm$ 13.3	0.012
AUDIT score $\geq$ 20	24 (73%)	39 (42%)	0.002
Detectable Breathalyzer (n=110)	12 (43%)	17 (21%)	0.022
Breathalyzer score (n=110)	0 (51)	0 (0)	0.006
Current IDU	6 (18%)	30 (32%)	0.132
Current non-IDU	15 (46%)	44 (47%)	0.893
Current Smoker	26 (79%)	78 (83%)	0.591
Homelessness	26 (79%)	70 (74%)	0.619
Major Comorbidities	8 (24%)	15 (16%)	0.288
Mental health issues	25 (76%)	67 (71%)	0.620
Receiving treatment for mental health	13 (39%)	46 (49%)	0.344
Micronutrient deficiency (n=101)	7 (26%)	10 (14%)	0.140
Mean BMI	25.3 $\pm$ 4.7	24.1 $\pm$ 4	0.197
Mean waist/hip ratio	0.96 $\pm$ 0.09	0.92 $\pm$ 0.08	0.021
HCV RNA positive (n=125)	17 (52%)	32 (35%)	0.091

Table 5. 3: Baseline demographic and clinical factors in those with and without clinically significant hepatic fibrosis (CSHF), (LSM $\geq$ 8kPa).

CSHF	**Univariate analysis**			**Multifactorial regression analysis**		
	Odds ratio	95% C1	P value	Odds ratio	95% C1	P value
Age ≥ 50	1.07	0.48 – 2.37	0.87			
Male Gender	2.03	0.71 – 5.83	0.2			
Alcohol AUDIT questionnaire score	1.04	1.01 – 1.07	0.01			
Total alcohol units/week	1.01	1.005 – 1.014	<0.001	1.01	1.00 - 1.02	0.002
Current IDU	0.47	0.18– 1.27	0.138			
Current other recreational drugs	0.95	0.43 – 2.10	0.89			
Current Smoker	0.76	0.28 – 2.06	0.59			
Homelessness	1.27	0.49 – 3.31	0.62			
Major Comorbidities	1.69	0.64 – 4.44	0.29			
Mental Health	1.26	0.51 – 3.14	0.62			
Micronutrient deficiency	2.24	0.75 – 6.65	0.15			
HCV RNA positive	1.99	1.05 – 5.20	0.094	2.93	1.12 – 7.66	0.029

Table 5. 4: Unifactorial and multifactorial regression analysis of baseline demographic and clinical variables predicting clinically significant hepatic fibrosis, CSHF (LSM ≥8 kPa).

5.4 Clinical predictors of cirrhosis

Tables 5.5 and 5.6 show the baseline demographic and clinical factors associated with cirrhosis vs no cirrhosis and the unifactorial/multifactorial analysis of clinical predictors of cirrhosis among the study cohort, respectively. With regards to age, 10/21 (47%) of those with cirrhosis were aged $\geq$ 50 with 50/106 (48%) without cirrhosis being in the same age group. Independent predictor of cirrhosis was alcohol units/week (OR: 1.014, 95% CI 1.009-1.020, $p<0.001$) (Table 5.6). A cut-off of $\geq$ 95 alcohol units /week demonstrated a sensitivity and specificity for predicting cirrhosis of 81% & 76%, respectively with an area under the curve (AUC) of 0.847 (Figure 5.1).

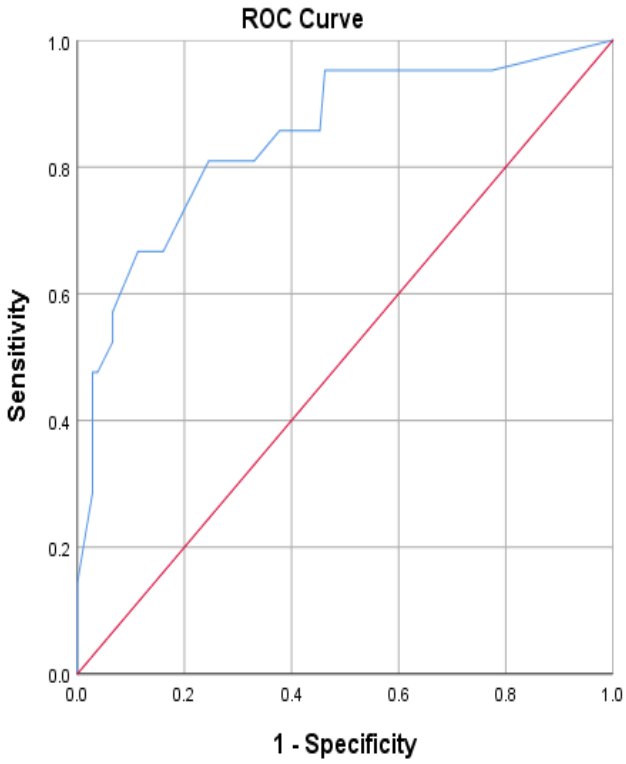
In addition to the significant association with alcohol use disorder parameters, patients with cirrhosis were less likely to have active drug use. The prevalence of HCV viremia was comparable between those with cirrhosis vs those without cirrhosis (42.9% vs 38.5%, $p = 0.707$). Similar to patients with CSHF, the mean waist/hip ratio was significantly higher among cirrhotic patients (Table 5.5).

Factor	**Cirrhosis (n = 21)**	**No Cirrhosis (n = 106)**	**P value**
Age ≥ 50	10 (48%)	50 (47%)	0.97
Male Gender	17 (81%)	80 (75%)	0.589
Alcohol units/week	200 (190)	28 (88)	<0.001
Alcohol > recommended	20 (95%)	63 (59%)	0.002
Hazardous alcohol drinking	18 (86%)	43 (41%)	<0.001
Alcohol AUDIT questionnaire score	27.8 ± 11.3	14.8 ± 13.3	<0.001
AUDIT score ≥ 20	19 (90%)	44 (42%)	< 0.001
Detectable Breathalyzer (n=110)	11 (65%)	18 (19%)	<0.001
Breathalyzer score (n=110)	14 (84)	0 (0)	<0.001
Current IDU	2 (10%)	34 (32%)	0.036
Current non IDU	10 (48%)	49 (46%)	0.907
Current Smoker	16 (76%)	88 (83%)	0.458
Homelessness	16 (76%)	80 (75%)	0.944
Major Comorbidities	6 (29%)	17 (16%)	0.173
Mental health issues	17 (81%)	75 (70.8%)	0.339
Receiving treatment for mental health	8 (38%)	51 (48%)	0.4
Micronutrient deficiency (n=101)	4 (25%)	13 (15.3%)	0.341
Mean BMI	25.4 ± 5.1	24.2 ± 4.0	0.206
Mean waist/hip ratio	0.98 ± 0.09	0.92 ± 0.08	0.003
HCV RNA positive (n=125)	9 (43%)	40 (39%)	0.707

Table 5. 5: Baseline socio-demographic and clinical factors in those with and without cirrhosis (LSM ≥ 13kPa).

Factor	**Unifactorial analysis**			**Mutifactorial analysis**		
	Odds ratio	95% C1	P value	Odds ration	95% CI	P value
Age ≥ 50	1.02	0.40 – 2.60	0.97			
Male Gender	1.38	0.43 – 4.48	0.59			
Alcohol units/week	1.014	1.009-1.020	<0.001	1.013	1.005-1.020	0.001
Alcohol AUDIT questionnaire score	1.09	1.04 – 1.14	<0.001			
Current IDU	0.22	0.05 – 1.01	0.05			
Current non-IDU	1.06	0.41 – 2.70	0.91			
Current Smoker	0.66	0.21 – 2.02	0.46			
Homelessness	1.04	0.35 – 3.11	0.94			
Major Comorbidities	2.09	0.71 – 6.16	0.18			
Mental health issues	1.76	0.55 – 5.64	0.34			
Micronutrient deficiency	1.85	0.52 – 6.62	0.35			
HCV RNA	1.20	0.46 – 3.10	0.71			

Table 5. 6: Unifactorial and multifactorial regression analysis of socio-demographic and clinical predictors of cirrhosis (LSM ≥13kPa).



Area under the curve	P value	95% Confidence Interval	
		Lower Bound	Upper Bound
0.847	< 0.001	0.748	0.946

Figure 5. 1: Shows area under the curve (AUC) analysis for alcohol units/week in detecting cirrhosis. AUC = 0.847.

5.5 Clinical predictors of chronic HCV infection

Table 5.7 lists the demographic and clinical factors in those with and without chronic HCV (positive HCV RNA); with Table 5.8 showing unifactorial and multifactorial regression analysis for the same subgroups. Those with a positive HCV had a significantly lower prevalence of alcohol use disorder but were more likely to be active IDU as well as other recreational drug use and current smokers. Moreover, they were more likely to be homeless and have psychiatric illnesses (Table 5.7). On multifactorial analysis, independent predictors of a positive HCV RNA were the AUDIT questionnaire score ($\geq$20), current IDU, current other recreational drugs, and CSHF (Table 5.8).

HCV RNA	HCV RNA Positive (n=49)	HCV RNA Negative (n = 76)	P-value
Age ≥ 50	15 (31%)	44 (58%)	0.003
Male Gender	39 (78%)	57 (75%)	0.553
Alcohol units/week	12 (85)	70 (100)	0.01
Alcohol > recommended (> 14 units/week)	23 (47%)	59 (78%)	< 0.001
Hazardous alcohol drinking	16 (33%)	44 (58%)	0.006
Alcohol AUDIT questionnaire score	8 (24)	24 (24)	0.089
AUDIT score ≥ 20	19 (39%)	44 (58%)	0.037
Detectable Breathalyzer (n=109)	13 (28%)	15 (24%)	0.599
Breathalyzer score (n=109)	0 (4)	0 (0)	0.762
Current IDU	25 (51%)	10 (13%)	<0.001
Current non IDU	33 (67%)	25 (33%)	<0.001
Current Smoker	47 (96%)	55 (72%)	0.001
Homelessness	44 (90%)	50 (66%)	0.002
Major Comorbidities	7 (14%)	15 (18%)	0.435
Mental Health	41 (84%)	50 (66%)	0.028
Receiving treatment for mental health	31 (41%)	27 (55%)	0.117
Micronutrient deficiency (n=101)	4 (10%)	13 (22%)	0.116
LSM ≥ 8 kPa	17 (35%)	16 (21%)	0.091
LSM ≥ 13 kPa	9 (18%)	12 (16%)	0.707

Table 5. 7: Sociodemographic and clinical factors in those with and without chronic HCV (positive HCV RNA).

Factor	Unifactorial analysis			Multifactorial analysis		
	Odds ratio	95% C1	P value	Odds ratio	95% C1	P value
Age ≥ 50	0.32	0.150 – 0.686	0.003			
Male Gender	1.30	0.546 – 3.095	0.553			
Total alcohol units/week	0.997	0.993-1.001	0.210			
Alcohol AUDIT questionnaire score	0.96	0.938-0.991	0.009	0.94	0.90 - 0.98	0.001
Current IDU	6.88	2.882- 16.402	<0.001	3.33	1.07 - 10.39	0.038
Current other recreational drugs	4.21	1.958- 9.043	<0.001	4.05	1.49 - 11.01	0.006
Current Smoker	8.97	1.999 – 40.283	0.004			
Homelessness	4.58	1.62- 12.94	0.004			
Major Comorbidities	0.68	0.26 – 1.81	0.436			
Mental Health	2.67	1.09 – 6.51	0.032			
Micronutrient deficiency	0.39	0.12 – 1.30	0.125			
LSM ≥ 8 kPa	1.99	0.89 – 4.46	0.094	6.80	2.04 - 22.72	0.002

Table 5. 8: Unifactorial and multifactorial regression analysis of baseline demographic and clinical predictors of a positive HCV RNA.

5.6 Chronic HCV treatment outcomes

All treated patients received DAA based therapy only. Twenty-nine patients were willing to engage with treatment and were considered to be stable enough to initiate DAA therapy as determined initially by AH with input from SV if needed. Of the 29 receiving HCV treatment in this study, 9 (31%) had CSHF, 4 (14%) had cirrhosis while 12 (41%) were active IDU and 9 (31%) had alcohol dependence (AUDIT $\geq$ 20) at the time of screening. On an ITT basis, SVR rates were 24/29 (83%), treatment completion being 27/29 (93%). Table 5.9 shows the outcomes of the DAA-based treatment and SVR rates in the 29 individuals who received HCV treatment.

VALID Study ID	LSM kPa	HCV Genotype	DAA regimen/ duration (weeks)	Completed	SVR	IDU Pre-treatment	Alcohol use Pre-treatment and AUDIT scores
2	26.3	1a	SOF/LDV + RBV (12 weeks)	Yes	Yes	No (ex IDU)	Yes (22)
11	12.1	1a	OBV/PTVr/DSV + RBV 24 weeks	No only 20/24 weeks	Yes	No (ex IDU)	Yes (23)
23	48	1a	OBV/PTVr/DSV+RBV + RBV 24 weeks	Yes	Yes	No (ex IDU)	Yes (21)
31	4.9	3a	SOF/VEL 12 weeks	Yes	Yes	No (ex IDU)	Yes (0)
33*	3.8	1a	OBV/PTVr/DSV+RBV 12 weeks then SOF/LDV for 12 weeks	Yes	Yes	No (ex IDU)	Yes (2)
42	11.8	1a	EBR/GZR+ RBV 16 weeks	No only 8/16 weeks	No	Yes	Yes (14)
43	34.3	3a	SOF/VEL 12 weeks	Yes	Yes	Yes	Yes (35)
47	7.9	3a	SOF/VEL 12 weeks	Yes	Yes	No (ex IDU)	No (0)
48	38	3a	GLE/PIB 12 weeks			No (ex IDU)	Yes (40)
56*	5.4	1a	OBV/PTVr/DSV 12 weeks then SOF/LDV 12 weeks	Yes	Yes	No (ex IDU)	Yes (22)
60	6	3a	GLE/PIB 8 weeks	Yes	Yes	No (ex IDU)	No (0)
61	4.3	1a	EBR/GZR + Riba 12 weeks	Yes	Yes	No (ex IDU)	No (0)
64	6	3a	SOF/VEL12 weeks	Yes	No	Yes	Yes (9)
67	4.8	3a	GLE/PIB 8 weeks	Yes	Yes	Yes	Yes (28)
74	3.7	1a	EBR/GZR + RBV 16 weeks	Yes	Yes	No (ex IDU)	Yes (27)
79	5.2	1 (likely)	SOF/VEL 12 weeks	Yes	Yes	Yes	Yes (24)
82	5.3	3a	SOF/VEL 12 weeks	Yes	No	Yes	No (0)
88	4.8	3a	GLE/PIB 8 weeks	Yes	Yes	No (ex IDU)	No (0)
97	4.7	1a	OBV/PTVr/DSV + RBV 12 weeks	Yes	No	No (ex IDU)	No (1)
101	4.8	1a	EBR/GZR 12 weeks	Yes	Yes	No (ex IDU)	Yes (31)
102	9	2b	GLE/PIB 8 weeks	Yes	Yes	Yes	Yes (2)
103	3.3	3a	SOF/VEL 12 weeks	Yes	Yes	Yes	No (0)

VALID Study ID	LSM kPa	HCV Genotype	DAA regimen/ duration (weeks)	Completed	SVR	IDU Pre-treatment	Alcohol use Pre-treatment and AUDIT scores
104	8.8	3a	SOF/VEL 12 weeks	Yes	Yes	No (ex IDU)	No (0)
108	5.6	1a	SOF/LDV 8 weeks	Yes	Yes	Yes	No (1)
109	5.4	3a	SOF/LDV 8 weeks	Yes	Yes	No (Ex IDU)	Yes (19)
112	5.4	3a	SOF/VEL 12 weeks	Yes	Yes	Yes	No (0)
113	8	1a	SOF/LDV 8 weeks	Yes	Yes	Yes	No (0)
116	3.1	3a	SOF/VEL 12 weeks	Yes	Yes	Yes	No (2)
122	5.5	3a	SOF/VEL 12 weeks	Yes	No	No (Ex IDU)	No (2)

Table 5. 9: VALID study HCV treatment data and outcomes.

LSM liver stiffness measurement, IDU injecting drug use, SOF/LDV sofosbuvir/ledispavir, OBV/PTVr/DSV Ombitasvir/ Paritaprevir/Dasabuvir, SOF/VEL sofosbuvir/velpatasvir, EBR/GZR elbasvir/grazoprevir, GLE/PIB Glecaprevir/pibrentasvir, SOF/VEL/VOX sofosbuvir/velpatasvir/voxilaprevir.
* Treated as part of the STOP HCV1 study

5.7 Correlation and agreement between liver stiffness measurement and ELF and APRI scores

There was moderate correlation between LSM and ELF score (Log values Spearman correlation 0.553, $p<0.001$ (Figure 5.2). There was moderate agreement between LSM and ELF scores for clinically significant hepatic fibrosis (Kappa value 0.536, $p<0.001$, Table 5.10) and good agreement between LSM and ELF for cirrhosis (Kappa value 0.734, $p<0.001$, Table 5.11). The correlation between LSM and APRI score was also moderate (Spearman correlation 0.588, $p <0.001$ (Figure 5.3). In comparison to ELF, APRI had a lower degree of agreement with LSM for both clinically significant hepatic fibrosis (Kappa value 0.452, $p<0.001$) and cirrhosis (Kappa value 0.510, $p<0.001$) (Table 5.12 & 5.13).

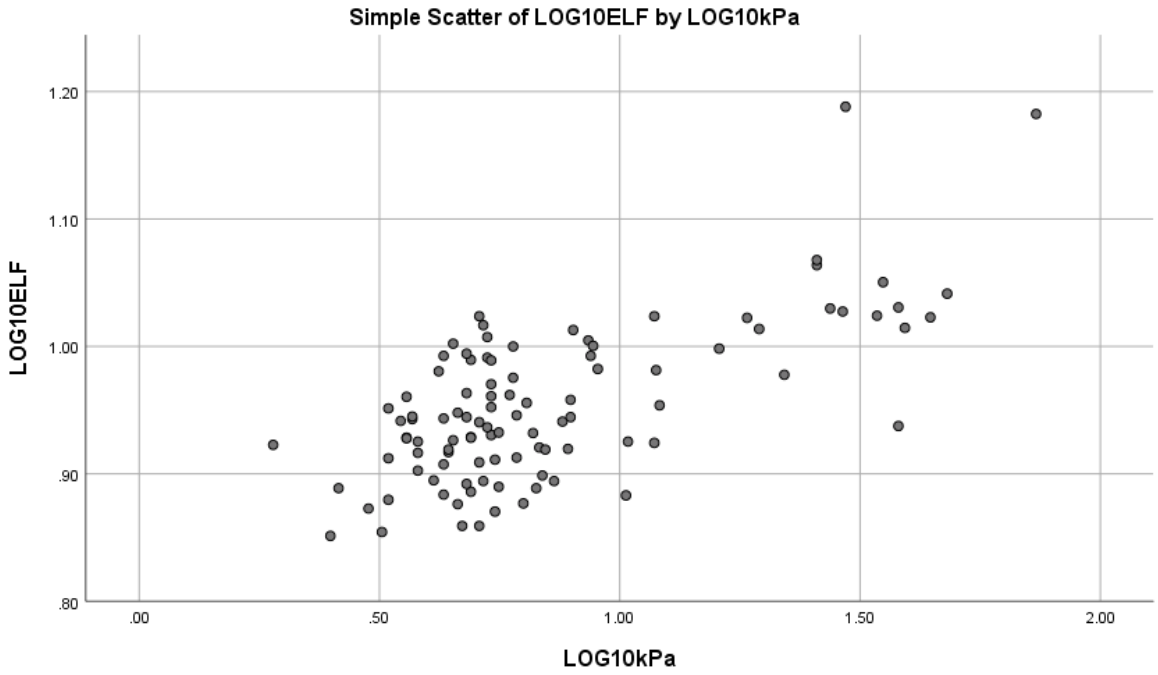


Figure 5. 2: Scatter plot showing correlation between Log values of LSM in kPa and ELF score (Spearman correlation 0.553, p value <0.001).

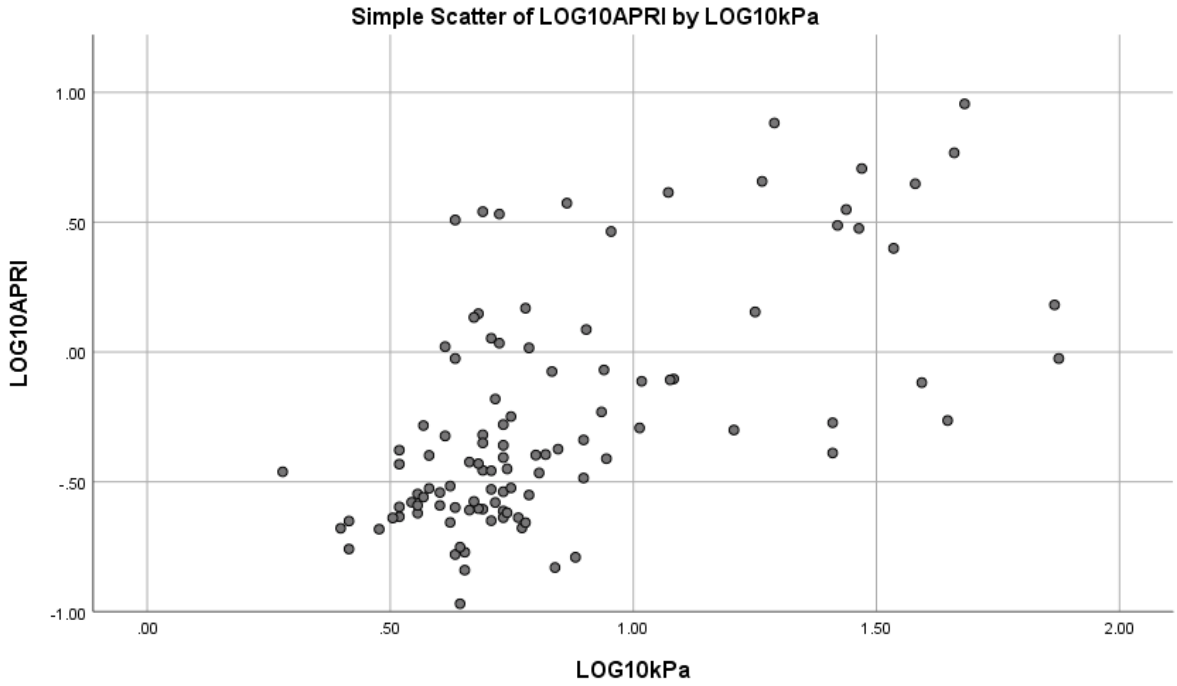


Figure 5. 3: Scatter plot showing correlation between Log values of LSM in kPa and APRI score (Spearman correlation 0.588, p value <0.001).

		ELF		
		No CSHF	CSHF	Total
LSM	No CSHF	63	9	72
	CSHF	10	19	29
Total		73	28	101

Table 5. 10: The degree of agreement between LSM value and ELF score for the diagnosis of CSHF (defined as LSM ≥8kPa, ELF > 9.8), Kappa = 0.536, p <0.001, n=101.

		ELF		
		No Cirrhosis	Cirrhosis	Total
LSM	No Cirrhosis	82	2	84
	Cirrhosis	5	12	17
Total		87	14	101

Table 5. 11: The degree of agreement between LSM value and ELF score for the diagnosis of cirrhosis (defined as LSM ≥13kPa, ELF > 10.51), Kappa = 0.734, p <0.001, n=101.

		APRI		
		No CSHF	CSHF	Total
LSM	No CSHF	73	5	78
	CSHF	15	13	28
Total		88	18	106

Table 5. 12: The degree of agreement between LSM value and APRI score for the diagnosis of CSHF (defined as LSM $\geq$8kPa, 1.5<APRI<2), Kappa = 0.452, p <0.001, n=106.

		APRI		
		No Cirrhosis	Cirrhosis	Total
LSM	No Cirrhosis	82	6	88
	Cirrhosis	8	10	18
Total		90	16	106

Table 5. 13: The degree of agreement between LSM value and APRI score for the diagnosis of cirrhosis (defined as LSM $\geq$13kPa, APRI $\geq$ 2), kappa = 0.510, p <0.001, n=106.

CHAPTER 6: Laboratory results of VALID study

6.1 Baseline laboratory findings

The number of patients who had Th17 MSD cytokine panel, MMP-2 and CK-18, and ELF biomarkers analysed were 97, 79, 99, and 101, respectively.

Only cytokines with more than 33% of the analysed population (n=97) having detectable levels were included. Of the 97 patients with cytokines data analysed, IL-6 was detectable in 76 (78%), IL-10 in 42 (43%), IL-17A in 37 (38%), and IL-22 in 52 (54%). Only two patients had undetectable levels of IFN-γ, while all patients had a detectable level of TNF. As reported in the Methods section (Chapter 4), undetectable cytokine values were assigned half the lower detection limit of the assay. The median concentrations of the various cytokines and biomarkers are summarized in Table 6.1. There were several outlier results for the cytokines included in the analysis (Figure 6.1).

Serum CK-18, MMP-2 and ELF biomarkers were detectable in all patients included in the analysis.

Cytokine	No. of patients	Median	Interquartile range (IQR)
IFN-γ (pg/ml)	97	12.5	8.6
IL-6 (pg/ml)	97	1.4	1.5
IL-10 (pg/ml)	97	0.3	0.4
IL-17A (pg/ml)	97	1.0	1.4
IL-22 (pg/ml)	97	0.5	0.5
TNF (pg/ml)	97	2.8	1.2
MMP-2 (ng/ml)	79	228.7	120.3
CK-18 (U/L)	99	37.0	212.7
HA (ng/ml)	101	31.7	48.1
PIIINP (ng/ml)	101	8.1	6.3
TIMP-1 (ng/ml)	101	200.0	89.4

Table 6. 1: Median and IQR of the serum concentrations of the cytokines, senescence markers and ELF biomarkers.

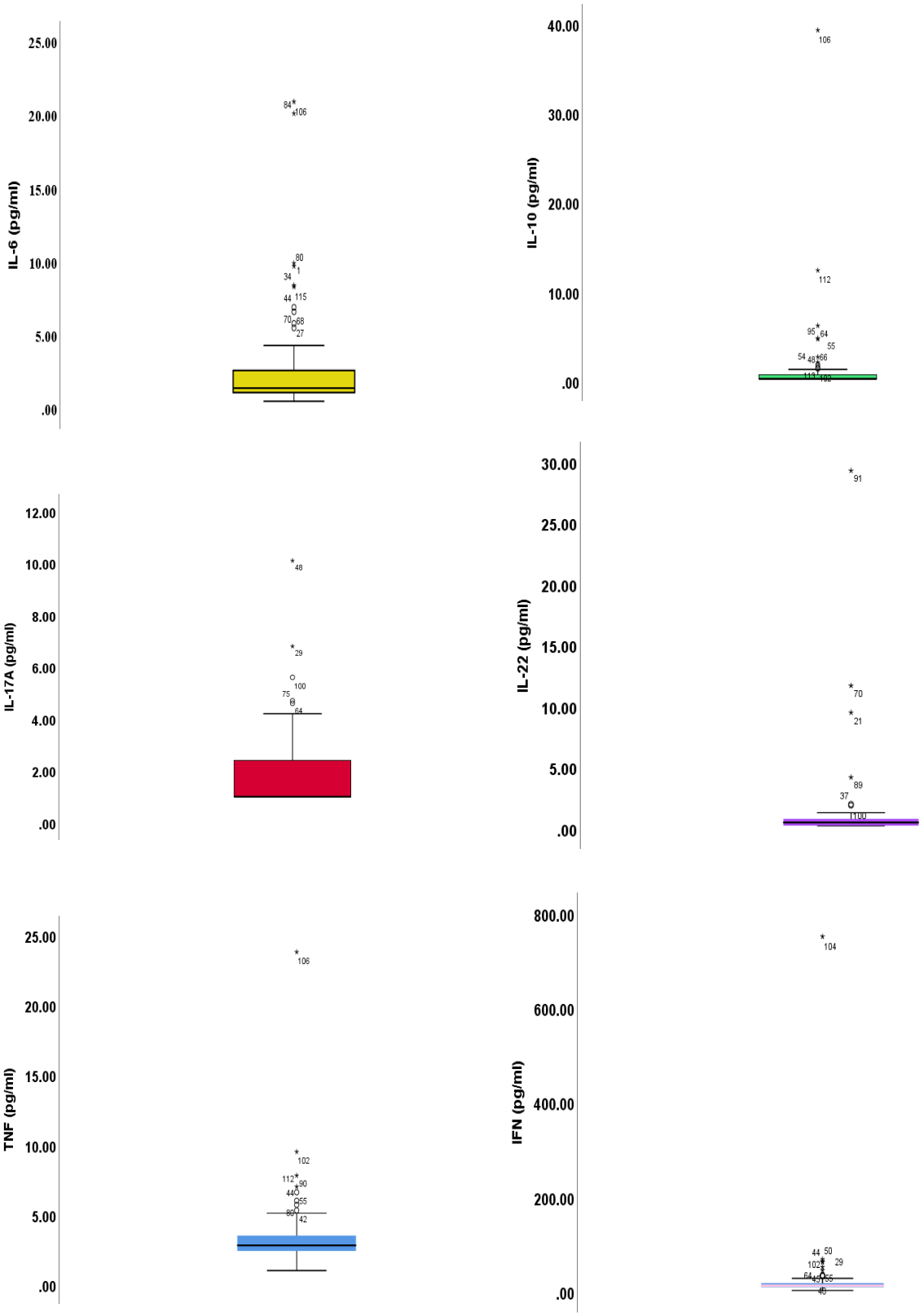


Figure 6. 1: Boxplots showing the median and distribution of the serum concentrations of the cytokines included in the analysis (IFN-γ, IL-6, IL-10, IL-17A, IL-22, TNF).

Circles indicate “outlier” values while asterisks (*) denote extreme “outliers”.

6.2 Serum cytokines and biomarkers in patients with CSHF

Table 6.2 shows the median (IQR) levels of serum cytokines, senescence and ELF biomarkers in those with and without CSHF. The former had significantly higher levels of IL-6, IL-10, IFN-γ, TNF, senescence biomarkers (MMP-2 and CK-18), and ELF biomarkers (HA, PIIINP, TIMP-1) (Figure 6.2). More than 50% of patients without CSHF had undetectable IL-10 and IL-17A levels (64% and 67% respectively). Patients with CSHF had a significantly higher percentage of detectable IL-6 and IL-10 levels (Table 6.3).

There were no differences in the median concentrations of IL-17A or IL-22 between those with and without CSHF. Even removing the outliers using the ROUT method did not result in significant differences. For IL-17A, the ROUT method identified five outliers in the no CSHF group, and one in the CSHF group; for IL-22, four values in the no CSHF group and two in the CSHF group were identified as outliers.

Cytokine/Biomarkers	CSHF	No CSHF	P value
Th17 Cytokines			
IL-10 (pg/ml)	0.6 (0.73)	0.25 (0.45)	0.049
IL-17A (pg/ml)	1.5 (1.78)	1 (1.2)	0.106
IL-22 (pg/ml)	0.65 (0.65)	0.5 (0.45)	0.169
Other cytokines			
IFN-γ (pg/ml)	16 (10.7)	10.8 (6.4)	0.002
TNF (pg/ml)	3.2 (1)	2.7 (1.15)	0.05
IL-6 (pg/ml)	2 (1.48)	1.3 (1.60)	0.001
Senescence biomarkers			
MMP-2 (ng/ml)	259.8 (171.3)	205.7 (107.6)	0.006
CK 18 (U/L)	347.7 (552.2)	25 (47.1)	<0.001
ELF biomarkers			
HA (ng/ml)	76.5 (82.5)	25.8 (35.9)	<0.001
PIIINP (ng/ml)	10.2 (11.6)	6.6 (3.2)	<0.001
TIMP-1 (ng/ml)	271 (154.3)	168.3 (57)	<0.001

Table 6. 2: Median (IQR) levels of serum cytokines, senescence and ELF biomarkers in those with and without CSHF (test of significance =Mann-Whitney test).
IL = interleukin, IFN-γ =interferon-gamma, TNF= tumour necrosis factor, MMP-2= Matrix metalloproteinase-2, CK= cytokeratin, HA= Hyaluronic acid, PIIINP= Procollagen III amino terminal peptide, TIMP-1= Tissue inhibitor of metalloproteinase- 1.

	CSHF (n=28)	No CSHF (n=69)	P value
Detectable IL-6	26 (93%)	50 (73%)	0.027
Detectable IL-10	17 (60%)	25 (36%)	0.027
Detectable IL-17A	14 (50%)	23 (33%)	0.126
Detectable IL-22	17 (61%)	35 (51%)	0.371

Table 6. 3: Proportion of detectable levels of IL-6, IL-10, IL-17A, IL-22 cytokines in those with/without CSHF (test of significance = Chi square).

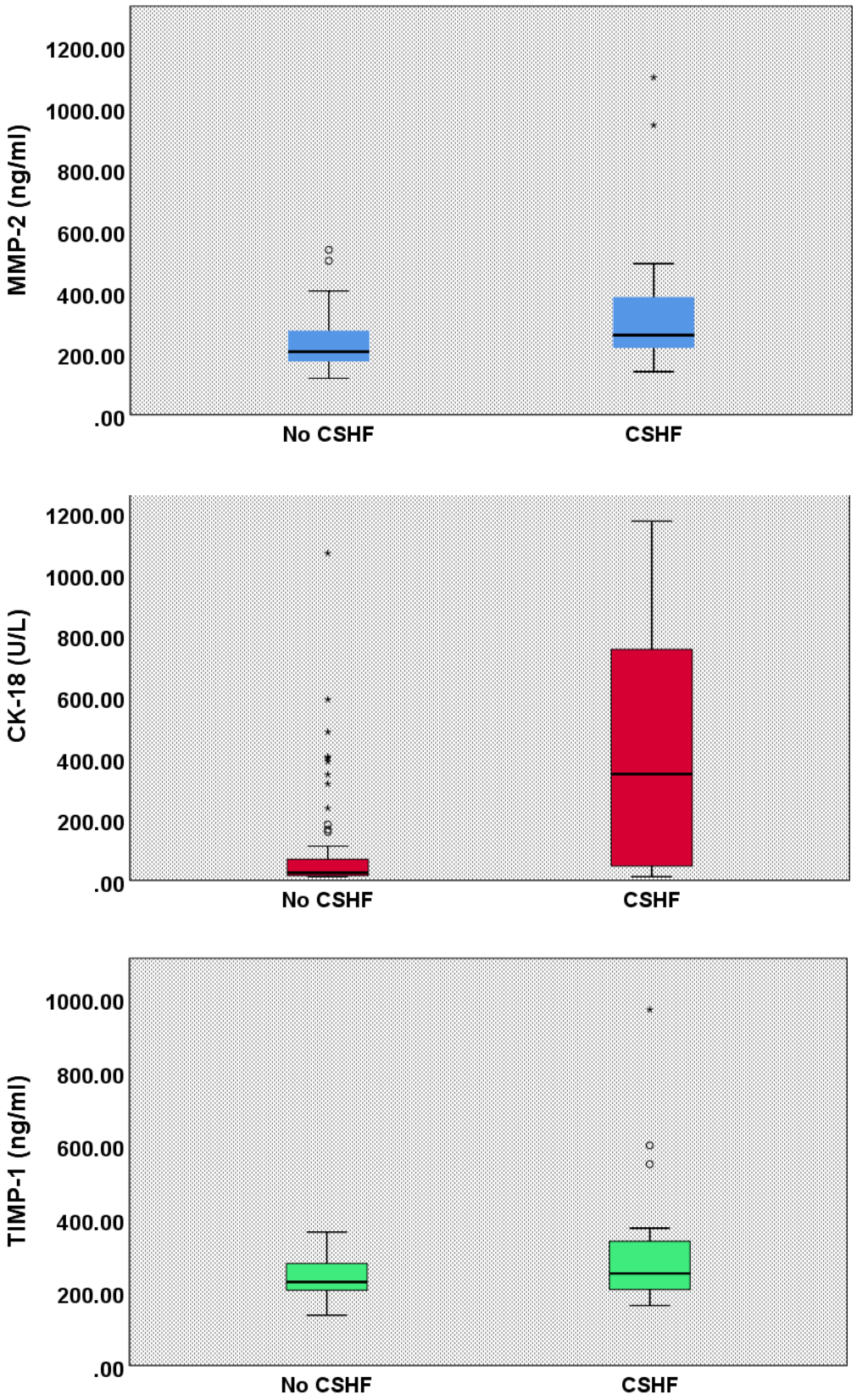


Figure 6. 2: Boxplots showing significantly raised median concentrations of senescence markers (MMP-2, CK-18, TIMP-1) in those with CSHF compared to those without CSHF. Circles indicate “outlier” values while asterisks (*) denote extreme “outliers”.

6.3 Serum cytokines and biomarkers in patients with cirrhosis

Those with cirrhosis had significantly higher levels of IL-6, IFN-γ, senescence biomarkers (MMP-2 and CK-18) and ELF biomarkers (Table 6.4).

More than 50% of patients without cirrhosis had undetectable IL-10 and IL-17A levels (61% and 65% respectively). Although there were higher proportions of those with cirrhosis with detectable levels of IL-6, IL-10, IL-17A, IL-22 cytokines, the results were not statistically different (Table 6.5).

Following removal of outliers, the median serum concentration of IL-17A was observed to be significantly raised in patients with cirrhosis vs no cirrhosis (1.7, IQR: 2.1 vs 1.0, IQR: 1.1, p= 0.039), (Figure 6.3). The same applied to IL-10 as its median level was significantly higher in those with cirrhosis vs without cirrhosis after removal of the outliers (0.6, IQR: 0.6 vs 0.25, IQR: 0.43, p= 0.0142). For IL-17A, the ROUT method identified 4 outliers in the no cirrhosis and one in the cirrhosis group; for IL-10, 8 values in the no cirrhosis group were identified as outliers.

Cytokine/Biomarker	Cirrhosis	No Cirrhosis	P value
Th17 cytokines			
IL-10 (pg/ml)	0.6 (0.60)	0.25 (0.45)	0.155
IL-17A (pg/ml)	2.7 (2.5)	1 (1.2)	0.054
IL-22 (pg/ml)	0.80 (0.72)	0.5 (0.55)	0.159
Other cytokines			
IFN-γ (pg/ml)	18.9 (13.7)	11.3 (7)	<0.001
TNF (pg/ml)	2.9 (1)	2.8 (1.2)	0.442
IL-6 (pg/ml)	2.8 (1.9)	1.3 (1.7)	<0.001
Senescence biomarkers			
MMP-2 (ng/ml)	360.8 (230.7)	214 (107.6)	0.002
CK 18 (U/L)	415.5 (640.8)	25 (111.6)	<0.001
ELF biomarkers			
HA (ng/ml)	96.2 (141.3)	26.4 (36.3)	<0.001
PIIINP (ng/ml)	18.7 (13.9)	6.6 (3.7)	<0.001
TIMP-1 (ng/ml)	312.9 (185.7)	171.8 (61.9)	<0.001

Table 6. 4: Median (IQR) concentrations of serum cytokines, senescence and ELF biomarkers in those with and without cirrhosis (test of significance =Mann-Whitney test).
IL = interleukin, IFN-γ =interferon-gamma, TNF= tumour necrosis factor, MMP-2= Matrix metalloproteinase-2, CK= cytokeratin, HA= Hyaluronic acid, PIIINP= Procollagen III amino terminal peptide, TIMP-1= Tissue inhibitor of metalloproteinase- 1.

	Cirrhosis (n=17)	No Cirrhosis (n=80)	P value
Detectable IL-6	16 (94%)	60 (75%)	0.082
Detectable IL-10	11 (65%)	31 (39%)	0.05
Detectable IL-17A	9 (53%)	28 (35%)	0.167
Detectable IL-22	11 (65%)	41 (51%)	0.312

Table 6. 5: Proportion of detectable levels of IL-6, IL-10, IL-17A, IL-22 cytokines in those with/without cirrhosis (test of significance = Chi square).

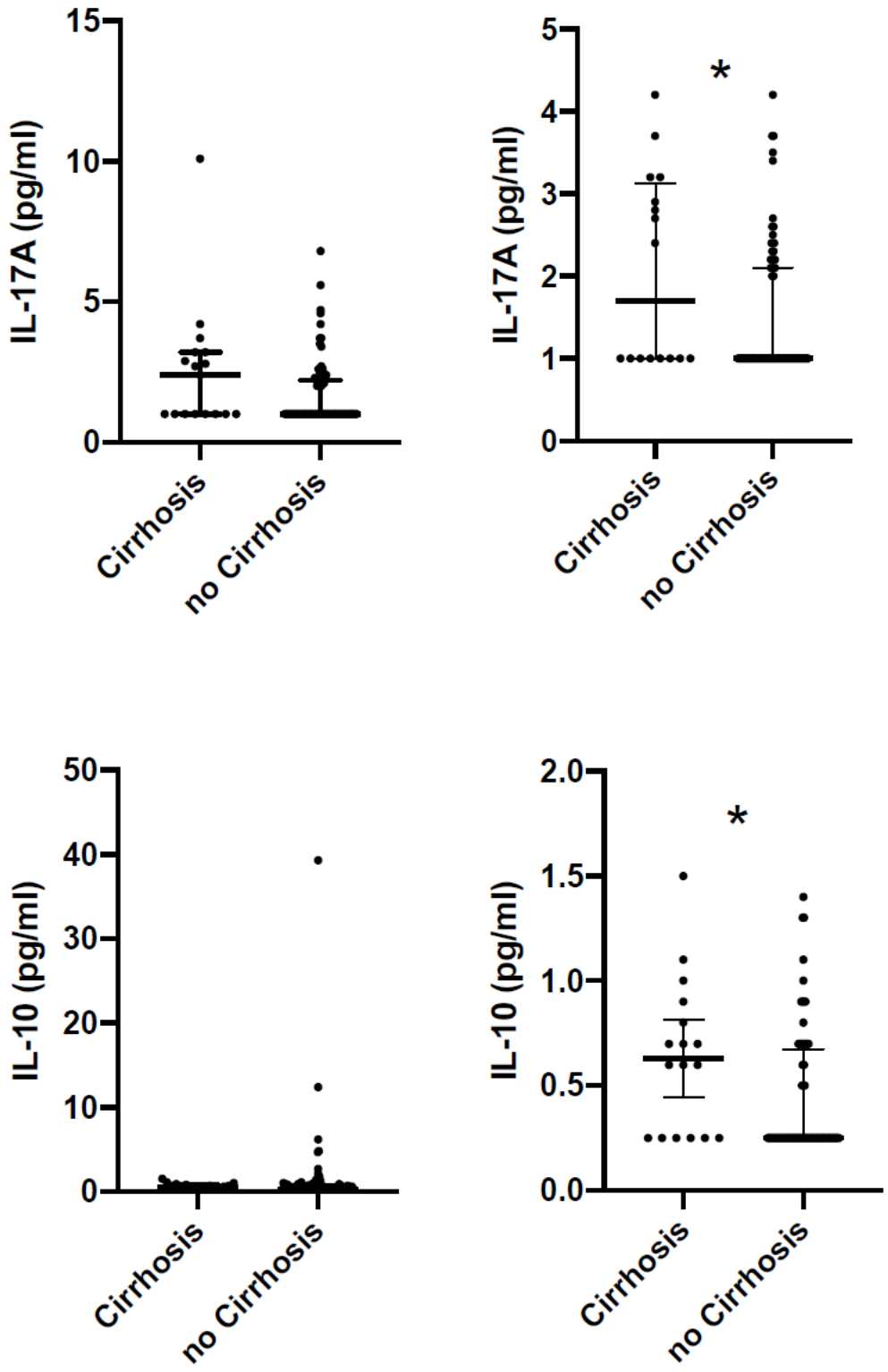


Figure 6. 3: Comparison of IL-17A (top) and IL-10 (bottom) between those with/without cirrhosis before (left) and after (right) removal of outliers [IL-17: cirrhosis vs. no cirrhosis (1.7, IQR: 2.1 vs 1, IQR: 1.1, p= 0.039), IL-10: (0.6, IQR: 0.6 vs 0.25, IQR: 0.43, p= 0.0142)]. Outliers were removed using the ROUT method (outliers removed: for IL-17A, 4 in the no cirrhosis and one in the cirrhosis group; for IL-10, 8 in the no cirrhosis group).

6.4 Serum cytokines and biomarkers in those with positive HCV RNA

Compared to those without HCV viremia, those with a positive HCV RNA had significantly higher levels of Th17 cytokines (IL-22, IL-10), TNF, hepatic senescence, and ELF biomarkers (CK-18, PIIINP and TIMP-1) (Table 6.6). Even after removal of the outliers, there were no differences in the concentrations of the remaining cytokines between the two groups.

In the HCV negative subgroup, undetectable levels of IL-10 and IL-17A was observed in more than 50% of the cases (78% and 68% respectively), whereas IL-17A was undetectable in 53% of the HCV RNA positive patients. The proportion of HCV RNA positive patients with detectable IL-10 levels was significantly higher than that of HCV RNA negative patients (Table 6.7).

Cytokine/Biomarker	HCV RNA positive	HCV RNA negative	P value
Th17 cytokines			
IL-10 (pg/ml)	0.7 (1.2)	0.25 (0.0)	<0.001
IL-17A (pg/ml)	2 (1.5)	1 (1.4)	0.171
IL-22 (pg/ml)	0.5 (0.45)	0.6 (0.75)	0.026
Other cytokines			
IFN-γ (pg/ml)	13.3 (13.2)	11.3 (7.4)	0.176
TNF (pg/ml)	3.7 (2.2)	2.7 (0.8)	<0.001
IL-6 (pg/ml)	1.5 (1.9)	1.4 (2.1)	0.911
Senescence biomarkers			
MMP-2 (ng/ml)	229.2 (109.9)	217.7 (123.7)	0.489
CK 18 (u/L)	182.8 (388.6)	25 (86.8)	0.005
ELF biomarkers			
HA (ng/ml)	55.6 (64.8)	27.3 (35.0)	0.103
PIIINP (ng/ml)	8.7 (10.3)	6.6 (4.3)	0.001
TIMP-1 (ng/ml)	215 (98.8)	171.8 (71)	0.001

Table 6. 6: Comparison between the median (IQR) concentrations of cytokines and biomarkers in those with and without a positive HCV RNA (test of significance =Mann-Whitney test).
IL = interleukin, IFN-γ =interferon-gamma, TNF= tumour necrosis factor, MMP-2= Matrix metalloproteinase-2, CK= cytokeratin, HA= Hyaluronic acid, PIIINP= Procollagen III amino terminal peptide, TIMP-1= Tissue inhibitor of metalloproteinase- 1.

	HCV RNA Positive (n=38)	HCV RNA Negative (n=59)	P value
Detectable IL-6	31 (82%)	45 (76%)	0.536
Detectable IL-10	29 (76%)	13 (22%)	<0.001
Detectable IL-17A	18 (47%)	19 (32%)	0.133
Detectable IL-22	17 (45%)	35 (59%)	0.160

Table 6. 7: Proportion of detectable levels of IL-6, IL-10, IL-17A, IL-22 cytokines in those with and without positive HCV RNA (test of significance = Chi square).

CHAPTER 7: Discussion of VALID study outcomes

7.1 Evaluation of the hostel-based service

In general, the service uptake was excellent as 97% who attended for screening accepted the service and consented for study enrolment. The main reason for declining the service was the refusal to have blood samples taken as these individuals felt withdrawing blood samples from their veins will be challenging. This problem is expected in a cohort with a high prevalence of IDU due to poor venous access. Using whole capillary blood in dried blood spot testing (DBST) specimens is perhaps a good alternative for screening viral hepatitis in this cohort particularly that they are less invasive, quicker, and samples can be stored and transported without refrigeration (Vazquez-Moron et al., 2018). DBSTs could also be used to detect HCV RNA, and therefore screening for chronic HCV infection. Additionally, they do not require highly trained personnel, so they are helpful when a venous sample is difficult to obtain. Nonetheless, the lower limit of HCV RNA detection using DBST is generally high (2000IU), which may yield high rates of false negatives (Jack and Irving, 2020). A standard venous sample was still required in our study to check routine blood results. Moreover, a venous sample is needed to test the viral load and HCV genotype when applicable. Arguably, although not widely used, HCV genotyping can also be done using DBST, and according to Tuaillon et al. (2010), it may increase the chances of treatment follow-up in hard-to-reach individuals. The evidence around this area is still deficient, and moreover, our study also aimed to investigate the immunological and molecular mechanisms for fibrosis in this cohort, and hence further venous samples were

necessary to achieve this aim. One other approach could have been adopted and that is a combined approach of DBST followed by invitation for a full assessment and additional blood tests which has been trialled by several studies particularly in models based in substance misuse services (O'Sullivan et al., 2020, Tait et al., 2013). Tait et al. (2013) argued that DBST could be used as a complementary screening tool to conventional venepuncture to screen difficult to reach groups. In their study where 1123 DBST tests were undertaken for adults attending drug treatment and needle exchange centres, they demonstrated that 94.3% returned for their results, suggesting that this approach achieves good engagement. Of the 307 with positive HCV antibody test who were offered an onward referral to the specialist service, 249 attended and had their venous blood checked for HCV PCR, and of the 165 with positive PCR, 138 returned for further investigations. While in our model one of the hostel managers was trained to carry out DBST during the later stages of the recruitment process, Tait et al.'s approach could potentially carry the risk of selectively engaging those who test positive for viral hepatitis and therefore missing a significant proportion whose primary underlying aetiology for liver disease is related to alcohol use disorders (AUD).

The service provided in the VALID study was holistic, offering participants, a thorough history taking and blood sampling, alcohol and substance misuse assessment, detection of liver fibrosis and nutritional evaluation. Additionally, there was a close collaboration with the GP and hostel staff. This approach often referred to as the "one-stop-shop", is believed to be more practical and achieves multiple goals in one session. Nevertheless, it limits the number of patients and clients who could be reviewed in a single clinic session. The clinical consultations in this study were conducted solely by AH, which allowed for consistency and trust-building. The need for consistent and easy access services has been highlighted as a key factor in delivering care to homeless and vulnerable adults (van den Berk-Clark and McGuire, 2014). It was challenging to estimate the number of targeted vulnerable people who received an invitation to join the

study or its associated liver screening service. However, once attended, the uptake was extremely high. All participants were provided with a patient information sheet and had the details of the service outlined to them by AH. This could indicate that a brief explanation of the importance of liver screening to those vulnerable adults may well improve their understanding of their risks and enhance the opportunity for engagement. It could also be speculated that in order to improve the recruitment, the study briefing could be undertaken by general practitioners, substance misuse workers and potentially hostel staff who have regular contact with these vulnerable individuals on a daily basis provided that appropriate training is delivered to them. In essence, these key workers could distribute the initial recruitment advertisement to the targeted homeless and vulnerable population as a first step prior to their attendance at the screening site. This is akin to the peer-support model, where the screening process is undertaken by trained peer workers who demonstrate commitment and willingness. This approach has been described to improve the active recruitment of vulnerable and underserved populations (Stagg et al., 2019, MacLellan et al., 2015). The theoretical idea behind this approach is that peers usually share the same life experiences or characteristics as the targeted population which may allow them to support and engage those who have similar challenges (MacLellan et al., 2015, Surey et al., 2019). Furthermore, in Surey et al.'s study, peers were even trained to perform FibroScan as well as BBV screening.

The cohort enrolled in our study was primarily Caucasian males, and this is expected given the higher proportion of male residents in homeless hostels in the UK (Office for National Statistics, 2019). In fact, most of the studies looking into liver disease in hostel-based homeless populations described a similar finding (Boyce et al., 2009, Stein et al., 2012, Aisyah et al., 2018), (Table 3.2). In other countries like the USA, a considerable proportion of those regarded as homeless are veterans, which could also explain the male predominance (Fargo et al., 2012). Moreover, the systematic review detailed in Chapter 3 revealed that only a few studies focused

on exploring HCV amongst homeless women (Page et al., 2017). It is not clear why this is the case. However, one explanation is that most homeless women represent 'hidden homeless' population which in essence describes those who stay with friends or families and are not captured by official reports. This reporting bias needs to be factored in when designing services catering for homeless adults as homeless women are likely to be more vulnerable with higher rates of mental health problems and sexual abuse (Beijer and Andreasson, 2010, Lewis et al., 2003). Another factor that leads to women being underrepresented in these studies is that homeless women generally avoid being identified as homeless and are less likely to stay in hostels or shelters, perhaps for safety reasons.

Other reasons for under-representation of women are that homeless women tend to have easier access to jobs than their male counterparts, and thus may only experience temporary homelessness for a short period before moving on to a new job and stable housing (De Vet et al., 2019). Moreover, since most social services are proactive in aiding children (as a priority), particularly in the context of homelessness, mothers are likely to receive support lifting them from the homelessness situation.

The majority of patients in this study were recruited from Glenwood lodge hostel, which was the study's primary recruitment site. As illustrated in Chapter 4, the recruitment process involved mobilising key workers and hostel staff to encourage hostel residents to participate in the study and receive liver screening. Hence nearly two-thirds of patients recruited were living in hostels at the time of enrolment, and only a small number were rough sleeping. This recruitment model was a mixture of passive approach (allowing participants to attend and self-refer themselves to the recruitment clinic on specific dates) and incorporated an active case-finding component by involving hostel workers in the recruitment strategy. In addition, the service offered an integrated and multidisciplinary 'single stop' service where patients had all components of the screening and clinical assessment in a single appointment at one site to

minimise the number of visits required. This has positively influenced the participation and engagement. This holistic strategy is also similar to models based in addiction centres or dedicated community centres for homeless and vulnerable adults, which usually benefit from on-site integrated facilities (O'Sullivan et al., 2020, Hodges et al., 2019). The integration of services allows for better and holistic management of cases through social, drug and alcohol support, potentially resulting in better compliance and outcomes (Caires, 2017). Arguably, an active case-finding enrolment strategy by 'meeting vulnerable adults where they are' may potentially yield better engagement and recruitment of these at-risk populations. Active case-finding involves models that utilise mobile services such as medically equipped vans. An example of this approach is the model adopted by investigators in London, which offered viral hepatitis screening in conjunction with TB screening (Aisyah et al., 2018). Nevertheless, while this strategy offers a true active case finding recruitment model, mobile services do not provide homeless adults with a fixed site to refer to for follow up as in the case with the hostel/shelter-based approach where a specific location becomes known to the targeted group allowing easy access. The justification for utilising active case finding approach for services addressing vulnerable adults is that this cohort represents a difficult to reach group which could potentially act as a reservoir for HCV and therefore, hinder the process of HCV elimination if not screened and treated promptly. Moreover, PWAH tend to have competing needs and are likely to prioritise financial, addiction, and housing needs over physical health issues (Linn and Gelberg 1989). Hence, without direct engagement with these individuals and providing counselling and explanation, screening for and treating underlying liver disease and viral hepatitis in this cohort becomes virtually impossible.

The World Health Organisation (WHO) plans to eliminate HCV by 2030; it emphasizes risk reduction for PWIDs and removal of barriers to treatment for those at risk (Grebely et al., 2017b). This target of elimination has driven the need to develop community-based liver

screening services adopting an active-case finding strategy in the quest to pick up and recruit patients who are deemed ‘invisible’ to care or hard to reach. This process is also expected to educate and empower primary care providers and key workers to actively participate in the campaign of HCV elimination in a similar way we adopted in our model. Our hostel-based model recruited key workers and hostel staff to advertise for the service and encourage vulnerable adults to attend. If hostel key workers are sufficiently trained and formally assigned to assist with the recruitment, the model would be expected to yield better outcomes and higher engagement and recruitment rates. Nonetheless, the challenge with these hard-to-reach groups remains an area of ongoing debate and discussion. For example, despite 60,000 people estimated to have chronic HCV in London, nearly half remain undiagnosed (Public Health England, 2015b). Furthermore, the same report highlights that homeless people are thought to be 50 times more likely to encounter HCV, yet only a small percentage receive treatment. The Hepatitis C in England 2020 report indicated that chronic HCV prevalence among those reporting homelessness rose markedly from 29% in 2011 to 35% in 2018 (Public Health England, 2020). Moreover, among rough sleepers, the diagnosis or reporting of HCV infection increased from 22% to 32% between 2014 and 2017.

The model we implemented in our study was based on the provision of service in a semi-stable environment. However, data suggest that homeless people tend to move quickly from one temporary place to another (The Homeless Link Research Team, 2018) and that hostels provide accommodation for only a short period of time, meaning that many homeless and vulnerable adults residing in hostels who engage with medical services may find themselves forced to disengage due to moving places. This kind of hostel accommodation, known as medium support hostels, is the most common form of accommodation in the UK and offers vulnerable adults some sort of a bridge before moving onto stable, permanent accommodation. Moreover, around 20% of homeless accommodations in the UK are emergency-type accommodations,

also known as stage one, which comprises a temporary, short-lived accommodation such as winter shelters and night stop schemes (The Homeless Link Research Team, 2018). These shelters' temporary nature constitutes a disadvantage for hostel-based liver screening models and results in an increased rate of patients being lost to follow up. Another disadvantage of hostel-based services is that the majority serve single homeless adults, and hence a significant number of homeless families and women with children may not be captured in screening services set up in these hostels (The Homeless Link Research Team, 2018). The Future Hostel report (The Homeless Link Research Team, 2018) highlighted this issue of continuity of support and care indicating that both staff and residents reported a lack of ongoing support once a resident moves on from a hostel. More recently, a proposal was made to adopt a different strategy that focuses on providing permanent accommodation as the first step prior to the delivery of interventional measures addressing physical and psychological needs. The theoretical explanation behind this Housing First model is that it avoids the high rates of dropouts associated with other models that, in contrast, require vulnerable and homeless adults to display genuine commitment before the provision of stable housing (Pleace, 2018). The current traditional models also referred to as ‘treatment first’ models, focus on encouraging homeless adults to access and attend drug and alcohol services and demonstrate a degree of improvement in health and substance misuse outcomes with or without a reduction in offences rates before being declared as housing ready (Tsai et al., 2010b).

The newly introduced housing first strategy focusing on the delivery of permanent supportive housing, on the other hand, is thought to have the potential of reducing the rates of chronic homelessness and the overall costs of public spending on homelessness (Tsai et al., 2010b, Padgett et al., 2016). This strategy, which has emerged initially in the USA, is gaining considerable global attention, including in the UK where several pilot initiatives adopting the Housing First initiatives have taken place. While Housing First is effective with active

substance misuse (Palepu et al., 2013), it is unclear whether the same impact will be experienced in those with physical health problems. Concerning liver disease and management of viral hepatitis among vulnerable and homeless adults, it remains questionable whether this model will yield better outcomes than the current treatment first strategies. Nevertheless, a Canadian study (Kim et al., 2009) had previously established a link between unstable housing and prevalence of HCV with regression analysis indicating that unstable housing was independently associated with HCV infection giving rise to a relative hazard ratio of 1.47 (95% CI 1.02 – 2.13). The authors recommended that more efforts be undertaken to improve housing in order to reduce the incidence of HCV. Indeed, in our VALID study, the prevalence of HCV was also significantly higher among the homeless group than non-homeless individuals (47% vs 16.1%). Furthermore, a recently published review in the Lancet revealed that both permanent housing and income assistance strategies were able to improve housing stabilities but acknowledged the limitation of the current literature in establishing clear evidence regarding the impact of these interventions on the outcomes of physical and psychological health, substance misuse and quality of life (Aubry et al., 2020). It will be relevant to design further studies to explore if housing first strategies influence compliance and SVR rates compared to traditional models focused on screening vulnerable adults in hostels or dedicated community centres.

On the positive side, hostel-based models have the advantage of providing a near-patient service allowing for easy access for the targeted vulnerable adults. They also offer a fixed point of contact for clients. The hostel-based model appears to work more efficiently, as demonstrated in our study, by actively engaging hostel staff who can help with recruitment, follow-up and scheduling appointments. Nevertheless, to further assess these advantages, a qualitative study should be undertaken to explore the perception of both participants and hostel staff regarding the hostel environment's role in enabling better engagement and involvement

of PWAH with clinical screening services. In project ITTREAT, the qualitative assessment revealed positive impacts of the integrated service, and personalized community-based service played a crucial role in reducing barriers to HCV care for PWID (Phillips et al., 2020). Additional clinical services such as TB screening, foot clinics and infectious diseases services could be incorporated into a single integrated hostel-based clinic alongside the liver screening service. Presently, clinical activities offered in a hostel-based environment are frequently limited to a specific screening service with no opportunity to deliver a broadly integrated service unless sufficient time, effort and funding are put in place. Despite this clear advantage, some authors have raised concerns about offering services to vulnerable adults in dedicated centres as this may reinforce or aggravate the feeling of exclusion for some of these individuals (Lester, 2001). Furthermore, setting up such integration of clinical and non-clinical services in a hostel-based environment requires a high level of coordination and adequate resources to run multiple activities simultaneously in one site which may not be available or feasible in all community centres. Provision of funding to hostels and dedicated training to their staff may constitute a plausible solution and facilitate initiation of integrated hostel-based liver screening services. Other models such as street-based services and roadshows (Foucher et al., 2009, Stein et al., 2012), which have been previously trialled for screening vulnerable and homeless adults, lack the advantage of continuity and longitudinal care. Additionally, while the concept of remote consultations has been tested, evidence suggests that the degree of engagement and compliance with these services could be suboptimal (Andric et al., 2017).

The definition of homelessness is not unified in the UK; neither is the definition of a vulnerable adult. In the systematic review provided in Chapter 3, only a few studies provided specific definitions for a homeless adult as part of their methodologies. Moreover, the definition of homelessness varied significantly from definitions based on housing situations (i.e. unstable housing, rough sleeping) and others related to the utilisation of services dedicated to homeless

and vulnerable adults. This heterogeneity in describing homelessness constitutes a major barrier to holding comparative analysis between the various studies looking into liver disease in homeless adults. A vulnerable adult in this study, on the other hand, was identified by the participating GP surgeries and included, in addition to being homeless, any registered adult who had a known history of drug or alcohol misuse history (active or previous). This extended inclusion criteria applied to only one of the GP surgeries (BHWC) as the primary recruitment GP surgery, BHH (The Arch healthcare), catered for homeless adults only who, by definition, were all eligible for the study.

The study population's mean age was 47 year, with less than half aged 50 or above. This is in keeping with previous reports indicating that the average life span of homeless individuals is approximately around that figure (Vuillermoz et al., 2016, Hwang, 2000, Baggett et al., 2013, Medcalf and Russell, 2014). Additionally, the mean age described here in this study is also comparable to data from similar shelter-based studies highlighted in Chapter 3. In our study, age $\geq$ 50 years was defined as an elderly individual. An age of 50 or above, however, was not significantly associated with chronic liver disease. This could be partly explained by how the recruitment process took place in this study as it was phased, initially being limited to the elderly (defined as age 50 or above) and only being expanded later in the process to include all adults aged 18 or older. Similar to previous studies (Fazel et al., 2008, Nordentoft and Wandall-Holm, 2003), our cohort of homeless adults had a high prevalence of psychosocial comorbidities with almost two-thirds experiencing a mental health problem, and nearly half of them were on psychiatric medications. Mortality of homeless adults from liver disease is not fully investigated. In a recent report on deaths among homeless adults in England and Wales, diseases of the liver were the third cause, following accidents and suicides (Georgeson, 2018), accounting for 9%. In fact, those three causes of death constituted around 50% of all deaths of homeless people. This observation highlights the need for integrating services looking into

liver disease together with substance misuse and addiction. While we did combine substance misuse screening with our study-related liver screening service, interventions related to the former were challenging to implement. A more recent study by Aldridge et al. (2019) described a mortality rate from liver disease of 13%, which comes after death from cancer (18.2%). While a similar finding regarding cancer mortality among the homeless was recorded by a multi-centre analysis conducted by Henwood et al. (2015), their study showed that liver-mortality was considerably lower than the aforementioned studies, accounting for only 2%.

Moreover, the prevalence of substance misuse in our study was high, and nearly 70% were using one form of recreational drugs, but the prevalence of active drug injection reported by participants was 28%. A selection bias might have occurred due to referrals made by needle exchange services and spill over of cases from the project ITTREAT, which primarily addressed liver disease among substance misusers. On the other side, the figures presented in this study were based on self-reporting by participants, and therefore an underestimation may have occurred as participants may not have been willing to disclose the exact frequency and nature of their drug misuse habits. Where possible, cross-checking with available data from relevant GP and substance misuse services records was undertaken. The details of drugs or cocktail of drugs were not recorded in this study which may constitute a limitation. However, most of those reporting active drug use indicated that they were injecting daily or weekly, putting them at higher risk of contracting viral hepatitis and other BBVs. The validity of drug misuse data stemming from self-reports has been questioned previously and remains an area of debate. Morral (2000) revealed extensive underreporting of heroin and cocaine use in a sample of 701 methadone users and highlighted concerns regarding the validity of the treatment outcomes and needs assessment based on these inaccuracies. Data from the rough sleeping statistics in London (2017-2018) indicate that 43% had alcohol support needs and this figure has been consistent over the past few years (The Housing Statistical Release, 2019). A similar

proportion (40%) of this cohort required drug support while mental health problems were observed in half of the rough sleepers, which is comparable to the findings described in our study. However, it should be noted that only a small proportion of our study cohort were rough sleepers while the majority were in hostel-based accommodation.

The vast majority in our study were actively smoking at the time of recruitment; with non-smokers constituting less than 10% of the study population. This figure is comparable yet slightly lower than reports from other studies (Baggett and Rigotti, 2010, Baggett et al., 2013). Homeless adults reportedly smoke tobacco four times the general population (Baggett et al., 2013). Homeless smokers are also more likely to suffer from physical illness (Shelley et al., 2010). Furthermore, smoking-related cancer deaths among the homeless may reach as high as twice the rate observed among non-homeless people (Hwang et al., 1998). In Baggett and Rigotti (2010) study, among 28,000 homeless adults, the rates of deaths from lung cancer were significantly high, which may be linked to high prevalence of tobacco use. It should be noted that establishing an association between smoking and co-existing physical illness was beyond the scope of the VALID study.

Concomitant chronic illnesses may also have an impact on life expectancy. While other chronic infections such as TB have been reported in previous studies (Romero-Ortuno et al., 2012, Aldridge et al., 2018), the prevalence of TB and major comorbidities was relatively low in our cohort (Table 5.1) and did not influence the presence of clinically significant hepatic fibrosis or cirrhosis. A review by Medcalf and Russell (2014) indicated that the primary reasons for admission to hospital for homeless adults were alcohol and substance misuse related problems with other chronic illnesses and physical presentations being less common. Moreover, a recent study from Japan found that prevalence of non-communicable diseases (hypertension, impaired glucose intolerance and dyslipidemia) in PWAH was similar to the general population (Nishio et al., 2019). The latter finding may suggest that non-alcoholic fatty liver disease is unlikely to

be a major contributor to liver-related morbidity and mortality in PWAH. In a shelter-based convalescent centre from Amsterdam (van Laere et al., 2009), the primary physical illnesses among the 629 residents were skin disorders (37%) followed by respiratory problems (33%) and digestive disorders (24%). However, when they looked at the prevalence of chronic physical conditions, HIV/AIDS was found in 11%, while liver cirrhosis was evident in 5%. Furthermore, although both HIV and cirrhosis (together with malignancies) were independent predictors of mortality which was 13%, the authors did not discuss how co-existing chronic illnesses influenced liver disease. This area remains unexplored, and further studies may need to be done to elucidate any relationship between major comorbidity and progression of liver disease among PWAH.

Anthropometric assessment indicated that the population studied had relatively good nutritional parameters as evidenced by a normal BMI, mid-arm circumference > 23cm for males, >22 cm in females (Tsai et al., 2010a) and waist: hip ratio less than 1 (World Health Organisation, 2008). This is contrary to what would be expected in a population with high prevalence of homelessness. Nevertheless, most homeless individuals recruited in this study were living in hostels, as opposed to being in the streets (as rough sleepers), with relatively adequate access to hot meals and support from meal programmes. Results of the micronutrients levels showed some mild degree of micronutrient deficiency in a small proportion of participants. This was evidenced by below normal concentrations of any of phosphate, calcium, or magnesium. The majority did not require immediate intervention and their GPs were informed to repeat the test and/or provide replacement as required. Studies have previously demonstrated deficiencies of vitamin B1 and vitamin C, particularly in problematic alcohol drinkers (Ijaz et al., 2017) but serum vitamin levels were not checked as part of our VALID study. While education and provision of supplements in the form of vitamins are well-described interventions to address malnutrition among the homeless, in this study results were

communicated to their GP as nutritional education and counselling were not part of the study. The gaps in nutritional assessment represent an area for improvement, and future models screening for liver disease among homeless and vulnerable individuals should perhaps incorporate nutritional counselling and a clear referral pathway into the service.

7.2 Prevalence and predictors of CSHF in PWAH

CSHF was present in 26% of the study population as detected by liver stiffness measurement (LSM) using FibroScan. LSM has now been validated in most aetiologies of CLD as a non - invasive marker of hepatic fibrosis (Friedrich-Rust et al., 2008). In an observational study from Australia of PWAH, Bajis et al. (2019) found a prevalence of F2 (Metavir) fibrosis using FibroScan of 14%, whereas the prevalence of F3 and F4 was 5% and 14%, respectively. Similarly, Hodges et al. (2019) showed an F2 & F4 prevalence of 18 % and 16%, respectively. Hodges et al. (2019) used a model set up in a dedicated health care centre for homeless and vulnerable adults utilising integrated care approach. In our study, cirrhosis (i.e. LSM $\geq$ 13kPa) was observed in 17%, comparable to the studies mentioned above. Interestingly models based primarily in addiction centres had higher prevalence of clinically significant or advanced hepatic fibrosis. For instance, Crowley et al., 2017 showed that LSM >8.5kPa (significant fibrosis) was seen in 32.3% and LSM >12.5kPa (advanced fibrosis) in 20.3%. In our project ITTREAT based in a local substance misuse centre, 24% had cirrhosis though LSM cut-off values were lower (12 kPa) (O'Sullivan et al., 2020). In both ITTREAT and VALID studies, the FibroScan was performed in a non-fasting state. The general recommendation for transient elastography includes patients being fasted for 4 hours prior to the test as ingestion of food may increase the blood supply to the liver, and thus increase hepatic stiffness (Ferraioli, 2019). Finally, ongoing alcohol use can cause hepatic congestion and lead to falsely high LSM

readings (Patel and Sebastiani, 2020). Nonetheless, performing fasting FibroScans was not possible in our study, given that screening and enrolment were mostly opportunistic. Patients underwent FibroScan on the same day they attended and signed their consent and given the high prevalence of alcohol dependence it was not possible to ensure alcohol abstinence or at least reduction at the time of performing the FibroScan examination.

The mean ALT was 49 iu/L in this study. The predominantly normal LFTs among the study participants echo the findings discussed in Chapter 1 (Harman et al., 2015, Fracanzani et al., 2008), showing that most patients with raised liver stiffness measurement or biopsy-proven NASH tend to have normal LFTs and ALT. It concludes that liver enzymes should not be used for community screening for chronic liver disease, on their own.

In general, the development of clinically significant fibrosis and progression to cirrhosis among PWAH is not well explored, and more studies are required to further characterise the clinical predictors of fibrosis amongst this cohort. But in one study from the Boston Health Care for the Homeless Program looking into HCV infection among the homeless, 15.8% were found to have advanced fibrosis (Beiser et al., 2019). In multivariable regression analysis, alcohol use disorder and unstable housing were independently associated with advanced fibrosis. However, homelessness (defined as unstable housing), in this study, was not particularly associated with either significant fibrosis or cirrhosis. Additionally, this study only recruited patients with HCV, and therefore the prevalence of cirrhosis may not represent a true percentage among the overall homeless population.

In our study, independent predictors of CSHF were alcohol units/week and positive HCV RNA. While HCV is known to cause CLD in vulnerable adults, the role of alcohol often gets ignored. Alcohol units/week was an independent predictor of both CSHF and cirrhosis. This confirms the well-described role of alcohol consumption in the development of chronic liver disease

among vulnerable and homeless adults (Aisyah et al., 2018, Strehlow et al., 2012, Hodges et al., 2019).

Alcohol accelerates hepatic fibrosis in patients with chronic HCV and can favour decompensation of chronic liver disease, worsening the overall prognosis in these patients (Zarski et al., 2003). A Japanese study had previously documented a 1.5-2.5 increase in the risk of onset of cirrhosis and hepatocellular carcinoma (HCC) in patients with HCV-related liver disease who continue to drink moderately to heavily compared to those who were abstinent (Khan and Yatsuhashi, 2000). Another study revealed that those who have HCV and alcohol excess developed HCC at a younger age than those who have either risk factor alone (Yamada et al., 2011). Furthermore, the same study described that episodes of decompensation, including variceal bleeding, ascites and hepatic encephalopathy, were more likely to occur in HCV patients with active alcohol use. Likewise, one retrospective study of 6,354 patients concluded that the mortality rates of those with chronic HCV and alcohol dependence increased by two-fold compared to drinkers without HCV (Tsui et al., 2006). Another study by Singal et al. (2012) demonstrated that HCV was an independent predictor of mortality in patients admitted with alcoholic hepatitis.

This synergistic effect of alcohol and HCV on liver disease progression is believed to be due to the enhanced oxidative stress imposed by alcohol in HCV patients (Rigamonti et al., 2003). Additionally, the impact of alcohol consumption on HCV viral replication or HCV viral load is not fully clear (Gitto et al., 2014). These findings highlight the importance of addressing alcohol use disorders in homeless and vulnerable patients with HCV and raise the priority for early interventions to reduce harmful drinking in conjunction with HCV treatment. There is also a scarcity of studies attempting to address alcohol use disorder in patients with chronic HCV. A randomised trial by Proeschold-Bell et al. (2018) aims to compare the clinical effectiveness and cost-effectiveness of integrated alcohol treatment with “treatment as usual”

on alcohol consumption and economic outcomes among HCV patients, and we await the results with interest. At present, there are no conclusive reports to support a "safe limit" of alcohol consumption in individuals with HCV infection.

Alcohol use disorder is common among homeless individuals. In a large study from Boston between 2003 & 2008, alcohol-related mortality among homeless men and women was 6-10 times higher than housed individuals (Baggett et al., 2015). However, the role of alcohol as a risk factor for development of significant hepatic fibrosis is generally not well reported in the literature. As for the relationship with HCV, there is a need to determine the exact threshold of alcohol misuse behaviour that predicts the progression to clinically significant or advanced stages of fibrosis. Our study demonstrated that the alcohol AUDIT questionnaire was a useful and practical tool that could predict clinically significant hepatic fibrosis and cirrhosis in these individuals. We also showed that a cut-off value of 95 units of alcohol per week had high sensitivity and specificity for diagnosing cirrhosis in this cohort of vulnerable and homeless persons.

Positive HCV RNA was associated with CSHF on multivariate analysis but did not independently predict cirrhosis. One explanation for this is that HCV in this cohort contributes to the development of significant fibrosis. Still, the progression to cirrhosis is perhaps mainly driven by excess alcohol consumption which is the other major aetiological factor leading to CLD in this cohort. Another plausible explanation is likely related to the well-established evidence that, in subjects with chronic hepatitis C, progression to cirrhosis may take up to 40 years (Shiftman, 2014, Erman et al., 2019) with only one-third developing cirrhosis during the 20 to 30-year period after HCV acquisition (Lingala and Ghany, 2015). Moreover, a recent metanalysis showed an association between fibrosis progression and age at infection, duration, source, viral genotype and study population (Erman et al., 2019). It concluded that patients with an older infection age (42–45 years) demonstrated rapid progression relative to a younger

age (<30 years). In our study cohort, we could not establish the age of infection; but as this was a young cohort, we assume that most acquired the infection at a younger age.

The significantly higher mean waist/hip ratio in those with CSHF may indicate an element of NAFLD in this population. NAFLD among vulnerable adults is mainly linked to patients who suffer from mental health problems (Fuller et al., 2011). Recent data suggest a possible association between the use of various anti-psychotic medications and fatty liver development (Morlan-Coarasa et al., 2016). The high prevalence of mental health problems and more specifically, increased numbers of those who were actively receiving treatment at the time of recruitment could partly explain the involvement of fatty liver disease in the study cohort. However, we did not specifically perform a detailed assessment of medication use in our study.

Interestingly, the BMI did not appear to differ significantly between those with/without CSHF. We did not assess synergism between BMI and alcohol use, though previous studies have shown such an effect resulting in progression to cirrhosis (Bellentani et al., 2000). Moreover, almost half of the cohort with HCV in this study were genotype 3, which is associated with more pronounced steatosis compared to other genotypes (Adinolfi et al., 2013). Hepatic steatosis in patients with chronic HCV is in turn linked to the progression of liver fibrosis which adds to the multitude of the problem (Adinolfi et al., 2013).

7.3 High prevalence of chronic HCV among the study cohort

Two patients did not have full viral screening due to poor access and a small sample. Almost half of the study population had a positive hepatitis C antibody, which is slightly higher than the reported prevalence in some previous studies (Strehlow et al., 2012, Aisyah et al., 2018, Heaney et al., 2016). The high HCV seroprevalence can be explained by the high IDU prevalence and due to the nature of the study as it was anticipated that those who have concerns about their viral hepatitis status would more likely self-refer or be encouraged by their key workers to approach the service. This potential implication of referral or selection bias (Al-Hasan et al., 2011) should be recognised and considered when interpreting these observational findings pertaining to the prevalence of HCV amongst this cohort of vulnerable and homeless adults. There is also the potential effect of event-biased referrals, whereby participants would be referred for a specialist opinion when they have been observed to develop complications or thought to have advanced disease. The role of event-biased referrals in skewing data regarding HCV progression has been documented previously (Fu et al., 2007). It could not be entirely ascertained if infected individuals knew about their HCV infection as this was not addressed in the study. However, in a sample of 534 homeless adults from 41 shelters and meal programmes in Los Angeles, a high level of unawareness of hepatitis C status -described as "hidden" infection- was found with almost half of participants (46.1%) indicating lack of awareness of their infection (Gelberg et al., 2012). A qualitative study amongst PWAH who were injecting drugs found that a significant proportion was tested in an opportunistic manner without them actively seeking the test or being aware that a sample was taken for HCV serology (Grebely et al., 2014).

Despite that half of the population in our study had positive HCV antibody, only 37% (83% of those with positive antibody) were viraemic. Following acute HCV infection, up to 75% (Grebely et al., 2014) develops chronic HCV, which is consistent with our data. A recent study

showed that HCV clearance rate, defined as the proportion of infected persons who will spontaneously clear their infection after acute infection, ranged between 29.6 – 39.9% (Ayoub et al., 2018). We did not assess what proportion had prior HCV treatment but based on historical data and communication with GPs; this was likely to have been a negligible number.

Almost all participants in our study with chronic HCV had either genotype 1a or 3 infections. This is comparable to data on the distribution of HCV genotype among England's general population (Public Health England, 2020). In an early study by the Trent HCV Study Group (UK), the genotype of 304 infected HCV patients was 1 (47%), 2 (10%), 3 (39%), 4 (1%), and 5 (2%) (Mohsen and Trent HCV Study Group, 2001). Furthermore, a more recent estimate in 2012 indicated that in around 160,000 HCV infected patients in England, a significant majority (90%) had either genotype 1 or 3 (Public Health England, 2015a). However, this seems to be different compared to reports from outside the UK. For instance, in the USA, Barocas et al. (2017) reported that 79% of 64 homeless and marginally housed adults treated for HCV had genotype 1. Europe also appears to have a higher overall prevalence of genotype 1 than the UK but a lower prevalence of the latter than USA (Petruzziello et al., 2016). However, the distribution of HCV genotypes across the different regions in Europe is not homogenous as genotype 1 is lowest in Western Europe (55.1%) but highest in central Europe (70%) (Petruzziello et al., 2016). In general, there are at least 6 genotypes for HCV, and their prevalence depends on geographical distribution. Genotype 1 is generally the most prevalent worldwide. In contrast, genotype 4 is more prevalent in the Middle East and North Africa, particularly Egypt, comprising up to 80% of HCV infection in those regions (Yee et al., 2015). In our study, HCV genotype could not be established in a small number of patients (2, 4%) mainly because of low viral load. This phenomenon has also been reported previously (Saludes et al., 2019). HCV genotypes have a role primarily as epidemiologic markers and influence treatment choice, particularly in the new era of direct-acting antivirals (DAAs). In fact, HCV

genotype remains the most critical viral factor determining response to treatment, and hence the choice of DAAs regimens depends on the genotype (Yan and Wang, 2017). For instance, HCV genotype 3 has traditionally been considered the difficult to treat genotype with DAAs, although the SVR rates in genotype 2/3 are higher than the other genotype with IFN based therapy (Yan and Wang, 2017). The impact of HCV genotype on fibrosis progression remains controversial. In one study, HCV genotype 3 was associated with an increased risk of fibrosis progression (Bochud et al., 2009). It has also been shown that genotype 3 is associated with higher rates of HCC even after the achievement of SVR (El-Serag et al., 2016). This is relevant to our study cohort of vulnerable and homeless population in which genotype 3 was prevalent. The vast majority of those with genotype 1 in our study were genotype 1a. The latter has been linked to lower SVR rates than genotype 1b (Ara and Paul, 2015). In a large survey by Andriulli et al. (2015), patients with HCV genotype 1a were more likely to be younger, male, with a lower prevalence of advanced fibrosis or type 2 diabetes. Conversely, those with HCV genotype 1b were observed in a meta-analysis to be at higher risk of developing HCC (Raimondi et al., 2009).

Our study also explored factors associated with positive HCV RNA, independent predictors being current injecting and non-injecting drug use, mental health problems and CSHF. Additionally, we also found current smoking but lower alcohol AUDIT score to predict a positive HCV RNA. Prior studies have found alcohol use to be associated with higher HCV RNA levels (Peters and Terrault, 2002).

Independent predictors of HCV viraemia in our study were mostly consistent with other studies in vulnerable adults. HCV RNA prevalence among participants in a community homelessness centre with either injecting or incarceration history was 35%, relative to 4% in those without these risk factors (Bajis et al., 2019). History of imprisonment or incarceration was not formally assessed in our study, and therefore a link between this risk factor and HCV viremia could not

be ascertained. Other studies explored the relationship between clinical characteristics and HCV antibody instead of chronic HCV as defined by HCV viremia. In a sample of 387 participants from 8 dedicated healthcare centres for the homeless, Strehlow et al. (2012) showed that factors associated with HCV antibody positivity were injection drug use, imprisonment, and tattoos. Likewise, in Foucher et al. (2009) project, which was a street-based outreach service, factors associated with positive HCV serology by univariate analysis were age, IDU or cocaine use or alcohol use at inclusion, opioid replacement, housing, past history of imprisonment, elevated LSM value using FibroScan. These findings echo our results to a large extent as in our study HCV infection was also associated with clinically significant hepatic fibrosis. In addition, we also found that those patients who are actively using drugs other than injected ones had higher prevalence of chronic HCV. Although the details and routes of non-injection drug use were not explored in our study, there have been some suggestions in the literature that snorting cocaine and non-injection drug use being a potential factor for HCV acquisition (Scheinmann et al., 2007). Previous research indicates that HCV RNA is present in nasal secretions, and may be transmitted through equipment used for drug inhalation (Aaron et al., 2008). Nonetheless, evidence around this area remains inconsistent and inconclusive as some studies, on the other hand, demonstrated that snorting or smoking drugs were not significant risk factors for anti-HCV positivity among homeless (Hermanstyne et al., 2012).

Our study participants younger than 50 years old were more likely to have chronic HCV infection on univariate analysis. A more prevalent high-risk behaviour may explain this among younger vulnerable or homeless adults, but we did not explore the differences in substance misuse or behavioural factors between the younger and older groups. Those who drink heavily were more likely to have HCV, and indeed, the prevalence of hepatitis C was higher among those who were actively injecting drugs. This reflects that for those who have hepatitis C, management approach should be more holistic to reduce harm and risk of transmission by

addressing their drug injection habits and aiming for alcohol cessation to minimise the risk of progression of fibrosis to advanced stages. Furthermore, individuals with unstable housing were more likely to have chronic HCV. The same applied to current smokers and those with mental health problems who had a significant association with a positive HCV RNA. It is conceivable that a younger age increased the likelihood of high-risk behaviour.

A significant link between smoking and prevalence of positive HCV RNA was observed in our study. There appear to be similar concerns in the literature regarding smoking in individuals living with chronic HCV as the prevalence of smoking in people living with HCV was found to be up to 67% in one report, a figure that was thought to be even higher than in those with HIV (Shuter et al., 2017). Clearly, no direct causation between smoking and contracting HCV could be established, but it has been shown that chronic HCV increases susceptibility to tobacco-related diseases (Pessione et al., 2001). Moreover, smoking is reportedly associated with advanced liver fibrosis and progression to cirrhosis in people with HCV and hepatocellular carcinoma (Pessione et al., 2001, Chuang et al., 2010). This high percentage of smokers among homeless populations is relevant because, while HCV elimination is potentially achievable, this vulnerable group may still be left at risk of increased tobacco-related mortality and morbidity.

Moreover, compared to the general population, patients with chronic mental illness tend to have higher chronic HCV infection rates. Likewise, up to half of the patients with chronic HCV may have psychological problems (Rifai et al., 2010). More specifically, a hospital-based study from Japan displayed that rates of HCV are higher in patients suffering from schizophrenia (Nakamura et al., 2004). Similarly, a Swedish study confirmed that the risk of BBVs among patients experiencing severe mental illness is markedly elevated with odds of being HCV positive more than 6 times higher among this cohort of patients (Bauer-Staeb et al., 2017). This relationship is related to the increased prevalence of HCV risk factors among those with severe

mental illnesses, including drug injection and sharing of needles (O'Sullivan et al., 2020). However, more importantly, mental health problems may have a negative impact on compliance with therapy and engagement with the management process.

Additionally, some of the DAA treatment regimens used in treating HCV have significant and occasionally hazardous interaction with anti-psychotics and anti-depressants which often complicates treatments decisions (Roncero et al., 2018, Sockalingam et al., 2013). Prior IFN-based therapy was occasionally associated with severe neuropsychiatric side effects and new or worsening symptoms of depression. Nowadays, with the shift to DAAs that appear to have less neuropsychiatric side effects, the challenge remaining relates to avoiding psychotropic drug to drug interaction with the various DAA treatments. DAA regimens continue to evolve and are increasingly becoming safe to use in these scenarios. Despite the excellent safety profile of DAA, nevertheless, it is still crucial to address mental health problems among those with chronic HCV infection and pay particular attention to concomitant psychiatric medications. Again, as emphasised earlier, this endorses the need for integrated services in PWAH to address not just BBV but alcohol and substance use, mental health and housing.

7.3.1 Chronic HBV and HIV among the study cohort

In line with data from the UK (Martin et al., 2013, Health Protection Agency, 2011), the prevalence of a positive HBV serology was low in our study. In fact, none of the participants had chronic hepatitis B infection. The low HBV seroprevalence in PWAH is mainly due to the fact that HBV transmission through IDU is not as high as that for HCV. Chronic HBV infection is more likely to be prevalent among immigrants and refugees from African or Asian origin who encounter the infection mostly through vertical transmission at the time of, or shortly after, birth (Dusheiko, 2015). Our study cohort was predominantly Caucasian. In addition, according

to data from The Homeless Link Research Team (2018), only 14 hostels in the UK accepted refugees and asylum seekers, indicating that this population is a minority among those utilising hostel-based accommodation. While IDU is linked to chronic HBV development (Stein et al., 2012, Seal et al., 2000), the association is more evident in those who have other pre-existing risk factors such as black ethnicity and being born outside the host country. Such racial and immigration-related disparities appear to be independent of IDU (Shing et al., 2020). Interestingly, 21 (17%) of our participants had a past infection of hepatitis B, an observation which has been documented previously by Stein et al. (2012) and Haussig et al. (2018). More recently a large survey from USA among those with a history of IDU from 2001–2016, revealed that the anti-HBc positivity prevalence was 19.7% compared to 4.6% in the general population (Shing et al., 2020). Another survey from Germany by Haussig et al. (2018) found current HBV infection to be the case in 1.1%, while past HBV infection was found in 24%. The discrepancy in prevalence between active and past infection is an interesting one but could be partly explained by the high rates of spontaneous viral clearance after contracting HBV, compared to HCV with infections in adulthood leading, to chronic HBV in approximately <10 % of cases at times (Croagh and Lubel, 2014).

In our study, a considerable proportion had undetectable HBsAb or levels below 10IU/L (69/114, 61%) indicating insufficient immunity against hepatitis B. This was reported back to their GPs and the nurse in charge of vaccination where appropriate. However, longitudinal assessment of whether participants had engaged with their respective vaccination services was beyond the scope of this study. In Haussig et al. (2018) survey, the percentage of those who had vaccine-induced HBV antibodies was 32%. These findings support those vulnerable and homeless adults remain at risk of exposure to HBV infection. With the high prevalence of CSHF reported in our study population, vaccination against HBV might help mitigate their liver disease's further progression. Compliance of homeless adults with vaccination programme

is, however, another obstacle. Nyamathi et al. (2009) previously described that despite HBV vaccine availability; coverage has remained low among high-risk groups, including PWAH. In one study, compliance rates were as low as 28% for completion of HBV vaccination (Motta-Castro et al., 2009). Completion of vaccination following initiation of the vaccination process is another hurdle. In those with chronic HCV, Hernandez et al. (2009) reported that only 62% receiving the combined HAV/HBV vaccine completed the vaccination. Hence, this area warrants further exploration with qualitative studies looking at barriers to engagement and enrolment and cost-effective models of HBV vaccination strategies in these vulnerable groups. The same principles apply to hepatitis A vaccination for which similar recommendations exist (Alter, 2012). In the USA, Centre for Disease Control and Prevention and the Advisory Committee on Immunization Practices have recently recommended that all people experiencing homelessness should receive hepatitis A vaccination in addition to the Hepatitis B one (Doshani et al., 2019). Although HAV immunity was not checked in our VALID study cohort, in another study, 28.5% of participants with a history of IDU were found to have HAV antibodies, indicating that they had either naturally acquired and cleared the virus or had received the HAV vaccine (Shing et al., 2020).

HIV serology was positive in 3 patients (2.4%) in our study. All were already known to the HIV team, a reflection of the excellent HIV services locally. Nevertheless, a collaborative programme with the HIV team might constitute a good opportunity for integrated services and broadening of viral hepatitis screening and fibrosis assessment among homeless and at-risk populations. Our HIV seroprevalence is consistent with an earlier systematic review (Beijer et al., 2012). In Beijer et al.'s review, HIV seroprevalence varied widely between 0.3% and 21.1% (I^2>80%). While the review did not elaborate on the reasons behind this variability in prevalence, it recommended that local surveys should best guide service-planning and public health interventions. In an Iranian study by Doosti-Irani et al. (2017), HIV prevalence was

slightly higher at 6.5%; the risk factors were being single (vs. married), the use of hypnotics and temgesics and injecting drugs.

7.4 Better agreement between LSM values and ELF score in comparison to APRI among the study participants

A unique aspect of our study was the assessment of hepatic fibrosis using three various non-invasive tools in a community setting. In addition to liver stiffness measurement using FibroScan, APRI and ELF tests were performed representing indirect and direct biomarkers, respectively. Using APRI score, 17% were classified as having CSHF, which is lower than the percentage identified by TE. Unsurprisingly, therefore, kappa analysis showed poor agreement with LSM using TE for CSHF. The majority of those identified as having CSHF using APRI score had cirrhosis (15 out of 17) suggesting that APRI might be more accurate in detecting advanced fibrosis than early stages of fibrosis in this cohort. Although the use of indirect biomarkers such as FIB-4 and APRI is increasingly recognised in community screening as they are easy to obtain and need no sophisticated equipment or laboratory resources, only a small number of studies reported the application of indirect biomarkers in community screening for liver fibrosis among vulnerable and homeless populations. Beiser et al. (2019) used the FIB-4 index to stratify hepatic fibrosis among homeless adults recruited in a homeless community centre in Boston. They described a prevalence of F2-F3 of 15% while F4 was present in 18%. The proportion of patients identified as having cirrhosis is comparable to the percentage identified by APRI and FibroScan in our study. However, they did not perform any comparison with TE. In a further analysis by the same group (Beiser et al., 2020), they described a prevalence of advanced fibrosis of 15.8% using FIB-4 with independent predictors of the latter being AUD and unstable housing. In a hospital outpatient setting, Mendes et al. (2016)

compared the performance of APRI and TE in patients with HCV and highlighted that correlation between APRI and FibroScan for F≥2 was 100% and 84% for F≥3. In a sample of 109 patients with HCV, Gara et al. (2013) found that the degree of discordance between TE and APRI in diagnosing cirrhosis was 28%. Moreover, Alhankawi (2018) showed that in a cohort of 121 treatment-naïve chronic HBV and HCV monoinfected patients who underwent reference liver biopsy, APRI had intermediate accuracy in predicting significant fibrosis similar to the findings in our study. Additionally, the correlation between APRI and FibroScan score was significant with the correlation coefficient of r= 0.418 which is also comparable to the degree of correlation we demonstrated between LSM values and APRI score in our study. It is important to note; however, that our study demonstrated this correlation in a community-based setting involving a homogenous cohort of patients.

On the other hand, ELF test identified 26% of our cohort study as having CSHF, similar to the figure observed using TE. Among the study participants, the agreement of ELF with TE was better than that between the TE and APRI in relation to the detection of both CSHF and cirrhosis. ELF test has wide applications in all forms of CLD (Patel et al., 2020, Rosenberg et al., 2004). In our cohort of vulnerable and homeless adults, the aetiology for CLD was almost exclusively related to chronic HCV and alcohol excess. Hence, ELF test was an ideal direct biomarker to explore in this study. In one study by Thiele et al. (2018), in patients with ALD, ELF was more accurate in diagnosing patients with advanced liver fibrosis than indirect biomarker tests such as APRI, FIB-4, AST: ALT ratio and Age-platelet index. The study also concluded that, for patients in the community, ELF values below 10.5, had negative predictive values of 98% for detection of advanced fibrosis (Thiele et al., 2018). The cut-off used in this study is similar to the cut-off value we applied to diagnose cirrhosis in our study. Using the latter cut-off, only 11% of our study cohort were categorised as having cirrhosis and this

reflects the importance of selecting the optimum performance cut-off value that gives the best sensitivity of sensitivity.

In our study, we performed all tests simultaneously, as FibroScan was undertaken together in the same session with blood tests for both measurements of indirect biomarkers as well as ELF tests. To facilitate refining of screening pathways and to achieve cost-effective models, some recent studies prefer a sequential or tiered approach whereby serum biomarkers are checked first before calling patients for a FibroScan or vice versa (Heo et al., 2018). However, this was performed in a hospital cohort. One of the first studies to validate this stepwise approach was by Sebastiani (2009) combining APRI and Fibrotest-Fibrosure (SAFE: Sequential Algorithm for Fibrosis Evaluation) through which it was demonstrated that a significant percentage (50-80%) out of 2000 with chronic HCV avoided liver biopsy. In our study, liver biopsies were not performed, and therefore, comparison between APRI, ELF and TE against this "gold standard" was not possible. For this reason, while correlation and agreement analysis were undertaken between these three tests, the ability to compare the accuracy of each modality for the detection of hepatic fibrosis was limited.

7.5 Senescence markers and cytokine levels are raised in those with HCV and hepatic fibrosis in a community setting

Another unique aspect of this study was that we also explored the role of senescence markers in this cohort of vulnerable adults recruited in the community. Both CK-18 and MMP-2 were observed to be higher among patients with CSHF and cirrhosis, indicating that these biomarkers can be utilised for community screening. While CK-18 has been found to be elevated in various aetiologies of liver disorders, it has gained specific attention in patients with NAFLD. In particular, it is believed to distinguish between NAFLD and NASH (Chen et al.,

2007, Dyson et al., 2014). Elevated Serum level of CK-18 M30 has also been demonstrated previously in patients with chronic HCV (Jazwinski et al., 2012). Their study involving 267 treatment-naïve HCV patients and 100 health controls observed that the degree of fibrosis on liver biopsy correlated with serum level of CK-18. Moreover, the median serum level of CK-18 was higher in patients with chronic HCV compared with the controls. A similar finding was seen in our study, which demonstrated a significantly higher median level of CK-18 among patients with positive HCV RNA compared to those with negative HCV RNA. Despite that HCV is associated with steatosis, Jazwinski et al. (2012); could not establish a significant difference in CK-18 M30 levels between chronic HCV patients with or without steatosis. An Egyptian study (Abdel Haleem et al., 2013) revealed that CK-18-M30 was elevated and correlated significantly with the severity of inflammation and fibrosis stage on liver biopsy, serum ALT and viral load in chronic HCV patients. In our study, histological assessment was not undertaken, and the role of NAFLD in contributing to CLD among the vulnerable and homeless has not been investigated explicitly so the utility of CK-18 in relation to these aspects could not be established. While there were two patients with CSHF in our cohort who had no previous exposure to HCV or alcohol use disorder at the time of screening suggesting the possibility of NAFLD, the numbers are too small to draw any meaningful conclusions.

In contrast to other studies, patients with chronic HCV in our study did not have a statistically significant elevation of MMP-2 compared to non-viraemic patients. TIMP-1; however, was significantly raised in chronic HCV patients. Additionally, both TIMP-1 and MMP-2 levels were higher among those with CSHF and cirrhosis. MMPs, particularly MMP-2 and MMP7, have been associated with the development of fibrosis in patients with chronic HCV, and progression and regression of HCC (Lichtinghagen et al., 2001). Similarly, Walsh et al. (1999) demonstrated a rise in both TIMP-1 and TIMP-2 in HCV patients. MMP-1 has not been assessed in our study, but interestingly, in another report, it was found to be inversely

associated with severity of HCV infection (Murawaki et al., 1999). MMP-2 alongside MMP-8 and MMP-9 has also been demonstrated to be raised in ALD as discussed in Chapter 1. This is relevant to our study cohort in which alcohol is a major aetiological factor for the development of CLD. While disease-specific analysis was not performed in our current study, further research is necessary to assess whether MMP-2 and TIMP-1 are elevated equally in different aetiologies of liver disease (e.g., HCV and ALD). Furthermore, the correlation between senescence markers (MMP-2 and CK-18) and LSM values could be assessed with the view of determining the correct cut-off values of these biomarkers that could enable their use as community screening tests. Recent studies have identified that MMP-2 could attenuate hepatic fibrosis in patients with NAFLD and viral hepatitis (Geervliet and Bansal, 2020). This raises the exciting possibility of use of these biomarkers for longitudinal assessment of hepatic fibrosis.

Cytokine analysis was undertaken to examine the possible immunological mechanisms causing CLD in this cohort of patients. Many cytokine results had to be excluded from the analysis given that the levels were undetectable in most of the patients. This may be related to the assay's sensitivity; however, in previous studies, the sensitivity of measurement of pro-inflammatory cytokines using Meso Scale Discovery (MSD) -used in our analysis- was found to be satisfactory particularly in serum samples. Dabitao et al. (2011) compared the sensitivity of MSD to that of Becton Dickinson Cytometric Bead Array in a sample of patients with HIV and found that the former performed better for some cytokines. The multiplex technique is often criticised for requiring high sensitivity to allow detection of cytokines given the low concentration of samples used. Breen et al. (2011) checked the sensitivity of multiplex cytokine assays, including MSD across different sites in HIV samples. They demonstrated that the assays may vary in their ability to detect serum or plasma levels of cytokines which may jeopardise the reproducibility.

TNF and IFN-γ are pro-inflammatory cytokines produced primarily as part of the T-helper 1 (Th1) response and are known to mediate cytotoxicity and liver injury in the early stages of viral hepatitis (Laidlaw et al., 2017, Xia and Protzer, 2017). Unsurprisingly, both cytokines in our study were significantly increased in the sera of patients with CSHF and as well as HCV. TNF is considered a pleiotropic cytokine and is released by a variety of immune cells including cytotoxic T cells, natural killer cells, endothelial cells, dendritic cells, monocytes, and macrophages (Laidlaw et al., 2017). It is known to exert non-cytolytic antiviral effects and mediate antiviral activities by itself (Sun and Ran, 2004). The reports regarding IFN-γ in patients with chronic HCV appear somewhat conflicting. Kobayashi et al. (1998) showed a significant decrease in the number of IFN-γ-producing Th1 cells. However, Iwata et al. (1995) concluded that IFN-γ was elevated in HCV patients after stimulation with HCV core protein. Additionally, elevated IFN-γ levels were strongly associated with failure to respond to peg-interferon/ribavirin therapy (Lu et al., 2016). Both IFN-γ and TNF may inhibit viral replication in patients with chronic HCV and are also thought to be implicated in CD8+ cytotoxicity with previous reports describing a synergistic effect between the two (Laidlaw et al., 2017). Moreover, in chronic HCV, studies have shown that a correlation was present between IFN-γ and TNF production and progression of liver injury. While TNF was significantly higher in our cohort of HCV patients with positive PCR, IFN-γ did not have the same pattern. On the other hand, IFN-α which was not assessed in our study has been reported to have inhibitory effects on viral replication, and before the DAA era, it was the mainstay adjunct treatment for chronic HCV (Cheung et al., 2002).

TNF levels are also elevated in patients with ALD. In fact, in 260 patients with alcoholic hepatitis and 1180 with chronic HCV serum concentrations of TNF were found to be higher in the former (Neuman et al., 2015). They also described higher TNF levels in those with more advanced fibrosis similar to what we observed with CSHF. However, in our patients with

cirrhosis vs. no cirrhosis, TNF levels were similar. Studies have shown that there is a correlation between the production of proinflammatory cytokines in chronic HCV infection, such as IFN-γ and TNF, and progressive liver injury, while the regulatory cytokines such as IL-4 and IL-10 may modulate the pro-inflammatory immune response induced by the virus, allowing for milder and less severe consequences (Sun and Ran, 2004). Our study analysed IL-10, an anti-inflammatory cytokine that works by counterbalancing hyperactive immune response, thus protecting against excessive organ damage. IL-10 is produced by T-regulatory cells and Th17 and released by many cells in the liver such as hepatocytes, Kupffer cells, sinusoidal endothelial cells, hepatic stellate cells and lymphocytes. Together with IL-22, a Th17 cytokine, IL-10 is implicated in hindering hepatic fibrogenesis by preventing stellate cell activation, thus reducing collagen production (Hammerich and Tacke, 2014). In our study, serum concentrations of IL-10 were variable, being higher amongst the group with CSHF vs no CSHF but similar in those with cirrhosis vs no cirrhosis. A plausible explanation is that as IL-10 attenuates fibrosis, it is raised in the early-stage disease, but as the disease progresses its production is reduced leading to lower levels in advanced fibrosis.

IL-6 is another pro-inflammatory cytokine which is involved in numerous autoimmune conditions. It is secreted in the acute phase response to infection and tissue injury (Tanaka et al., 2014). Concerning liver disease, it is implicated in the process of hepatic regeneration; however, persistent elevation of its level may contribute to the development of HCC (Schmidt-Arras and Rose-John, 2016). In our study cohort, the serum level of IL-6 was significantly elevated in both subgroups of fibrosis (CSHF and cirrhosis). Interestingly, it was not significantly raised in patients with HCV viremia. These findings could indicate that in this cohort of patients, peripheral concentrations of IL-6 were raised primarily in relation to the process of fibrinogenesis and hepatic regeneration rather than in response to the transient acute inflammatory process caused by HCV. A review by Fallahi et al. (2012) demonstrated that, in

patients with HCV, IL-6 could be specifically related to a subgroup of patients with mixed cryoglobulinemia but did not discuss evidence of major involvement in the hepatic injury caused by HCV.

As illustrated in Chapter 1, the role of IL-17 in HCV infection is not as well established as is the case for chronic HBV infection. Chang et al. (2012) have indicated that Th17 cells circulating or infiltrating the liver were higher among patients with chronic HCV. Nevertheless, they did not establish a relationship between circulating levels of IL-17 and the progression of fibrosis. In our study cohort, despite the higher median peripheral serum levels of interleukin-17A in patients with CSHF, cirrhosis and HCV viremia, as well as the higher level of detectability in these subgroups, the results did not reach statistical significance. Nonetheless, after removing outliers, the difference in the median concentrations of IL-17 between those with and without cirrhosis (being higher in the former group) was significant. One interesting study looked into HCV patients undergoing liver transplantation and showed that patients with recurrence of HCV and significant graft fibrosis or cirrhosis had a higher level of IL-17 along with other pro-inflammatory mediators (Basha et al., 2011). A recent Egyptian study (Gomaa et al., 2019) showed that serum IL-17A was significantly elevated among HCV patients, and additionally, it demonstrated a positive correlation with ALT, viral load and fibrosis stage. IL-17F, on the other hand, was not significantly raised. In our study, both IL-17F and IL-17E were processed, but the concentrations were undetectable for most patients.

Plasma levels of IL-17 were also described to be dramatically raised in patients with ALD compared to those with chronic HCV, autoimmune liver disease or healthy controls in one study (Lemmers et al., 2009). Participants in our study had a higher prevalence of alcohol excess, but whether this has significantly influenced the findings can only be speculative at this stage as the disease-specific analysis was not performed.

While IL-22, a cytokine also secreted by Th17, is raised in both patients with HBV and HCV, it did not directly inhibit the viral replication (Pan et al., 2014). However, it does seem to promote the recruitment of inflammatory cells against the virus while exerting a protective effect against immune-mediated hepatic injury. In our cohort, IL-22 was raised in patients with HCV. It is to be noted that, in patients with chronic HCV, IL-22 has been previously shown to be associated with protection against progression of fibrosis and development of portal hypertension (Pan et al., 2014). The raised IL-22 may signify that a continuous process of degradation and remodelling mediated by Th17 is taking place.

7.6 High compliance and SVR rates among those who initiated HCV treatment

The number of patients in this study who received HCV treatment during the study period was 29, representing about 60% of the whole cohort with a positive HCV RNA (n=49). All patients were treated using DAAs. A considerable proportion was drinking alcohol dependent or actively injecting drugs at the initial assessment time (Table 5.9). However, ongoing alcohol use and IDU did not preclude HCV treatment if the patients were willing to engage.

Our ITT SVR rates of 83% and treatment completion rates of 93% are consistent with a recent meta-analysis in PWID (Graf et al., 2020) that reported treatment completion rates of ~97% with SVR amongst those on opioid substitution treatment and recent IDU/non-injecting use being 90.7% (95% CI 88·5-93·0) and 87.7% (95% CI 84.2%-91.3%) respectively. In fact, most recent guidelines recommend that PWID should be a high priority for HCV treatment both on an individual level and also to prevent onwards viral transmission (treatment as prevention strategy) (Grebely et al., 2015, Grebely et al., 2017a). The ITT SVR among the treated

subgroup of our study cohort is also similar to the SVR rates discussed in the systematic review in Chapter 3 which showed that of 750 treated, 636 achieved SVR (85%).

Active IDU has been associated with a lower SVR. In the ITTREAT study, the lowest SVR was seen in those with current IDU (79%). This is also consistent with the Iceland TRAP C study (SVR 82%), where even after accounting for the high (15%) dropouts, SVR was lower in those with IDU vs no IDU in last six months (89.9% vs 95.3%) (Olafsson et al., 2018). The Iceland TRAP C study also reported homelessness to be associated with a higher chance of persistent viraemia at > 12 weeks post-treatment [RR, 2.42 (95%CI 1.34-4.37), p = 0.007], with residence in a halfway house associated with lower risk (RR 0.37, 95% CI 0.12-1.16, p = 0.068) (Olafsson et al., 2018). Active IDU and homelessness should; however, not deter health care professionals from offering HCV treatment. Mathematical modelling suggests that with an 18-fold increase in HCV treatment (54/1000 PWID/ year), and assuming a 90% SVR, HCV seroprevalence can be reduced by 75% (to <15% within 15 years). An 80% SVR will only reduce impact by 12%-15%, still adequate for treatment as prevention strategy (Martin et al., 2013).

While HCV reinfection remains a concern in those with ongoing IDU, in a recent study, reinfection amongst recent and former PWIDs was 3.1/100 PYs (95% CI 1.9-23.5) and 1.4/100 PYs (95% CI 1.1-12.9) respectively, with only one individual receiving daily OST developing reinfection (Rossi et al., 2018). These data emphasise the need for integrated services offering HCV treatment in conjunction with harm reduction/OST and addressing housing needs. Additionally, if the DAA treatment is rapidly scaled-up amongst patients actively injecting drugs and PWAH to overcome the rates of infection then it is anticipated that re-infection rates will eventually decrease.

The integrated model and the close yet personalised monitoring of patients in this study were the key to the success of the HCV treatment. In Brighton, we had the unique advantage of home delivery of DAAs. Hostel workers and social workers were important facilitators in this model as they ensured the delivery of DAAs to the hostel and if required, also helped with directly observed treatment. This allowed for better engagement and compliance rates.

CHAPTER 8: Conclusions on the VALID study model

The VALID study demonstrated that a community hostel-based model could improve the overall linkage of care of PWAH with hepatology services. In this cohort with a high prevalence of HCV, AUD was an independent predictor of both CSHF and cirrhosis. Adding to this the high prevalence of IDU in this cohort, these findings necessitate the development of integrated services based in homeless hostels with the active engagement of hostel workers and other key workers. Moreover, as the VALID study model is easy to replicate, it has the potential of being adopted at a national level.

8.1 Strengths of the VALID study model

It is essential to underscore that collaboration with hostel managers and social workers was key to the success of this model of care for vulnerable and homeless adults. These workers facilitated the recruitment and follow-up of patients and their engagement with treatment resulting in excellent overall compliance rates. AH worked closely with hostel workers and often attended the local joint hostel managers meetings to promote the service and address any shortfalls or needs to improve the recruitment. Although the initial VALID model was designed to adopt a passive approach by holding a walk-in service in a fixed clinic, hostel workers' involvement in the recruitment process ultimately resulted in an active case finding model, hence improving the overall acceptance of the service.

While some community services for PWAH screen patients in primary care practices or substance misuse centres, this hostel-based model provided a near-patient service with easier

access for homeless people to be assessed and treated for liver disease. Another advantage of the VALID study is that it offered an integrated and multidisciplinary 'single stop' service where patients had all the screening and clinical assessment components in a single appointment at one site to minimize the number of visits required. The use of FibroScan was seen as a powerful screening tool facilitating the engagement with the service as it provided the clients with immediate results. Additionally, the objective nature of the LSM results given to the patients as a figure made it easier for them to understand the degree of liver fibrosis and allowed direct discussion regarding the risk of liver disease progression. The impact of the advice given, following the diagnosis of CSHF and cirrhosis, on alcohol reduction has not been assessed in this study. Nevertheless, a recent study (Matthews et al., 2019) demonstrated that a nurse-led clinic utilising FibroScan has the potential of encouraging heavy drinkers from socially deprived populations to engage with liver services.

Although the clinic dates and times were fixed, we offered flexibility in the appointments and often ad hoc clinic sessions were delivered to ensure the appointments suited the targeted group's erratic lifestyle. The research team also liaised with other teams providing care to homeless and vulnerable individuals in the community, such as needles exchange services and other viral hepatitis screening care points at the substance misuse service. This coordination ensured that patients could be approached and contacted at multiple care points avoiding loss to follow-up. The excellent communication within this larger community team ensured that eligible homeless and vulnerable adults were aware of this newly established VALID clinic as well as the other support services available to them in the community.

A good community screening model should guarantee that an effective intervention is made available once the disease is detected. An advantage of our VALID hostel-based service was the availability of the immediate intervention in terms of DAAs treatment for those who receive a diagnosis of HCV. The team used Glenwood lodge hostel as a delivery point for DAAs, and

the hostel managers frequently facilitated the collection of medications by the clients and raised concerns to the team when the medications were not delivered or not collected by the patients. This, in turn, allowed monitoring of compliance on a regular basis.

To our knowledge, this is the first community screening service for PWAH which utilised, in addition to TE, multiple serum biomarkers for screening of hepatic fibrosis including direct (ELF test) and indirect (APRI score) serum biomarkers in addition to senescence markers.

8.2 Limitations and potential areas for improvement

The model we delivered did not come without limitations and challenges. We identified several areas for further improvement and refining of the model both in terms of developing the service and data analysis:

- The service was confined to the homeless and vulnerable adults registered with only two GPs in Brighton, and this limited the number of patients who were able to participate in the study.

- The study was initially confined to elderly patients aged 50 or above and was only extended to include all adults above the age of 18 years a couple of years later, following further amendments and ethical approval.

- Screening and enrolment took place predominantly in one or two sites. Individuals living in hostels other than Glenwood lodge had to visit the latter hostel in order to be screened. Therefore, providing a semi-mobile service by holding clinics in different hostels may lead to higher recruitment rates and will make the service more readily available for a larger population. This limiting factor together with the initial restrictions on age at enrolment (explained above) could have contributed to the recruitment of less than 50% of the intended sample size detailed in Chapter 4.

- While the team made contacts with all relevant stakeholders to ensure they are aware of the service, most cases recruited were a result of active case finding by the hostel workers or direct referral by the clients' key workers. Direct involvement of other groups such as rough sleeping and homeless community teams that cater for homeless people in the planning of future services will enable formal endorsement by these services and favour more referrals and increased recruitment rates.

- Participants were more likely to refer themselves or be referred by their key workers if there was a high suspicion or prior history of HCV and hence this may have contributed to a falsely high seroprevalence of HCV. Treatment of HCV was also restricted by the number allocated to our ODN, limiting the number of participants who could benefit from timely intervention.

- One other limitation of our work was that additional direct correlation analysis between the various pro-inflammatory cytokines and senescence markers was not performed. Additionally, the absence of a gold standard, such as liver biopsy, did not facilitate undertaking an accurate comparison or correlation analysis, and limited our ability to validate the performance of each non-invasive modality for screening for liver fibrosis on its own.

- The MSD Th17 cytokine panel yielded a high percentage of undetectable cytokine concentrations which made the statistical analysis challenging, and there were also numerous outliers identified in the cytokine results. This may have undermined the association between cytokines levels and hepatic fibrosis, particularly for the IL-17 panel.

- Longitudinal assessment has not been undertaken both in terms of clinical and laboratory data. Further studies should aim to explore the incidence and factors associated with regression in fibrosis using the same non-invasive tools following alcohol cessation and HCV cure. Moreover, temporal changes in cytokine levels might yield better understanding of their role

in HCV infection and hepatic fibrosis than a single point of time measurement of concentrations.

- Further work should involve a qualitative analysis component exploring the acceptance and satisfaction levels of the study participants and hostel workers and to establish potential ways for expansion and replication of the model at national level.

8.3 Future considerations

The VALID model, which promotes the provision of services in sites visited by PWAH, is feasible and can be easily reproduced and adopted at both the regional and national levels. This can be achieved by expanding the model in multiple domains encompassing the recruitment process, services provided, geographical coverage, project outcomes and stakeholders involved. This expansion will help NHS England achieve its targets for eliminating HCV and address the needs of a hard-to-reach population.

In our model, the service was limited to patients registered at two GP surgeries in Brighton. Further development in the service requires the involvement of more geographically spread general practices and recruitment of homeless individuals in multiple hostels. To facilitate this at the local level, a semi-mobile service could be implemented whereby the recruiting team visits various hostels, each representing a geographical catchment area, using a mobile FibroScan. This approach is achievable nowadays given the introduction of the smaller and easy to carry around models of the FibroScan. Hostel workers should also be incentivised for coordinating and supporting such community liver services. The official endorsement of their contribution will enable more efficient recruitment of vulnerable individuals. Identification of general practices catering for homeless individuals at the national level is also crucial as

primary physicians running these services are pivotal to expanding the model. These general practices should be carefully selected based on agreements with the HCV ODNs covering the respective regions, thus facilitating the process of HCV treatment. The selection should also be based on the number and density of the affiliated homeless hostels these general practices cover.

The same hostel-based concept can be applied across England's various regions and localities with standardised outcomes and objectives. Non-clinical parameters should be incorporated, such as health economic, cost-effectiveness and qualitative measures in the form of patient-reported outcomes. The latter will necessitate contribution from expertise and specialists in qualitative research and health economics. The addition of health economics and patient-reported outcomes will allow estimation of how the interventions influence the screening and treatment uptake and the exploration of the acceptability and barriers to the interventions, respectively.

The scope of the clinical outcomes should also be widened to incorporate longitudinal data regarding regression of fibrosis (using sequential measurements of liver stiffness and serum biomarkers) and behavioural changes related to alcohol and substance use disorders. Alcohol reduction strategies could be integrated explicitly into the model by involving addiction specialists as part of a comprehensive multidisciplinary team running the service and by implementing validated interventions ranging from standardised advice to brief motivational interviews and referral to specialist addiction units. This is particularly relevant given the synergism between HCV and alcohol among homeless populations and outcomes of our VALID study and the systematic review in Chapter 3 confirming this vital observation.

To achieve sustainability in providing such an integrated care model, community nurses should coordinate the service, delivering effective care as part of a multidisciplinary team after

undertaking appropriate training. Data from our ITTREAT study as well as HepCATT study support this strategy and show that personalised care facilitated by a nurse provider improve overall engagement of vulnerable adults with liver services and HCV treatment (Phillips et al., 2020, Horwood et al., 2020). These findings culminated in a business case for a community nurse being devised and adopted by the HCV Trust and the British Viral Hepatitis Group.

Ultimately the goal of such national model is to achieve better outcomes in liver health among the homeless. Hence, a systematic methodology needs to be adopted to validate the success of the proposed national model from that perspective. A pre and post-intervention data collection is one strategy that could assess the usefulness of the model and requires determining baseline data before introducing the hostel-based service and then collecting similar data a few years later. The model can also be carried out in a cluster randomised trial that allows randomisation of groups or clusters of homeless individuals based on geographical location or the hostels covered by a specific GP practice. Cluster randomised trials have been utilised with success, specifically in community-based interventions (Hemming et al., 2015, Lorenz et al., 2018). The approach in this model could be achieved through the parallel group or the stepped wedge designs (Hemming et al., 2015). The latter design is preferable if sequential roll-out is planned as not all recruitment centres would be anticipated to initiate screening simultaneously.

The services provided in the national model should aim to be proactive and holistic and should involve social workers handling housing applications simultaneously since “housing first” may potentially yield better engagement and compliance with HCV treatment. Once the model is established, it could be combined with other health screening programmes targeting homeless individuals, such as HIV and TB screening and vaccination campaigns which will promote recruitment through cross-referrals between the various services. This is particularly relevant nowadays, given the coronavirus disease 2019 (COVID-19) situation and the concomitant

vaccination programme. During the COVID-19 first wave in the UK, the government introduced the “Everyone In” and COVID-PROTECT initiatives in March 2020, facilitating the temporary housing of rough sleepers and homeless individuals in unsuitable sheltered accommodation who were unable to self-isolate (Kirby, 2020). This move has been linked to the low rates of mortality from COVID-19 among homeless in the UK in the first wave as only 16 homeless adults were reported to have died of the disease by July 2020 (Office for National Statistics, 2020). Moreover, housing of homeless adults during the COVID-19 resulted in improved collaborative efforts between homeless GP practices and local authorities enabling the provision of outreach screening for physical and mental problems among this group. An interesting finding was that the number of homeless adults helped through emergency accommodation in hotels or private rented homes by the end of November 2020 was over 33,000; a figure that is significantly higher than that officially reported by the government (National Audit Office, 2021). The finding indicates that the ‘Everyone In’ initiative has exposed ‘hidden homelessness’ and defined the gaps between the official figures and actual numbers, thus laying the foundation for expanding the government plans to tackle rough sleeping and homelessness.

The proposed national liver screening service for the homeless can be incorporated into housing initiatives such as the “Everyone in” as they create a great window of opportunity for engagement with such a cohort and enhance the cooperation between multi-agencies. Such integration necessitates liaising directly with organised healthcare networks, voluntary sectors, non-commissioned organisations and GP practices covering these hotels and temporary accommodations. Additionally, funding is required to ensure appropriate social distancing measures and sufficient supply of personal protective equipment during the screening visits.

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APPENDICES

Appendix 1: Publications, presentations and awards

Publications

- Hashim, A., O'Sullivan, M., Williams, H. and Verma, S. (2017). Developing a community HCV service: project ITTREAT (integrated community-based test – stage – TREAT) service for people who inject drugs. *Primary Health Care Research & Development*, pp.1-11.

- Hashim, A. and Verma, S. (2017). A Dedicated Hostel-based Liver Service for Vulnerable/Homeless Adults: Response to: Needs Assessment of HCV-Infected Individuals Experiencing Homelessness and Implications. *Journal of Health Care for the Poor and Underserved*, 28(4), p.xi-xii.

- Hashim A,Macken L, Mcgeer M, Aithal GP, Verma S (2020). Community Models For Detection And Treatment of Hepatitis C Virus and Liver Disease Amongst People Who Are Homeless: A Systematic Review **(Submitted)**

- Hashim A, Bremner S, Grove J, Astbury S, Mengozzi M, O'Sullivan M, Macken L, Worthley T, Aithal GP, Verma S (2020). Clinical and Laboratory Outcomes from a Homeless-Hostel Based Liver Service for Vulnerable Adults: The VALID Study **(Awaiting submission)**

Presentations & abstracts

Nov 2019	Significant association of fibrosis and hepatocyte senescence biomarkers and cytokine profile with liver stiffness measurement amongst homeless individuals

	with liver disease in the community. AASLD, Boston, USA
Apr 2018	VALID study. RCP Quincentennial lecture. Update in Medicine, Brighton
Oct 2017	A dedicated hostel-based community liver service for Homeless and Vulnerable Adults: VALID (Vulnerable Adults LIver Disease) Study The liver meeting, AASLD, Washington, USA
June 2018	A dedicated hostel-based community liver service for Homeless and Vulnerable Adults: VALID (Vulnerable Adults LIver Disease) Study BSG annual meeting, oral presentation.
April 2017	Enhancing detection & treatment of chronic Hepatitis C virus in vulnerable (homeless) adults through dedicated community liver clinics. Amsterdam, Netherlands (EASL)
Sep 2016	Enhancing detection & treatment of chronic Hepatitis C virus in vulnerable (homeless) adults through dedicated community liver clinics. Paris, France (EASL HCV monothematic conference)
Sep 2016	A community liver service for the vulnerable homeless people: preliminary results of VALID (Vulnerable Adults LIver Disease) Study BASL annual meeting, Manchester

Awards related to PhD work/VALID study

- British Association for the Study of the Liver (BASL) commendation for top ranked abstracts (2016) – VALID study.
- Young Investigator Bursary – Monothematic special conference on HCV. European Association for the Study of the Liver (EASL), Paris (2016) – VALID study.
- Prize for best oral presentation. Internal Medicine and Research Audit Day (2016) – VALID study.
- VALID study ranked as finalist at the Roadmap to Sustainable Healthcare conference – Patients as partners (2016).
- Finalist – Royal College of Physicians Excellence in Patient care awards – VALID study (2017).
- Best poster presentation prize – British Society of Gastroenterology regional meeting 17/3/17, VALID study.
- British Association for the Study of the Liver (BASL) Travel Award – Sep 2017 – VALID study.
- Med Chi Society Travel Award. Brighton (June 2017). Support for attending the BSG meeting.
- RSM Wesleyan trainee of the year poster prize winner – VALID study 23/11/17.
- RCP Quincentennial lecture winner (London and South East/KSS) – VALID study, April 2018.

Appendix 2: VALID study research samples processing and storage protocol

This protocol was written by Matthew Pope and reviewed by Dominika Wlazly from the Clinical Investigation & Research Unit (CIRU) at the Royal Sussex County Hospital in Brighton.

1.0 Tests taken on storage blood samples

Serum samples	*EDTA Plasma Samples*	*EDTA WB Samples*	*NaHep Samples*
Biochemistry analysis	Cytokine analysis	Genetic Analysis	PBMC isolation
			Functional T-Cell Analysis

2.0 Sample Collection Instructions CIRU SAMPLES

2.1 Samples collection Kits

There are two separate collection kits to be created for the VALD study to be taken at each sampling visit.

Kit A is to be collected for research blood for storage and sent to CIRU, The Kit will contain pre labelled collection tubes and a request form.

Kit B is to be collected for research blood for PBMC separation and Function T-Cell analysis and sent to MRB at Sussex University, The Kit will contain pre labelled collection tubes and a request form. Template request form can be found in Appendix 2

2.2 Serum Samples

Conduct venepuncture according to local procedure and policy

Draw Serum samples first.
Serum samples are collected into 2x 5ml gold top vacuette, Serum Separator tube (SST) with clot activators

Draw the full 5ml into each of the 2 vacuettes where possible, using butterfly needle and vacutainer holder set, using the vacuum in the tube. N.B DO NOT remove the top from the tube as this will break the vacuum and render the tube useless.

After collection return collection to the collection kit and keep upright as much as possible.

Collection Tubes should be labelled with STUDY ID, INITIALS, DATE and TIME of DRAW, on the labels provided on the tube.

VALD*COLLECTION*

Here

SST Serum 5ml

Stick

Complete appropriate request form in the sample collection kit with contemporaneous data relating to the samples. Use the comments section to document and extraneous information relating to sample condition.

Templates of request forms are shown in Appendix 3

When all sampling is complete send sample to CIRU lab for processing

2.3 EDTA Plasma sample.
Conduct venepuncture according to local procedure and policy

Draw EDTA Plasma Samples second

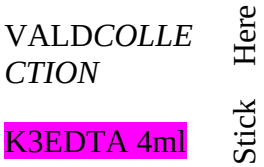
EDTA Plasma Samples are collected into 3x4ml purple top vacuette, K3EDTA Plasma tube

Draw the full 4ml of blood where possible into the 4ml EDTA tube using a butterfly needle and vacutainer holder set, using the vacuum in the tube. N.B DO NOT remove the top from the tube as this will break the vacuum and render the tube useless.

Gently invert the tube 5-6times to mix the blood with the anticoagulant.

After Mixing return the tube to the collection kit.

Collection Tubes should be labelled with STUDY ID, INITIALS, DATE and TIME of DRAW, on the labels provided on the tube.



Complete appropriate request form in the sample collection kit with contemporaneous data relating to the samples. Use the comments section to document and extraneous information relating to sample condition.

Templates of request forms are shown in Appendix 3

When all sampling is complete send complete sample kit to CIRU lab for processing

2.4 NaHep PBMC samples – MRB

Conduct venepuncture according to local procedure and policy

Draw NaHep PBMC Samples last

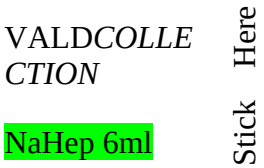
NaHep PBMC Samples are collected into 4x6ml green top vacuette, NH (sodium heparin) Plasma tube

Draw the full 6ml of blood where possible into the 6ml NaHe tube using a butterfly needle and vacutainer holder set, using the vacuum in the tube. N.B DO NOT remove the top from the tube as this will break the vacuum and render the tube useless.

Gently invert the tube 5-6times to mix the blood with the anticoagulant.

After Mixing return the tube to the collection kit.

Collection Tubes should be labelled with STUDY ID, INITIALS, DATE and TIME of DRAW, on the labels provided on the tube.



Complete appropriate request form in the sample collection kit with contemporaneous data relating to the samples. Use the comments section to document and extraneous information relating to sample condition.

Templates of request forms are shown in Appendix 3

When all sampling is complete send complete sample kit to MRB Research Technician for processing

3.0 Sample processing Instructions CIRU SAMPLES

3.1 Processing Serum Samples

The lab should receive 2x 5ml SST gold top serum separator tube.

Samples are required to be processed and frozen within 4 hours of collection

Samples should be allowed to clot at room temperature for a minimum of 30mins maximum of 2hrs before centrifugation.

After samples have clotted; centrifuge at 1500g / 3500rpm for 15mins at room temperature

After centrifugation, using a non-sterile pasture pipette, transfer approximately 1ml (or more if available) of serum each, into 4x2ml non-sterile cryovials

Discard collection tube

Cryovials should be labelled with FreezerPro Labels please refer to sample labelling section 7.0

After processing transfer samples to VALD freezer box in the -80 freezer.

Document samples on sample log in the VALD Study laboratory folder.

3.2 Processing Plasma EDTA samples and cell pellet

The lab should receive 3x 4ml EDTA purple top Plasma tube.

Samples are required to be processed and frozen within 4 hours of collection

Centrifuge 2x 4ml EDTA tubes at 1500g / 3500rpm for 15mins at room temperature and reserve 1x4ml EDTA tube for aliquoting as Whole Blood

From 1 x 4ml EDTA Tube aliquot 2x2ml Cryovial with 1.5-1.8ml ml of Whole blood.

After centrifugation, using a non-sterile pasture pipette transfer approximately 1ml (or more if available) of plasma each, into 4x2ml non-sterile cryovials.

Discard collection tubes

Cryovials should be labelled with FreezerPro Labels please refer to sample labelling section 7.0

After processing transfer samples to VALD freezer box in the -80 freezer.

Document samples on sample log in the VALD Study laboratory folder.

4.0 Sample processing Instructions MRB

4.1 Processing NaHep PBMC Samples

Samples should be processed as per MRB FK lab PBMC processing protocol and MRB VALD t-cell activation protocol (Appendix 6 and Appendix 7)

Storage Cryovials should be labelled with FreezerPro Labels please refer to sample labelling section 7.0

After processing transfer samples to VALD freezer box in the -80 freezer.

Document samples on sample log in the VALD Study laboratory folder MRB.

5.0 Sample labelling

Storage cryovials should be labelled using Freezer Pro Labels that are produced by entering the samples onto the tissue tracking software.

Please refer to Appendix 3 for quick reference sheet for entering the VALD study samples onto Freezer Pro.

6.0 Sample Logs

The central sample log form should have an entry completed for each instance of samples being received into CIRU lab. There is a separate

The log form acts as a confirmation of the samples received and processed by CIRU lab.

The page number should be documented when each new sheet is added to the sample log.

Shipping dates and information should be completed at the bottom of the form, when the samples leave the custodianship of CIRU lab freezers at RSCH site.

The template for the sample logs is located in Appendix 4 and Appendix 5

7.0 Shipping Samples

The end of the study from a CIRU lab perspective will be defined as when the last of the 80 patient target recruitment study storage samples has been collected.

Shipping intervals will occur every 6 months or when every 4th box of (400) samples is collected. Samples shall be transferred up to Sussex University Site CIRU Archive Freezer.

Transfer of samples shall be done, by the CIRU Lab Technical Manager, at -80^{o}C using either -80^{o}C ice packs or Dry Ice as available. Transfer is done same day and samples spend less than 4 hours out of the freezer “on ice”.

The samples remain on Freezer Pro Tissue tracking software, under and different location in the CIRU ARCHIVE FREEZER until they are destroyed as part of their analysis.