COLLEGE OF MEDICINE AND HEALTH SCIENCES

SCHOOL OF PUBLIC HEALTH

CLINICAL AND SOCIAL DETERMINANTS OF LIVER FIBROSIS AMONG HEPATITIS C VIRUS INFECTED PATIENTS IN RWANDA

A dissertation submitted in partial fulfillment of the requirements for the degree of

MASTER OF PUBLIC HEALTH

By

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DEDICATION

This piece of work is dedicated to:

To God the Almighty,

To my Beloved Parents,

To my Brothers and sisters,

To my Friends and Relatives,

To my classmates and SPH

lectures

To my Supervisor.

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This dissertation for the award of a Master's degree would not have been successful if there were no joint efforts in terms of moral support and guidance from various persons to whom I am addressing my heartfelt recognition.

I would like to extend my sincere gratitude and genuine appreciation to God, the Almighty for abundant blessings, guidance and protection to keep me alive and unconditional love during my work and studies.

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Last but not least, my sincere thanks go to all my colleagues, friends and relatives for their support and being by my side throughout my life.

I say, "May our Almighty God bless you.

Edith KAMPETA

ABSTRACT

Background: Liver fibrosis prevalence is poorly understood in the Rwandan context, it is of much importance to know the staging of liver fibrosis in Hepatitis C Virus infected patients. Biopsy is the gold standard to assess liver fibrosis but very expensive and can‟t be accessed everywhere, this makes Non-invasive methods, Aspartate to Platelet Ratio Index score included to be very useful in assessing that, thus hindering the severity of fibrosis that leads to cirrhosis and finally to liver cancer.

Methods: This is a descriptive analytical cross-sectional study of secondary data from Simplifying Hepatitis C Antiviral therapy in Rwanda for Elsewhere in the Developing world (SHARED) study that was done in 2016 at Rwanda Military Hospital (RMH). Our aim is to determine the prevalence of Liver fibrosis among HCV infected participants and we used results of serum biomarkers that were tested in the laboratory to determine liver fibrosis.

Results: The prevalence of liver fibrosis in our study population as calculated using the APRI score is 15.8%. Socio-demographic statistics indicate that the mean age of our study population was 61.8±14.1 and most of our participants were female with a proportion of 62%. The majority of the study participants had primary education (45.5%) followed by secondary education at 25.9% and 16.5% had no education at all. Eighty-two percent of the study participants were of low socio-economic status (SES) 16.1% were of middle income and only 1.7% was regarded as of high SES. 63.4% of the study population were jobless whereas 16% had paid jobs (Table1). In our study population 14.2% were alcohol consumers whereas 85.8% were not, 57.2% had 0-1 sex partners, 26.6% had 2-4 sex partners, 5-10 and ≥11 sex partners had 8.1%. More than a half of the participants (50.8%) are of normal weight (BMI between 18.5 and 24.9) and 42.8% are under weight (BMI less than 18.5). It is noteworthy that only 1.7% was obese and 4.8% were overweight. The HIV prevalence in our study population is 9.1% and most laboratory tests showed that most individuals had normal test results except for GGT (9–48U/L). (Table2)

Discussion and conclusion: HCV infection is one of the main causes of liver fibrosis, the prevalence of liver fibrosis in Rwanda is poorly understood, this study is among those that can contribute to our understanding of liver fibrosis among HCV infected individuals. APRI score would be of much preference to be used in the Rwandan context to assess the development of liver fibrosis.

Key words: HCV, Acute HCV, Chronic HCV, Liver fibrosis, HCV Ab, Hepatocellular carcinoma, APRI score, SHARED study,

LIST OF ACRONYMS

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APRI	Aspartate to platelet ratio index
AST	Aspartate aminotransferase
BMI	Body Mass Index
FIB-4	Fibrosis-4
GGT	Gamma-Glutamyl transferase
HBV	Hepatitis B virus
HCVAb	Hepatitis c virus Antibodies
HCV	Hepatitis C virus
HCC	Hepato Cellular Carcinoma
HIV	Human Immune-deficiency virus
TBIL:	Total bilirubin

DEFINITION OF KEY TERMS

Hepatitis C infection is a liver disease caused by the Hepatitis C virus (HCV): the virus can cause both acute and chronic hepatitis, ranging in severity from a mild illness lasting a few weeks to a serious lifelong illness. A significant number of those who are chronically infected will develop cirrhosis of liver cancer (WHO).

Acute HC refers to the first several months after someone is infected. Acute infection can range in severity from a very mild illness with few or no symptoms to a serious condition requiring hospitalization. For reasons that are not known, about 20% of people are able to clear, or get rid of, the virus without treatment in the first 6 months. Presence of HCV within six months of acquiring infection(1).

Chronic HCV: Chronic hepatitis C is known as the persistence of HCV virus in the blood for more than 6 months after onset of the acute infection(2).

Liver fibrosis: Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases. Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires liver transplantation. It is the first stage of liver scarring (2).

Liver Cirrhosis: Cirrhosis is a condition in which the liver slowly deteriorates and is unable to function normally due to chronic, or long lasting, injury. Scar tissue replaces healthy liver tissue and partially blocks the flow of blood through the liver, a more serious problem when scar tissue builds up and takes over most of the liver (3).

APRI score: AST to platelet ratio index. it is the score that establishes the relationship between serum aspartate aminotransferase levels and platelet count(3).

Risk factors/Determinants: A risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury (WHO). Conditions or variables associated with a lower likelihood of positive outcomes and a higher likelihood of negative or socially undesirable outcomes.

The social determinants of health: The SDH are the specific features of, and pathways by which, societal conditions affect health. Examples include income, education, occupation, service availability, sanitation, and access to resources linked to health(4).

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CHAPTER I: INTRODUCTION

1.1. BACKGROUND

Globally, an estimated 71 million people are infected with chronic hepatitis C virus (HCV) infection, 1.34 million deaths have occurred due to HCV infection in 2015, a number that way exceeded HIV caused deaths annually and a comparable number for the deaths due to Tuberculosis(4). HCV associated deaths in 2015 were mainly caused by chronic liver disease such as decompensated cirrhosis and liver cancer. In Africa, the HCV prevalence is 2.9 and globally it is estimated to be 2.5%(5). HCV is increasingly highlighted as a great in high-income countries such as Europe, Canada and the United States, The burden in the African region remain unknown and thought to be highly variable across geographic area(6). Sub Saharan Africa presents the highest burden of disease in the world, Eastern Mediterranean and Western Pacific are the WHO regions with HCV high prevalence 4.6% and 3.9% respectively. Despite its high prevalence and highly infectious nature, HCV remains under-diagnosed and underreported in Africa (with the exception of Egypt), most of the available data on HCV are outdated which has given much attention to HCV in Africa(6).

Cirrhosis related deaths have almost doubled from a number of 53 000 in 1980 to 103 000 in 2010. In the southern region of Africa, the prevalence of cirrhosis-associated mortality is about half that of the central, eastern, and western regions of Africa. These patterns are consistent with the regional prevalence of hepatitis B, hepatitis C, and hepatitis D disease. Cirrhosis-associated mortality in the Central African Republic, Gabon, Malawi, Uganda, and Côte d"Ivoire was ranked in the top 10th global percentile in 2010(7) In sub-Saharan Africa, HCV is the second leading cause of end-stage liver disease and hepatocellular carcinoma related-morbidity(4).

Rwanda has been classified by the World Bank as the country among low-income countries that has well-established achievements in maternal and child health and control of human immunodeficiency virus (HIV), tuberculosis and malaria. It was also one of the few countries in sub-Saharan Africa that has proven evident based achievement mostly on the health-related millennium development goals. Hepatitis C has not remained behind in the health problems to be keenly given a full attention just like other epidemics (8). In the Rwandan population, HCV seroprevalence has recently been estimated to be 3.1% of the 11.9 million people (9).

Same researchers have reported that, in 2011, the Government of Rwanda established its hepatitis control unit under the Division of HIV/AIDS, STIs and Other Blood Borne Infections at the Rwanda Biomedical Centre. The objective was to develop a specific programme for the prevention, care and treatment of hepatitis B and C. In 2013, the viral hepatitis technical working group was set up, comprising health ministry specialists, clinicians, academic researchers, laboratory experts, and private sector representatives. The group began to meet regularly to provide technical advice for the design and implementation of the programme. At that time, a national policy on viral hepatitis prevention and management in Rwanda was developed and published to provide specific guidance to health- care providers and facilities on the implementation of the clinical guidelines (9).

Hepatitis C virus (HCV) is mostly transmitted through exposure to infectious blood. This may be possible through transfusions of HCV-infected blood and blood products, contaminated injections during medical procedures, and sharing of objects among injecting drug users. Sexual or interfamilial transmission is also possible, but is much less common(10). Prevention of HCV focuses on eliminating potential risk of exposure to the virus. Most people who are chronically HCV infected individuals remain unaware which expose them to a high risk of developing severe chronic liver disease and continue transmitting it unknowingly to other people(4).

In developing countries, Rwanda inclusive, people do not consistently do the general body check-up, liver function included, due to ignorance or financial constraints. In fact, there is no full access to healthcare services due to lack of health coverage, inaccessibly located healthcare facilities, and increased health cost. These services are expensive because of several reasons including usage of imported drugs and machines, absence of specialists and limited qualified staff at the health facilities, to deal with advanced stages of diseases which worsen the situation. Individual habits like smoking, excessive alcohol consumption, unprotected sex with various partners, drug abuse, auto-medication, etc. also handicap normal liver functions. Conducive practices like blindly using traditional medicines mostly lead to chronic liver disease and finally to cancer.

HCV infection starts by acute infection to chronic infection and finally to advanced stage of fibrosis(cirrhosis). It’s progression may be due to the above-mentioned alcohol intake, HIV and HBV coinfection, older age or lasts to 20-50yrs of infection before reaching the advanced stage(cirrhosis)(5). (See fig 1).

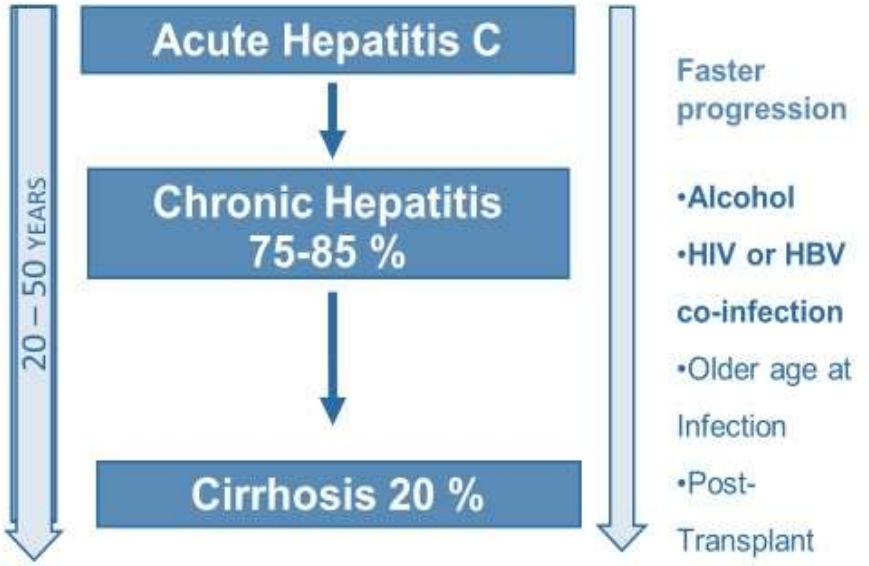

Figure 1. Natural history of HCV infection(6).

Screening for HCV infection is done using either ELISA-based HCV serological testing or Rapid Diagnostic Tests (RDTs). If positive, HCV RNA test is done to confirm chronic HCV infection. Anti-HCV is generally not detectable in patients with initial signs or symptoms of hepatitis C and generally develops between 2 and 8 weeks after evidence of liver injury. Some persons may not test positive for 6-9 months after onset of illness(6).

All patients who screen positive for HCV antibody should also be screened for HBV and HIV infections. Hepatitis C viremia may be detected by RT-PCR within 4-8 days after infection(11).

In Rwanda, the screening of HCV is done by detecting the presence of HCV antibody (ELISA or Rapid Test) If HCV Ab is positive and confirmed with a positive HCV RNA test, the patient is confirmed to have HCV chronic infection and should be evaluated for treatment. If HCV RNA test is negative, the patient will be informed that the infection has been cleared and will receive appropriate counselling for prevention (1).

This study aims to find out the magnitude of liver fibrosis in HCV patients, the socio-demographic and clinical factors associating with liver fibrosis in HCV infected patients in the Rwandan population.

1.2 Problem Statement

Globally, 180 million people live with hepatitis C virus. HCV virus being the leading cause of liver fibrosis thus cirrhosis in the USA, it presents a global burden of 160 million people with chronic infection(12). Hepatitis C is among the top 20 causes of death in German (17).It causes 26,000 deaths annually(18).

Africa presents the highest WHO HCV estimates of 5.3% where Egypt, being the most affected, has 17.5% of HCV global cases (13). Disproportionately, Sub-Saharan Africa (SSA) being the least to finance healthcare with <1% of the global spending, has 24% of the HCV global burden (14). Hepatitis C virus infection can take only 14 days to develop into a disease after exposure, though it can go up to 180 days. While currently, there is no Vaccine for HCV infection (15), as many as 85% of HCV infected people fail to eliminate HC viruses from their body, thus making acute infection to develop into chronic infection(16).

HCV cases have been reported in Rwanda, the Ministry of Health has put in place a national guide for the diagnosis and treatment of the disease. In 2016, HCV infection in Rwanda was estimated to be 3.1% of 11.9 million Rwandans in that year and 4.7% among HIV/AIDS patients as per data from blood donor Surveillance(8).

Even if there are effective clinical interventions for HCV in Rwanda, the spread of the infection continues to rise due unawareness of the population about the disease. Although there are no published statistics about awareness of HCV infection in Rwanda, some Rwandans remain ignorant about the disease, especially in rural areas.

Clinical and social factors dramatically influence the development of liver fibrosis or cirrhosis among HCV infected patients. Co-infections of the HCV with one or more of HBV, HAV, HIV, non-alcoholic fatty liver disease, diabetes and others speeds up development of the disease together with risky health behaviors like smoking and substance abuse(19)(20).

Decreased awareness, financial constraints, social-cultural factors are barriers to early HCV diagnosis and treatment(21)hence disease progression to liver fibrosis and its end stage, liver

cirrhosis. In Rwanda, due to how recent the national strategies to reduce the burden of the disease are, there is no much information on liver fibrosis in HCV infected individuals.

1.3. Purpose of the Study

With an increasing burden of HCV infection and liver fibrosis worldwide, in Africa, especially SSA, it is important to understand the developing liver fibrosis in HCV infected patients in Rwanda and this analysis will contribute towards that area of scientific knowledge. In addition, this study will inform policy makers about the prevalence of liver fibrosis among HCV patients in Rwanda.

1.4 Objectives

1.4.1. General Objective

To determine the prevalence and determinants of liver fibrosis among HCV infected patients.

1.4.2. Specific objectives

- ✓ To determine the prevalence of liver fibrosis in HCV infected patients.
- ✓ To describe socio-demographic, clinical factors and unhealthy behaviors of HCV infected patients.
- ✓ To determine the clinical factors associated with liver fibrosis among HCV infected patients.

1.5 RESEARCH QUESTIONS

- ✓ What is the magnitude of liver fibrosis in HCV infected individuals?
- ✓ What is socio demographic characteristics associated with liver fibrosis in HCV infected individuals?
- ✓ Which clinical characteristics are associated with liver fibrosis among HCV infected individuals in Rwanda?

1.6. SIGNIFICANCE OF THE STUDY

Data generated from this study will serve as a roadmap for policy makers to develop policies on disease prevention and diagnosis using effective, efficient, non-invasive lab tests as opposed to biopsy which is invasive, time consuming, expensive and not affordable by a good number of Rwandans. Finally, the results of this study will be a basis for further research in the same domain.

CHAPTER II. LITERATURE REVIEW

2.1. Overview of Liver fibrosis

Liver fibrosis is the excessive accumulation of extracellular matrix proteins including collagen that occurs in most types of chronic liver diseases(7). Advanced liver fibrosis results in cirrhosis, liver failure, and portal hypertension and often requires liver transplantation.

The main causes of liver fibrosis in developed countries include chronic HCV infection, alcohol abuse, and non-alcoholic steatohepatitis(8). Currently, it is considered a model of the wound-healing response to chronic liver injury. Fibrosis is considered as a precursor to cirrhosis and establishing the severity of liver fibrosis helps predict liver related morbidity and mortality and emergence of complications of portal hypertension. Cirrhosis is the last stage of fibrosis which occurs mainly in response to viral and toxic-metabolic insults. Liver fibrosis is the main determinant of long-term outcome in chronic liver diseases.

Chronic liver disease includes fibrosis, cirrhosis and hepatic decompensation=hepatocellular carcinoma(9).

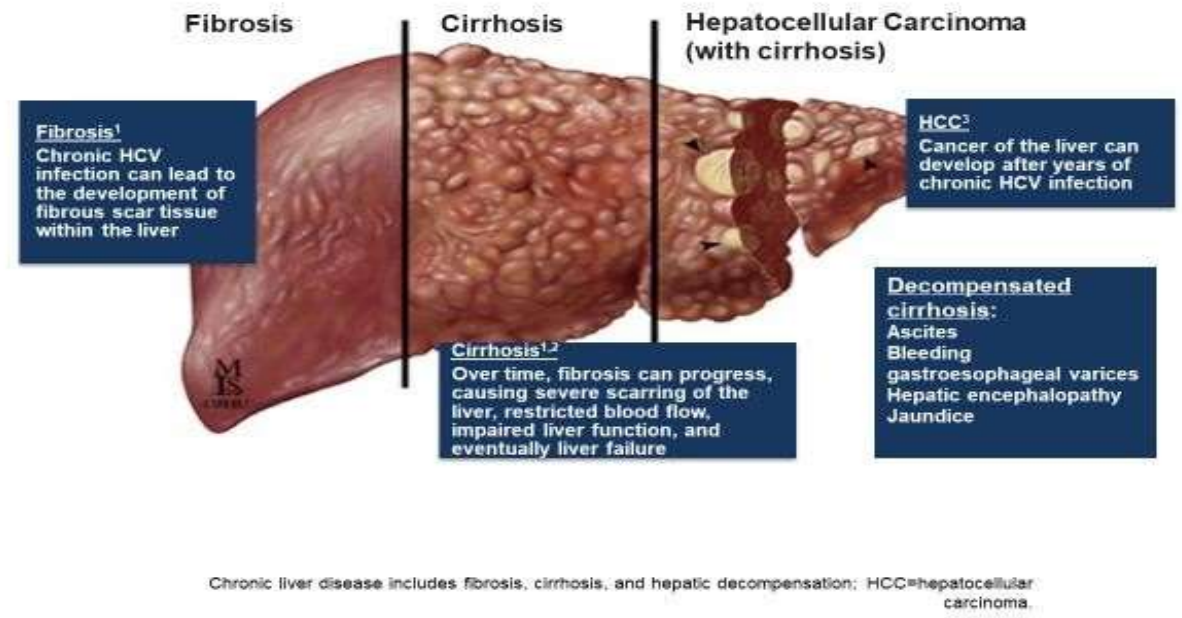

Figure 2. Illustration of liver fibrosis, cirrhosis and HCC (6).

Little is known about the prevalence of liver fibrosis in the general population. (22). HCV infection is amongst the major determinants of liver fibrosis/cirrhosis and it is aggravated by alcohol and smoking (tobacco and marijuana); insulin resistance; and coinfection with hepatitis B virus, human immunodeficiency virus type 1(10). There is a synergic effect between HCV infection on one hand, and one or more of alcohol abuse, co morbidity of non-alcoholic fatty liver disease, chronic viral hepatitis and others to cause liver cirrhosis(23). the worldwide mortality attributable to cirrhosis and primary liver cancer due to fibrosis is around 1.5 million death per year, with in France (1/100 of world population) a similar mortality rate around 15,000 death per year(24). The stage of liver fibrosis is considered as a gold standard to the management and forecasting the progress of HCV infection(25). Signs and symptoms of liver fibrosis/cirrhosis may appear on the skin such as jaundice, itching, redness of the palms of hands, swelling of peritoneal cavity, legs, breast due to fluid build-up in these parts of the body. Psychological effects could include confusion, sleepiness, incoherent speech due to toxins build up in brain. Other symptoms include loss of appetite, hemorrhage, tiredness, fragile bone, and loss of weight (26).

2.2. Social characteristics of liver fibrosis

Social determinants of health can be defined as the situations in which we are born in and grew up in(4). In this context; education, health services cost and accessibility of health services, and other demographic characteristics are key. They influence our wellbeing either positively or negatively. These conditions influence a person‟s opportunity to be healthy, his/her risk of illness and life span. They comprise social injustice and other preventable differences which result in uneven distribution of health determinants in people(27). Demographical determinants of liver fibrosis and generally of hepatitis c infection in Rwanda and elsewhere in the world can be known as age, gender, location, social economic status, different profession of the population and people should be aware and taken care of by the health care providers and the policymakers in increasing the awareness of the disease to hinder the spread of the disease in the nation due to not enough knowledge of the population. Social-cultural health behaviors can also be detrimental to the normal function of the liver. Perceived ways of illnesses, personal behaviors and habits, and community‟ perceptions about different health practices should all be looked at while trying to maintain our liver healthy.

Progression of fibrosis can be accelerated by factors such as age, duration of HCV infection, sex, confection with HBV or HIV and alcohol intake.

Also, Diabetes and insulin resistance not only increase fibrosis but are also predictors of liver fibrosis particularly in patients harboring genotype-1(28).

2.3. Clinical determinants of liver fibrosis

Liver fibrosis often goes unrecognized unless the patient manifests symptoms from complications of cirrhosis. When a patient presents with liver disease, it is important to exclude or confirm cirrhosis, especially when the presentation is with incidental findings of elevated serum aminotransferases, unexplained thrombocytopenia, or abnormal liver imaging.

Julien Massard and colleagues have reported Cigarette smoking, alcohol consumption, HIV co-infection, Body mass index and diabetes to be significantly associated with liver fibrosis(29). however, the current study has found only elevated transaminases to be associated with liver fibrosis among the HCV infected individuals. The scope of clinical characteristics of HCV infected patients, in relation to development of liver fibrosis or cirrhosis, is confined into two main physiological changes among HCV infected participants; Change in vital signs and symptoms, and laboratory test or biomarkers. Currently the study found out biomarkers especially liver function tests with calculated scores can easily determine whether a person is developing liver fibrosis and most especially if Hcv infected.

2.4. Diagnosis of Liver fibrosis

Liver biopsy is considered the gold standard for diagnosing and assessing liver fibrosis. The liver biopsy provides information on both the grade (degree of inflammation that reflects ongoing liver disease injury) and the stage (amount of currently established fibrosis)(30). However, there are some limitations to the use of liver biopsy:

- ✓ It is invasive
- ✓ Costly
- ✓ Painful
- ✓ Sampling error
- ✓ Inter-observer variability (31).etc.

Non-invasive methods for assessing fibrosis are therefore increasingly used instead of liver biopsy and may ultimately replace biopsy when the indication is solely to establish fibrosis

severity in patients with liver disease diagnosis(32). However, liver biopsy is still currently utilized by clinicians to augment non-invasive fibrosis estimates.

Diagnosing and assessing the degree of liver fibrosis is important in predicting liver-related morbidity and mortality and the emergence of related complications(33).

Non-invasive methods to estimate hepatitis fibrosis are commonly used in clinical practice as a more accessible and less costly strategy than liver biopsy for stratifying patients according to risk just like liver biopsy would do (34). If a combination of non-invasive methods provides a clear-cut assessment of hepatic fibrosis then further assessment with liver biopsy is generally not needed(30). These methods have been proven to provide necessary information for the prognosis of HCV infection(35). They include laboratory tests, scores and indices which have been developed for liver fibrosis among HCV-infected patients(23) and they are increasingly becoming the most chosen for liver fibrosis(36). It was proven that Aspartate to Platelet Ratio Index (APRI) is a useful tool to assess liver fibrosis from its mild to advanced stages (35). With which our study is focusing on.

2.4.1. Calculation formula of APRI Score

$$\textbf{APRI} = \frac{\dfrac{\text{AST Level}}{\text{AST upper limit of normal}}}{\text{Platelet count (109l)}}$$

APRI: stands for AST-Platelet Ratio Index and is one of the simplest marker panels that can diagnose significant fibrosis and cirrhosis with acceptable accuracy(37). It has been extensively evaluated in HCV diagnosis. A metanalysis including 40 studies and a total of 8739 hepatitis C patients showed that APRI had an area under the receiver operating characteristic (AUROC) of 0.77 for the diagnosis of significant fibrosis. Recent studies indicate that APRI was comparable to other, more complex established panels in excluding advanced but not moderate fibrosis. In a comparison of four tests (FibroTest, APRI, FIB-4, and Forns‟ Score) before and after telaprevir treatment of 1208 chronic HCV patients, APRI showed the most significant decrease (38).

2.4.2. Normal ranges of biomarkers used in the calculation of APRI score and others.

Normal levels of Alanine Transaminase (ALT) ranges from 7-56 units/liter whereas the normal range for Aspartate Transaminase is 10-40units/liters (39). Gamma-glutamyl transferase (GGT) ranges from 9 to 48 U/L(40) and the Alkaline Phosphatase(ALP) range from 44 to 147 international units per liter (IU/L)(41).

Bilirubin is a product of hemoglobin catabolism, is transported to the liver by the blood stream bound to albumin. The liver then converts bilirubin to bilirubin glucuronide to be excreted from the body mostly by the kidneys. The normal ranges for total Bilirubin are 0.1 to 1.2 mg/dL (41).

2.5. Roles of using of Non-invasive methods in Rwandan context

APRI score can be preferred in the Rwanda context for it:

- ✓ Does not require investment in new device
- ✓ Does not require additional workforce training
- ✓ Access to the tests are readily available across the country
- ✓ Low cost of testing compared to other sources
- ✓ Non-Invasive
- ✓ Blood draws can be combined with other blood draw to reduce time spend on staging. However, there may be times when liver biopsy can be useful at the specialized level, but this is subjective to it's availability in the country.

2.6. Impact of Liver fibrosis on HCV infected patients

Liver disease is becoming a major cause of the death all over the globe. From different recent publications, it was documented that In China, approximately, liver diseases affect 300 million people, therefore having a major impact on the worldwide burden of the liver diseases resulting in deaths also (42). The onset of liver fibrosis is related to morbidity and mortality that occur after the cirrhosis was developed. Normally, the progression to cirrhosis occurs after 15 to 20 years. Major complications of cirrhosis may include renal failure, ascites, variceal bleeding and hepatic encephalopathy. (Cirrhosis itself can be a risk factor for developing hepatocellular carcinoma (35).

Further studies had proven that patients knowing the status of their health, being HCV positive and due to physicians" advices, already infected Hcv patients adopt the habit of alcohol intake and smoking reduced, start to eat appropriately with balanced diet, reduced heavy exercises for those reported that they do tiresome exercises and all those

measures can lead to improved liver‟s health with positive impact(43). Most studies have proven that if patients get advices from their physicians it is of most important and of great value if physicians follow-up on their patients and try to give some behavior change advices, this will lead most of the HCV infected Rwandans and other population to prolong life even though chronically Hcv infected from less alcohol consumption and reduced unhealthy behaviors such as multiple sex partnerships.

2.7. Conceptual framework

The Below conceptual framework describes factors that serve as independent variables for the purpose of this study and these are socio demographic characteristics such as age, gender, education level, social economic status and occupation of HCV patients. Factors related to unhealthy behaviors of HCV patients such as alcohol intake and number of sex partners, lastly it describes the clinical characteristics of our study population namely BMI, HIV status and liver function tests (ALT, AST, ALP, GGT and Total bilirubin) that all contribute to the outcome variable.

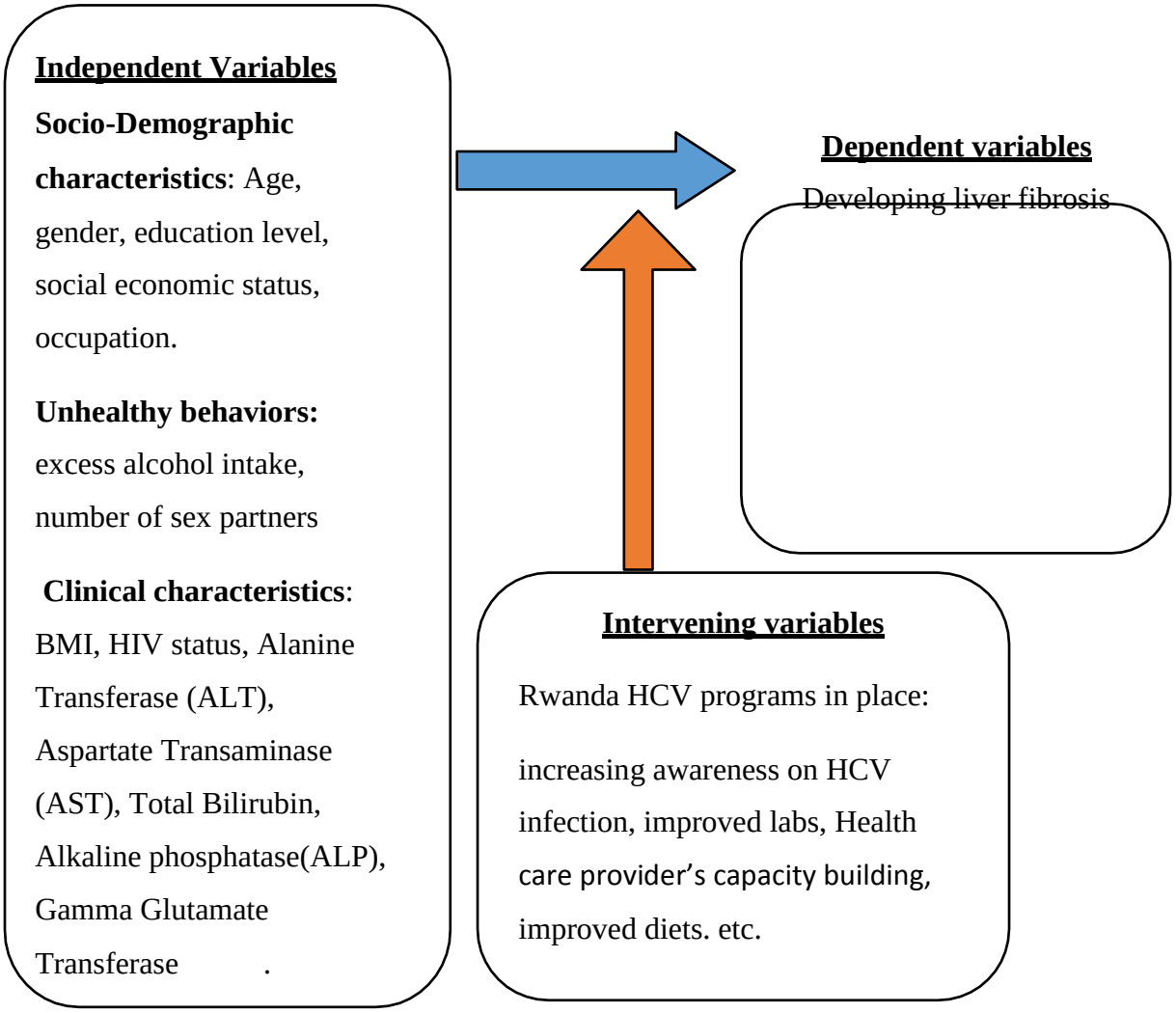

Figure 3. Conceptual frame work describing factors used for the purpose of this study.

CHAPTER III. METHODS

3.1. Study Design

This is a descriptive analytical cross-sectional study of secondary data from Simplifying Hepatitis C Antiviral therapy in Rwanda for Elsewhere in the Developing world (SHARED) study(44).

3.2. Study setting

The study was implemented at Rwanda military hospital participants were from 4 referring hospitals in Rwanda, these are: (Centre Hospitalier Universitaire de Butare, Centre Hospitalier Universitaire de Kigali, Rwanda Military Hospital, and King Faisal Hospital).

3.3. Study population

The study population used in this study were HCV positive patients that were referred to the SHARED 1 and 2 studies from four referral hospitals in Rwanda. The referring clinician would complete a patient referral form and the patient information recorded in an electronic waiting list database, assisted by a research study data officer.

3.3.1 Inclusion criteria

- ✓ Willing and able to provide written informed consent
- ✓ Age ≥ 18 years
- ✓ HCV RNA ≥ 10^3 IU/mL at Screening
- ✓ HCV genotype 1 or 4 at Screening as determined by the Central Laboratory.
- ✓ genotype result will exclude the participant from study participation
- ✓ Screening ultrasound excluding hepatocellular carcinoma (HCC)

Acceptable laboratory values including:

- ✓ Haemoglobin ≥8.0 g/dL
- ✓ Platelet count ≥40,000/mm3
- ✓ AST, ALT, and alkaline phosphatase ≤10 × ULN
- ✓ Calculated creatinine clearance (CrCl) ≥30 mL/min

3.3.2 Exclusion criteria

- ✓ Current or history of clinical hepatic decompensation (i.e., ascites, encephalopathy)
- ✓ Active tuberculosis

- ✓ Other clinically-significant illness (except HCV and/or HIV)
- ✓ Active Hepatitis B infection
- ✓ Difficulty with blood collection and/or poor venous access.
- ✓ Pregnant or nursing female
- ✓ Active HCV drugs

3.4. Data sources

This analysis used data collected at RMH in 2016 in the SHARED study, this study was a partnership between Partners in health (PIH), University of Rwanda (UR), Stanford university and Rwanda Military Hospital. Participants were enrolled following a developed electronic list of HCV patients from four referral hospitals and they were screened and enrolled into the study. Participants' social demographic information was collected, data from a designed questionnaire were collected, the body mass index was calculated as weight tested in the laboratory at RMH. HIV status was tested using allere HIV combo rapid test and rather tested for viral load using COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test and HCV viral load was tested using Abbott diagnostics. Liver function tests were tested using Cobas 6000 analyser series.

3.5. Definition of Variables

In this study, the outcome variable is a binary variable, the APRI score (≤0.5, ≥1.5) cut off index which shows the development of liver fibrosis, if the value of APRI score is less or equal to 0.5, it surely indicates that there is no fibrosis present. Contrary if it becomes 1.5 or higher, it strongly indicates liver fibrosis. Independent variables include socio-demographic characteristics such as age (in years), gender (male, female), education level was collected as No education, primary, vocational, secondary and university level, social economic status (SES) was collected in terms of how much is the monthly household income and then categorized into low, middle- and high-income categories, Occupation of participants was also categorized as paid jobs, jobless and other. Two behavioral characteristics, the number of sex partners and alcohol intake were included and these were categorized as 0-1, 2-4, 5-10 and 11 and above life-time sex partners and "No" or "Yes" respectively. We also included a couple of clinical characteristics including the body mass index (BMI) as underweight, normal, overweight and obesity and the HIV status (negative vs positive). Liver function tests were collected as continuous variables but later categorized into normal and increased categories.

3.6. Data processing and analysis

Data in Excel were exported into STATA15.1, Descriptive statistics using frequencies and percentages were determined for categorical variables as all variables are categorical. Bivariate analysis was performed to determine the relationship between each variable and liver fibrosis status, using a binary logistic regression. We also performed multivariable logistic regression to assess the model between the significantly associated variables and the liver fibrosis status. Analyzed data were presented in tables. A 95% confidence interval was calculated and level of significance was set at p-value equals 0.05.

3.7. Ethical considerations

Data analyzed for this study were de-identified data with less confidentiality issues. Participants‟ privacy and confidentiality were maintained by using study codes and identification numbers. Also, the participants were informed that treatment will be freely provided and a small amount of money was given to cover their travel. Participants‟ consent to participate in the shared study was also sought as the first step of participants‟ participation. Ethical clearance was initially given by the Rwanda national ethics committee (RNEC) before the start of SHARED study.

CHAPTER IV. RESULTS

4.1 Socio-demographic, unhealthy behaviors and clinical characteristics of HCV infected patients

Socio-demographic statistics indicate that the mean age of our study population is 61.8±14.1 and most of our participants were female with a proportion of 62%. The majority of the study participants had primary education (45.5%) followed by secondary education at 25.9% and 16.5% had no education at all. Eighty-two percent of the study participants were of low socio-economic status (SES), 16.1% are of middle income and only 1.7% was regarded as of high SES, 63.9% of the study population were jobless whereas 16% had paid jobs. The social demographics are shown in the following table. (Table 1).

Table 1. Socio-demographic characteristics of HCV infected patients

Characteristics	Frequency	Percentage
Age group		
18-34	17	5.72
35-54	56	18.86
55-74	173	58.25
>75	51	17.17
Gender		
Female	184	61.95
Male	113	38.05
Education level		
No education	49	16.5
Primary	135	45.45
Vocational	7	25.93
Secondary	77	2.36
University	29	9.76
Socio-economic status		
Low income	244	82.15
Middle income	48	16.16
High income	5	1.68
Occupation		
Paid job	47	15.82
Jobless	190	63.97
Other	60	20.2
Total	**297**	**100**

4.2 Unhealthy behaviors and clinical characteristics of HCV infected Patients

In our study population 14.2% were alcohol consumers whereas 85.8% were not and 57.2% had 1 sex partner, 26.6% had 2-4 sex partners and 8.1% was both for 5-10 and 11 and above sex partners. Descriptive statistics of the clinical and laboratory characteristics show that more than a half of the participants (50.8%) were of normal weight (BMI between 18.5 and

24.9) and 42.8% were under weight (BMI less than 18.5). It is noteworthy that only 1.7% were obese and 4.8% were overweight. The HIV prevalence in our study population was 9.1% and most of the laboratory tests showed that most individuals had normal test results except for GGT (9–48U/L). (Table 2).

Table 2. Unhealthy behaviors and clinical characteristics of HCV infected Patients n=297

Characteristics	Frequency	Percentage
a. Unhealthy behaviours		
Alcohol intake		
No	255	85.86
Yes	42	14.14
Number of sex partners		
0-1	170	57.24
2-4	79	26.6
5-10	24	8.08
11 and above	24	8.08
b. Clinical characteristics		
BMI		
Under weight	127	42.76
Normal	151	50.84
Over weight	14	4.71
Obesity	5	1.68
HIV Status		
Negative	270	90.91
Positive	27	9.09
AST		
Normal	169	56.90
Increased	128	43.10
ALT		
Normal	223	75.08
Increased	74	24.92
ALP		
Normal	269	90.57
Increased	28	9.43
GGT		
Normal	120	40.40
Increased	177	59.60
TBIL		
Normal	275	92.59
Increased	22	7.41
Total	**297**	**100**

4.3 Prevalence of liver fibrosis among HCV infected patients

The prevalence of liver fibrosis in our study population as calculated using the APRI score being greater or equal to 1.5 was found to be 15.8%.

Table 3. Prevalence of liver fibrosis by APRI score

APRI score	Frequency	Percentage
APRI (≤1.5)	**250**	**84.18**
APRI (≥1.5)	**47**	**15.82**
Total	**297**	**100**

4.4. Fibrosis according to socio-demographic, clinical and laboratory characteristics

The bivariate analysis showed that some socio-demographic and behavioral characteristics were associated with the outcome variable (liver fibrosis). The patients with primary education were 7.7 times more at risk of developing liver fibrosis than those with university (OR=7.7, CI=1-58.7), and participants with secondary school were 37.3 times more at risk of developing fibrosis than those with university (OR=37.3, CI=3.08-452). The odds of participants with middle income were 0.192 and this finding was statistically significant and might indicate that being in middle income was a protective factor for developing liver fibrosis (OR=0.192, CI=0.045-0.82). The population with only 1 sex partner were 2.3 times more at risk of developing liver fibrosis than those with 2-4 sex partners (OR=2.38, CI=1-5.6). Age, gender, alcohol intake and occupation of the participants were all not statistically significantly associated with liver fibrosis. Both clinical factors (HIV status and BMI) were not statistically significantly associated with the outcome variable (liver fibrosis). As expected, all laboratory tests (being increased) showed a statistically significant association with liver fibrosis, and this is shown in the following table (Table 4).

Table 4. Bivariate analysis of socio-demographic, clinical and lab characteristics by liver fibrosis (n=297)

Characteristics	OR	95% CI	p-value
Age group			
35-54	1		
18-34	1		
55-74	1.964	0.776-4.967	0.154
>75	1.550	0.498-4.820	0.449
Gender			
Male	1		
Female	1.100076	0.575-2.101	0.773
Education level			
University	1		
Illiterate	5.463415	0.646-46.142	0.119
Primary	7.660377	0.999- 58.707	**0.05****
Vocational	1.944444	0.217 -17.390	0.552
Secondary	37.33333	3.083-452.04	**0.004*****
Socio-economic status			
Low income	1		
Middle income	0.1922705	0.045-0.821	**0.026****
High income	1		
Occupation			
Paid job	1		
Jobless	1.125839	-0.102-2.354	0.072
Other	1.191652	-0.148-2.531	0.081
Alcohol intake			
No	1		
Yes	0.0723212	-0.806- 0.951	0.872
Number of sex partners			
2-4	1		
0-1	2.385093	1.003-5.670	**0.049***
5-10	2.057143	0.547-7.736	0.286
11 and above	2.057143	0.547-7.736	0.286
BMI			
Normal	1		
Under weight	1.618804	0.841-3.115	0.149
Over weight	1.894737	0.484-7.413	0.359
Obesity	1.736842	0.184-16.371	0.63
HIV Status			
Positive	1		
Negative	2.5	0.571-10.932	0.224
AST			
Normal	1		
Increased	3.366748	2.168-4.565	**0.000*****
ALT			
Normal	1		
Increased	2.357554	1.66-3.054	**0.000*****
ALP			
Normal	1		
Increased	1.612291	0.783-2.44	**0.000*****
GGT			
Normal	1		
Increased	1.967889	1- 2.927	**0.000*****
TBIL			
Normal	1		
Increased	1.240654	0.308-2.173	**0.009*****

4.4 Simple and Multivariable logistic regression for variable associating with liver fibrosis

In our study population, education level and the SES were statistically significantly associated with liver fibrosis where patients with vocational training were 30.5 times more at risk of developing liver fibrosis than those with university level (OR=47.1, CI=2.21-1000). Patients that had only 1 sex partner are 3.35 times more at risk of developing liver fibrosis than those with 2-4 sex partners (OR=3.23, CI=1-10.2). In addition, all laboratory tests were statistically significantly associated with liver fibrosis where patients with increased AST values are 18.7 times more at risk of developing liver fibrosis than those with normal values. 3 times more at risk for ALT, 4.9 for ALP and 5.8 for TBIL (total bilirubin) times more at risk of developing liver fibrosis. Except for the GGT where the odds of it being increased was protective with odds ratio of 1.3.

Multivariable logistic regression (reduced model) put together all variables that have found to be associated with liver fibrosis; education level continued being associated with liver fibrosis by 47 times more at risk of developing liver fibrosis in patients with vocational training than in those with university level, having 0-1 sex partners was 3.23 times more at risk of developing liver fibrosis than in those with 2-4 partners. And patients with increased results for AST, ALT, ALP and Total bilirubin are 22,3,5.7 and 6 times more at risk of developing liver fibrosis than in those with normal results respectively. (Table 5).

Table 5. Multivariate model of factors associated with liver fibrosis

Characteristics	Full model			Reduced model		
	OR	**95% CI**	**p-value**	OR	**95% CI**	**p-value**
Socio-economic status						
Low	1					
Middle	0.490252	0.089-2.681	0.411			
High	1					
Education level						
University	1			1		
Illiterate	3.485538	0.28-43.235	0.331	5.19	0.471-57.26	0.178
Primary	4.758805	0.48-47.11	0.182	6.73	0.748-60.5	0.089
Secondary	1.257061	0.106-14.83	0.856	1.40	0.125-15.66	0.783
Vocational	30.54255	1.28-728.2	**0.035***	47.09	2.218-1000	**0.013****
Number of sex partners						
2-4	1			1		
0-1	3.354439	1.042-10.789	**0.042***	3.23	1.01-10.2	**0.047***
5-10	2.946696	0.471-18.4	0.248	2.884	0.46-18.06	0.258
11 and above	3.119961	0.617-15.77	0.169	3.238	0.649-16.15	0.152
AST						
Normal	1					
Increased	18.71356	4.29-81.52	**<0.001*****	21.9105	5.22-91.869	**<0.001*****
ALT						
Normal	1					
Increased	2.990217	1.169-7.647	**0.022****	3.005	1.198-7.537	**0.019****
ALP						
Normal	1					
Increased	4.930933	1.386-17.53	**0.014****	5.682	1.638-19.708	**0.006*****
GGT						
Normal	1					
Increased	1.312181	0.388-4.435	0.662			
TBIL						
Normal	1					
Increased	5.799892	1.326-25.3	**0.02****	5.963	1.396-25.46	**0.016****

Finally, education level, number of sex partner and liver function tests (AST, ALT, ALP and TBIL) were the only ones found to be associated with liver fibrosis with respective odds ratios 47,3.2,22,3,5.7 and 6 after a model made using logistic regression. It is important to note that the odds ratios have changed slightly and sometimes significantly for some factors when compared to the simple logistic regression done for each variable suggesting possible confounding or interaction.

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1. Discussion

Viral hepatitis is one of the global health concerns and a major infectious disease, in sub- Saharan Africa, the viral hepatitis is highly prevalent with an underreported burden of the disease, the magnitude of the disease varies across different population and regions(45). The suggested overall seroprevalence of HCV infection in sub-Saharan Africa from a meta- analysis done has been reported to be 2·98%(46). HCV infection is one of the main causes of liver fibrosis, Few studies investigate the prevalence of liver fibrosis in the general population, Koehler et al, reported prevalence of liver fibrosis of 5.6% in patients aged 45yrs and above, another study done in hongkong has reported the prevalence of 2% among subject aged 18-72yrs, 7% of fibrosis prevalence has also been reported from French population aged 45yrs and above(22).

The prevalence of liver fibrosis in Rwanda is poorly understood, this study is among those that can contribute to a better understanding of the factors predicting liver fibrosis among HCV infected patients. The prevalence of liver fibrosis among our study population was found to be 15.8%, it is much higher and because the study has enrolled only HCV positive patients above 18yrs of which the fibrosis has not been assessed since onset of the infection, this might have contributed in the high prevalence.

Our major finding was lined in social and clinical determinants where education level having been exposed to vocational training, having 0-1 sex partners and the laboratory liver function tests were independently significantly associated with liver fibrosis as determined by the APRI score (table 3). A study done by Thierry Poynard on the prevalence of liver fibrosis and risk factors in a general population using non-invasive biomarker (APRI) has found age to be significantly associated with liver fibrosis ($P < 0.003$) (24). unfortunately, this contradict with our findings that showed the age of our population not being associated with liver fibrosis with (OR=1.96, CI=0.77-4.96) in group of 55-74 yrs. and (OR=1.55, CI=0.49-4.82) for those above seventy-five years old, The current study has reported alcohol consumption not being associated with liver fibrosis with (P-value=0.872) which is in line with what Thierry poynard and colleagues have reported(24).

The current study has proven significant association of subjects in middle class of economic status, those on vocational training as part of their education level and the number of sex partners to be associated with liver fibrosis by APRI score (Table 4).

This probably means that subjects in middle class earn little money or remain incapable which makes them not being able to thoroughly check-up on their liver function tests and follow-up leading to the severity of the liver inflammation, subjects with less education may be limited to knowledge of how important is to check-up on their lives which makes them progressively develop liver fibrosis and surprisingly subject with 0-1 number of sex partners were found to be associated with liver fibrosis instead of those exposed to more than 11 and above. However, this may be due to couples who stay long together without knowing their HCV status and transmit it between them since one of them might have been exposed to the disease long ago. The prevalence of HIV in the Rwandan population has remained the same for years at around 3% (DHS) and it was not expected that in our study population, the prevalence of HIV was 9.1% and there was no association with liver fibrosis (p=0.224)(Table 3) this is partly due to the small sample size of our study. contrarily Michelle Dall Piazza and colleagues have reported HIV viremia to be associated with significant fibrosis by APRI score(22).

There are a number of available reliable non-invasive tools to measure liver fibrosis including the APRI score. The current study was interested on APRI score to assess the magnitude of liver fibrosis among our study population. This has given away in looking at the feasibility of non-invasive tests with which APRI score is calculated from, due to high number of people being served by the labs, these should be highly preferred in the health care settings(24). Of more interest, we have been able to understand the clinical factors influencing the development of liver fibrosis. The current study has reported increased liver function tests except for the GGT to be significantly associated with liver fibrosis, this results in an increased APRI score which might have contributed to the rise of fibrosis prevalence among our study population. We found APRI score to preferably be used in detecting liver fibrosis agreeing with Monica Salum and colleagues who reported that APRI is the preferred serological marker Among non-invasive liver fibrosis tests that has the highest diagnostic value and high sensitivity(81.7%), specificity(95%) together with a high predictive value of (96.1%) to be largely used instead of biopsy to monitor the evolution of chronic hepatitis c(47).

5.2. Limitations of the study

- Need for comparison of lab tests for HCV infected with that of non-infected patients to determine the magnitude of the association.
- This being a cross sectional analysis, we cannot determine the temporal and causal relationship between the associated variables and the outcome.
- This study has only enrolled patients from 4 referral hospitals, it might be necessary to conduct similar studies in health centers and district hospitals to get further information on fibrosis development.
- The study has enrolled only 297 HCV patients sent by referring physicians, a need to extend the number of patients across the country to be enrolled is needed to strengthen the findings of this study on the detection of liver fibrosis in HCV positive patients.

5.3. Conclusion

Liver fibrosis which is mainly found in HCV infected patients is of public health concern and since it is preventable through screening and laboratory testing, liver function tests are key factors to be considered and when checked at a time, can be a better way of preventing the disease. Education level, number of sex partners and elevated liver function tests are the independent predictors that have found to be the significant factors associated with liver fibrosis in HCV infected patients.

Following up on HCV infected patients and testing their liver function tests together with calculating their APRI scores could significantly determine the developing of liver fibrosis and should be the first step in the evaluation of liver fibrosis and cirrhosis in HCV infected patients. This could largely avoid expensive liver biopsies which is usually the gold standard method for determining liver fibrosis. Some of the experimental serum markers, especially those that are liver-specific/liver enzymes, combined with physical and clinical examination of HCV infected patients could lead to nearly replacement of the biopsy technique in the future and would give more insight to HCV policy makers and health care providers in order to reduce the extent of liver fibrosis in the Rwandan population.

5.4. Recommendations

There is a need to approach the issue of developing liver fibrosis among HCV infected patients by the following recommendations:

- Encourage couples to early check on their HCV status before one may transmit it to another unknowingly.
- Increasing awareness on management of HCV infected patients so they could not develop fibrosis by practicing unhealthy behaviors such as alcohol consumption, and multiple sex partnerships.
- Emphasize medical doctors to always determine the APRI score while diagnosing the patients, for it has been approved to give same results a of biopsy.
- Further studies and analyses are recommended in order to understand other possible factors behind the increasing prevalence of liver fibrosis among HCV infected Rwandan patients.

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