ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

SCHOOL OF MEDICINE

DEPARTMENT OF INTERNAL MEDICINE

RETROSPECTIVE ANALYSIS ON TREATMENT OUTCOME OF CHRONIC HCV INFECTED PATIENTS, THE EXPERIENCE WITH DAAs AT ADDIS ABABA, ETHIOPIA FROM JANUARY 2018 TO JANUARY 2020.

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TREATMENT OUTCOME OF CHRONIC HCV INFECTED PATIENTS, THE EXPERIENCE WITH DAAs AT ADDIS ABABA, ETHIOPIA FROM JANUARY 2018 TO JANUARY 2020.

A Thesis submitted to the Department of internal medicine, College of Health Sciences, of Addis Ababa University in Partial fulfillment of the requirements for the Specialty Program in Internal Medicine

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ABSTRACT

Background: HCV is a multisystem disease with significantly increased morbidity and mortality. Around 130-150 million people are chronically infected with HCV worldwide. The genotypic distribution of HCV is variable geographically and treatment outcome with DAAs in-turn is variable.

Objectives: to assess the treatment outcome of chronic HCV infected patients treated with DAAs at TASH and Adera specialty clinic, Addis Ababa, Ethiopia.

Methods and Materials: A retrospective study was conducted to describe treatment outcome of chronic HCV infected patients treated with DAAs at TASH and Adera Specialty clinic from January 2018 to January 2020. All patients treated with DAAs over the study period and accessible clinical data were included in this study. Data was analyzed by using the latest SPSS version 26.

Result: a total of 84 patients were included, 47(56.0%) of whom were females and mean age of 49±10.6 years. Viral genotype was documented for 51(60.7%) patients and 39(76.5%) of them had genotype 4. Diabetes and Hypertension were the commonest comorbidities identified in this study being present in 16.7% and 21.4% of cases respectively. Seventy-seven (91.7%) patients were treatment naïve and 34(40.5%) had evidence of liver cirrhosis based on imaging findings. Overall SVR12 was achieved in 76 (90.5%) patients. SVR12 occurred in 93.5% of patients who are non-cirrhotic and 83.5% of patients who are cirrhotic. APRI score of ≥ 0.7 was found to be associated with non-response to therapy. Fatigue and Nausea were the commonest side effects identified in 17.9% of patients with no reported life-threatening complications.

Conclusion: Treatment of chronic HCV infected Ethiopian patients with DAAs resulted in high SVR12 rate with minimal safety concerns.

Grant source: Addis Ababa University (AAU), college of health sciences, school of medicine.

Key words: Hepatitis C virus, Direct antiviral agents, SVR, TASH.

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List of Abbreviations and Acronyms

AAU: Addis Ababa University

ADR: Adverse Drug reaction

ALT: Alanine Transaminase

AST: Aspartate Transaminase

CKD: Chronic kidney disease

DAAs: Direct Antiviral agents

DCV: Daclatasvir

DM: Diabetes mellitus

EGD: Esophago-gastroduodenoscopy

HBV: hepatitis B virus

HCC: Hepatocellular carcinoma

HCV: Hepatitis C virus

HIV: Human Immunodeficiency virus

HTN: Hypertension

IHD: Ischemic Heart disease

INF: Interferon

LDV: Ledipasvir

PT: Prothrombin time

SOF: Sofosbuvir

SVR: sustained Virologic response.

TASH: Tikur Anbessa Specialized Hospital

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1. INTRODUCTION

1.1. BACKGROUND

Hepatitis C virus (HCV) is an enveloped positive sense single stranded RNA virus belonging to the genius Hepacivirus in the family of flaviviridae. There are 8 HCV genotypes and several subtypes based on the viral genetic sequence analysis(1).This viral genotypes have variable geographic distribution and response to antiviral therapy.

Worldwide Genotype 1 is the commonest, with a widespread geographic distribution in USA, Europe and Australia followed by genotype 3 which is predominantly located in the southern and southeast Asia(2). Genotype 4 on the other hand is the main infectious cause in northern, central and east Africa(2–8).

The virus is transmitted mainly parenterally. People who inject drug have the highest risk of getting the infection where-as transmission through unsafe medication injection with poor infection prevention protocol leads to transmission in health care facilities. The other possible ways of transmission are blood transfusion, vertically and sexually especially in men who have sex with men(9,10).

The initial treatment for HCV was interferon (IFN) based therapy. However the efficacy of this regimen was low and it was associated with more toxicity(11). Recently the introduction of Direct antiviral agents (DAAs) has revolutionized the treatment outcome of patients with HCV. they are better tolerated and achieve high sustained virologic response (SVR) with short duration of therapy(11).

Among the newer antiviral agents, Sofosbuvir-Ledipasvir which is approved for genotype 1,4,5, and 6 is commonly used in Ethiopia. Reasonable number of patients are also treated with the pan genotypic regimens of Sofosbuvir and Velpatasvir or Sofosbuvir-Daclatasvir. In choosing an appropriate regimen, clinicians take into account the patient treatment history, HCV genotype and subtype, stage of hepatic fibrosis, the efficacy, genotypic coverage, cost and availability of drugs among others.

1.2. Statement of the problem

Chronic HCV infection is a systemic disease with both hepatic and Extrahepatic manifestations including increased risk of Diabetes, depression, cardiovascular, neurologic, renal and variable immune mediated disorders(12–17). It is associated with an increased risk of hepatic related and all-cause mortality as well as morbidity(18). worldwide it remains to be among one of the leading causes of cirrhosis, hepatocellular carcinoma (HCC) and Liver transplantation(19,20).

The World Health Organization (WHO) estimated that there are 130–150 million people who are chronically infected with HCV worldwide. Having 11 million people infected with chronic HCV, its prevalence in Africa is around 1%. Viral hepatitis is responsible for an estimated 1.4 million deaths per year which is comparable to that of HIV and tuberculosis. of the 1.4 million deaths, approximately 48% is attributable to hepatitis C virus. HCV is also a growing cause of mortality among people living with HIV. About 2.9 million people living with HIV are co-infected with hepatitis C virus(21,22).

A systemic review and met analysis done in 2016 on 24 papers here in Ethiopia showed the overall pooled prevalence of anti-hepatitis C virus antibody (anti-HCV) as 3.1% (95%CI: 2.2–4.4). it also showed that people who are HIV positive has a higher anti- HCV antibody than HIV negative people (5.5%, 95%CI: 3.8–7.8%, p = 0.01)(23).

Because of the global burden of HCV and the availability of highly effective drugs for HCV, in 2016 the WHO launched a program to eliminate HCV as a public health threat by 2030(22). However, the limited real-world data on effectiveness of DAAs combined with the cost and availability of this drugs in low socioeconomic countries like Ethiopia have a negative impact on achieving this goal.

1.3. Significance of the study

Treatment outcome of HCV is affected by the viral genotype and subtype among other factors. To date, there is no study in Ethiopia which assessed the efficacy of DAAs even though viral genotype is different from the west. By addressing this knowledge gap, I believe this study will be valuable for both clinicians and policy makers. it will also be a baseline study for further research.

2. LITERATURE REVIEW

2.1. Molecular Epidemiology of HCV

A comprehensive review of available studies on genotypic distribution in Pakistan from 2010 to 2015 showed genotype 3 as the most prevalent Genotype (69.1%), followed by genotype 1 (7.1%), 2 (4.2%) and 4 (2.2%). Genotype 5 and 6 both accounted for approximately 0.2%(24).

A retrospective analysis of 451 patient samples from India, genotype 3 was found to be the commonest (63.85%) followed by 1 (25.72%), 4 (7.5%) and 6 (2.7%). Genotype 2 was detected from only one patient (0.002%) and there was no report of Genotype 5(25).

Another study from Thailand analyzed 588 blood samples from outpatient clinics and blood donors. In this study the most common HCV strains were genotype 3 (46.1%), genotype 1 (32.5%), genotype 6 (20.9%) and genotype 2 (0.5%)(26).

Genotype analysis of 230 samples from Venezuela, HCV genotype 1 was found to be the commonest (63%), followed by Genotype 2 (33%) and 3 (4%)(27).

A study from the republic of Congo involving 887 samples from 2005- 2007, of which 50 (5.6%) had positive HCV serology and 31 (60%) were viremic showed Genotype 4 as the commonest strain with subtypes of 4c in 8 (25.8%), 4h in 2 (6.5%), 4k in 3 (9.7%) and 4r in 8 (25.8%)(28).

In Gabon, they enrolled 4,042 people from 220 randomly selected villagers and 455 (11.2%) were found to be seropositive. Genotype analysis was done for 211 (46.4%) of the 455 seropositive participants. Of these 194 (91.9%) were genotype 4 (HCV-4), 12 (5.7%) were genotype 1, and five (2.2%) were genotype 2(29).

In Nigeria they analyzed 60 RNA positive samples. Genotypic analysis of these samples revealed that genotype 1 was the commonest, accounting for 51 cases (85%) followed by Genotype 2 (n=9, 15%)(30).

A retrospective study of 1,070 samples (865 in patient group and 205 in blood donors) from South Africa showed Genotype 5a as the most prevalent genotype (n=355, 35%), followed by genotype 1 (n=323, 31%)(31).

A systematic review and met analysis of 47 genotype studies conducted in Egypt showed genotype 4 as the commonest genotype (94.1%), followed by genotype 1 (4.0%), genotype 2 (1.3%), genotype 3 (0.8%) and genotype 5 (0.1%)(32).

A study conducted in five geographic regions of Ethiopia using samples from 46 voluntary healthy blood donors revealed genotype 4 as the predominant genotype (n=35, 77.6%) followed by 2 (n=6, 12.2%), 1 (n=4, 8.2%), and 5 (n=1, 2.0%). Seven subtypes were identified (1b, 1c, 2c, 4d, 4l, 4r and 4v), with 4d (34.7%), 4r (34.7%) and 2c (12.2%) being the most frequent subtypes(4).

Another prospective clinical treatment follow-up study conducted in Addis Ababa on 200 adults with chronic HCV revealed Genotype 4 in 120 (60%) of patients followed by genotype 1 (n=34, 17%), genotype 2 (n= 27, 13.5%) and genotype 3 (n= 19, 9.5%). Seven patients (3.5%) had mixed genotype 1 and 4 infection(3).

2.2. Treatment Outcome with DAAs

A single center, open-label cohort, non-randomized phase 2a trial was conducted in USA to analyze the efficacy of Ledipasvir and sofosbuvir for hepatitis C genotype 4. treatment naive or interferon treatment experienced patients were included. They were given 90 mg ledipasvir and 400 mg sofosbuvir as a single combination tablet once per day for 12 weeks. 21 patients were enrolled in this study.

Twenty (95%, 95% CI 76–100) of the 21 patients treated with ledipasvir and sofosbuvir achieved SVR12 including 7 patients with compensated Cirrhosis. 1 patient was non-adherent to medication and discontinued at 5^{th} week. The most common adverse events were diarrhea, fatigue, nausea, and upper respiratory infections. No deaths, serious adverse events, or grade 3 or 4 adverse events occurred(33).

A phase 2, multicenter, open-label study was done in France. They evaluated the efficacy and safety of a fixed dose combination tablet of ledipasvir and sofosbuvir administered for 12 weeks. A total of 44 treatment naïve and IFN experienced patients were enrolled of which, majority were white (82%) and male (64%). Among treatment-experienced patients, 41% had cirrhosis, but only 5% of treatment-naive patients did have cirrhosis.

Of the 44 patients, 41 (93%) reached the primary endpoint of SVR12. Similar percentages of treatment naive (95%) and -experienced (91%) patients achieved SVR12. All 3 patients who did not achieve SVR12 had virologic relapse within 4 weeks of the end of treatment. All the 3 patients were male, 2 had genotype 4r HCV, 1 had genotype 4b and all 3 had baseline HCV RNA of > 800,000 IU/ml. The most common adverse events in this study were asthenia, headache, and fatigue. no patients experienced a serious adverse event or discontinued treatment because of an adverse event(34).

A phase 3, multicenter, randomized, open-label study was conducted in USA and Europe, involving previously untreated HCV genotype 1 infected patients. Patients were randomly assigned in a 1:1:1:1 ratio to receive LDV-SOF in a fixed-dose combination tablet once daily for 12 weeks, LDV-SOF plus ribavirin for 12 weeks, LDV-SOF for 24 weeks, or LDV-SOF plus ribavirin for 24 weeks. 16% of enrolled subjects had cirrhosis, 12% were black, and 67% had HCV genotype 1a infection.

The rates of sustained virologic response were 99% (95% confidence interval [CI], 96 to 100) in the group that received 12 weeks of LDV-SOF; 97% (95% CI, 94 to 99) in the group that received 12 weeks of LDV-SOF plus ribavirin; 98% (95% CI, 95 to 99) in the group that received 24 weeks of LDV-SOF; and 99% (95% CI, 97 to 100) in the group that received 24 weeks of LDV-SOF plus ribavirin. No patient in either 12-week group discontinued LDV-SOF because of an adverse event. The most common adverse events were fatigue, headache, insomnia, and nausea(35).

Another phase 3, randomized, open-label study was conducted in USA. In this study, only INF experienced patients were enrolled. A total of 440 patients were randomly assigned to receive LDV and SOF in a once-daily, fixed-dose combination tablet for 12 weeks or LDV-SOF plus ribavirin for 12 weeks or LDV-SOF for 24 weeks, or LDV-SOF plus ribavirin for 24 weeks. 20% of the 440 patients had cirrhosis and 79% had HCV genotype 1a infection.

The rates of sustained virologic response were high in all treatment groups: 94% (95% CI,87 to 97) in the group that received 12 weeks of LDV-SOF; 96% (95% CI,91 to 99) in the group that received 12 weeks of LDV-SOF and ribavirin;99% (95% CI, 95 to 100) in the group that received 24 weeks of LDV-SOF; and 99% (95% CI, 95 to 100) in the group that received 24 weeks of LDV-SOF and ribavirin. No patient discontinued treatment owing to an adverse event. The most common adverse events were fatigue, headache, and nausea(36).

A phase 3, multicenter, double-blind, placebo-controlled study involving untreated and previously treated patients with chronic HCV genotype 1, 2, 4, 5, or 6 infection, including those with compensated cirrhosis was conducted in USA, Canada, Europe, and Hong Kong. Patients were randomly assigned to receive SOF and VEL in a once-daily, fixed-dose combination tablet or matching placebo for 12 weeks. Treatment was given for 624 patients, of which, 34% had HCV genotype 1a, 19% genotype 1b, 17% genotype 2, 19% genotype 4, 6% genotype 5, and 7% genotype 6. 8% of patients were black, 19% had cirrhosis, and 32% had been previously treated for HCV.

The rate of SVR among patients who received SOF-VEL was 99% (95% CI, 98 to >99). Of the 121 patients who had cirrhosis, 120 (99% [95% CI, 95 to >99]) had SVR. None of the 116 patients receiving placebo had a sustained virologic response. The most common adverse events were headache, fatigue, and nausea. Serious adverse events were reported in 15 patients (2%) in the SOF-VEL group and none in the placebo group(37).

A real-world, prospective study involving 45 HCV genotype 4 infected treatment-naïve, non-cirrhotic, and non-HIV or HBV co infected patients was conducted in Saudi Arabia. Mean log10 HCV RNA was 6.26 ± 6.32 IU/mL and most (91.1%) had baseline HCV RNA levels <6 million IU/ml. The most frequent comorbidities were hypertension and diabetes mellitus (20.0% each). Concomitant medication was taken by 18 patients (40.0%), of whom two took proton pump inhibitors (PPI).

In this study, Overall SVR12 was 97.8% (95% CI: 88.2%–99.9%); one patient (2.2%) relapsed post treatment. No serious adverse events or discontinuations were reported. Eighteen patients (44.4%) had 38 adverse events related to LDV/SOF; the most frequent was headache(38).

A retrospective cohort study of patients with hepatitis C virus who originated from Africa was conducted in England. A total of 91 patients, majority from sub-Saharan Africa, were found to have chronic HCV infection. Majority of these patients were infected with genotype 1; 55 (60.4%) and genotype 4; 26 (29%). 63 of the 91 patients took different combinations of DAAs and SVR was achieved in 56/63 (89%) overall, yet only in 21/28 (75%) of the unusual G1 subtypes. Six treatment failures occurred with SOF/LDV compared to 1 failure on a PI-based regimen. The SVR rate for all other genotypes and subtypes was 100%. The presence of an unusual genotype 1 African subtype or the use of a NS5A inhibitor-based regimen were both significantly associated with a lack of SVR(39).

A single arm prospective study in Rwanda assessed the efficacy of fixed dose combination of 90 mg LDV and 400 mg SOF administered for 12 weeks. They enrolled 300 patients from Feb 6, 2017, and Sept 18, 2017. All patients were infected with Genotype 4 and 4 patients (1%) had genotype 1 coinfection. Of these, 29 (10%) participants were co-infected with HIV, three (1%) had previous HCV treatment, and 68 (23%) participants had cirrhosis.

Overall, 261 (87%, 95% CI 83–91) of the 300 enrolled participants achieved SVR12. But only 27 (56%, 95% CI 41–71) of 48 participants with genotype 4r achieved SVR12 compared to 234 (93%, 90–96) individuals with other subtypes. The most common adverse events were hypertension (97 [32%]), headache (78 [26%]), dizziness (61 [20%]), and fatigue (56 [19%]). No adverse events resulted in treatment discontinuation. In this study, there was significant association between genotype 4r and an APRI score of more than 1·0 with a lack of SVR12(40).

A prospective observational study was conducted in Egypt, between March 2016 and November 2016 involving HCV Genotype 4 infected treatment naïve patients. Eligible patients received Sofosbuvir 400 mg and Daclatasvir 60 mg daily for 12 weeks. 183 patients were found eligible and took the treatment. SVR12 was achieved in 96% of patients treated with this regimen. medications were tolerated with no notable adverse events in 114 patients (64.4%). 22 patients (12.4%) experienced fatigue, 21 patients (11.9%) experienced headache, 11 patients (6.2%) experienced diarrhea, and 9 patients (5.1%) experienced nausea(41).

Another multicenter prospective study was conducted involving 300 Egyptian patients with chronic genotype 4 HCV. Both treatment-naive or treatment-experienced patients were involved. Non-cirrhotic naïve patients were treated with SOF-DCV for 12 weeks. Weight-based ribavirin

was added to this regimen when treating cirrhotic patients and/or treatment experienced patients who received prior interferon therapy. Duration of treatment was extended to 24 weeks with addition of weight-based ribavirin only in treatment-experienced patients who failed to respond to sofosbuvir plus ribavirin regimen.

From the 300 treated patients, 278 (92.67%) achieved SVR12. SVR12 rates of 196 (96.55%) from 203 non cirrhotic and 82 (84.54%) from 97 cirrhotic patients were reported. SVR12 in treatment-naïve and treatment-experienced patients were 94.12% and 87.01%, respectively. only 59 patients (19.7%) reported minor adverse events. The main adverse events were, fatigue in 27 patients (9%), anemia in 17 patients (5.67%), headache in 12 patients (4%), and insomnia in 7 patients (2.3%). Older age, liver cirrhosis and low platelet count were the factors that were significantly associated with non-response to treatment(42).

A prospective treatment follow-up study from Egypt tried to assess the efficacy and safety of 400 mg SOF- 90 mg LDV versus 400 mg SOF and 60 mg DCL given for 12 weeks patients. They enrolled 100 treatment naïve, non-cirrhotic genotype 4 infected patients and were randomly allocated to the two groups. In this study, SVR12 was achieved in 98% and 96% of patients receiving sofosbuvir plus ledipasvir and sofosbuvir plus daclatasvir, respectively with no statistically significant difference. No serious adverse drug effects occurred and there was no drug discontinuation. The most common adverse events reported were headache, and fatigue with no significant difference between the two groups(43).

A recently published prospective study conducted in Ethiopia revealed an overall SVR12 rate of 98.8%. One hundred sixty-four patients infected with genotype 1 to 5 were involved. Nineteen percent of the study participants had evidence of liver cirrhosis. In this study, SVR12 rate was 93.5% among those who are cirrhotic and 100% among those who are non-cirrhotic(44).

3. 0BJECTIVES

3.1. General Objective

To determine treatment outcome of chronic HCV infected patients treated with DAAs at TASH and Adera Specialty clinic, Addis Ababa, Ethiopia, from January 2018 to January 2020.

3.2. Specific Objectives.

- To assess the efficacy of DAAs in achieving SVR12.
- To assess the Effect of Genotype and viral load on treatment outcome of DAAs.
- To assess the impact of Underlying liver fibrosis on treatment outcome of DAAs.
- To assess the comparison between the different DAAs in achieving SVR12.
- To assess the effect of comorbidities on treatment outcome of DAAs.
- To assess proportion of patients who developed DAA related side effects.

4. METHODS AND MATERIALS

4.1. Study area

The study was conducted at two HCV treatment centers in Addis Ababa Ethiopia. These are TASH and Adera internal medicine specialty clinic. TASH is one of the oldest and largest tertiary university hospitals located in the Central part of Addis Ababa Ethiopia. In both TASH and Adera clinic, chronic HCV infected patients are managed with the most experienced consultant gastroenterologists available in Ethiopia.

4.2. Data collection period

Data was collected from April 1, 2020 – July 30, 2020 GC, TASH, Addis Ababa, Ethiopia

4.3. Study Method

Cross-sectional Retrospective study was conducted using data collected from HMIS, patient card, electronic medical record, pharmacy registry and other patient data registries to assess treatment outcome of chronic HCV infected patients using pretested questionnaire.

4.4. Source and study population

4.4.1. Source population

The source population of this study was all patients who have follow up at the adult GI follow-up unit of TASH and Adera specialty clinic during the study period.

4.4.2. Study population

The study population was all HCV infected patients who were treated with DAAs during the study period at TASH and Adera Specialty Clinic.

4.5. Inclusion and Exclusion criteria

4.5.1. Inclusion Criteria

- Chronic HCV infected patients treated with DAAs during the study period

4.5.2. Exclusion Criteria

- Incomplete information in the document

4.6. Study Variables

4.6.1. Dependent variable

- ✓ SVR12
- ✓ Hospital admission

4.6.2. Independent variables

- ✓ Sociodemographic factors including age, sex, place of residence.
- ✓ Degree of Liver fibrosis before Treatment initiation
- ✓ Baseline HCV RNA level
- ✓ Type of HCV genotype and subtype
- ✓ Prior treatment for HCV
- ✓ Hematologic and biochemical profiles of study subjects (Hgb, MCV, PLT, Urea, Creatinine, AST, ALT, ALP, PT, PTT, INR, Albumin and Bilirubin)
- ✓ Comorbidities (HBV, HIV, HTN, DM, IHD, …)
- ✓ Concomitant intake of other medications

4.7. Operational definitions

Sustained Virologic response (SVR12): Is defined as undetectable (< 15 IU/ml) HCV RNA level 12 weeks after end of therapy with DAAs.

DAA induced ADR: defined as patient reported or lab-oratorically detected abnormalities which are labeled as DAA induced side effects by the treating physician.

Treatment failure: defined as the presence of detectable (> 15 IU/ml) serum HCV RNA 12 weeks after completion of DAAs.

4.8. Sample size and sampling technique

The sample size was calculated based on single population proportion formula. Since there were no prior studies done in Ethiopia, it was calculated using SVR12 rate of 95% from studies done in Egypt which has similar genotypic distribution of HCV like Ethiopia. Using this proportion with 95 % confident interval (CI) and 5% margin of error, the calculated sample size was.

$$n = \frac{Z^2 p(1-p)}{d^2} = \frac{1.96^2 \times 0.95(1-0.95)}{0.05^2}$$

n = Sample size

Z = standard statistical value, under normal distribution curve, with significance level at 5% (Za/2=1.96)

P = proportion; most studies showed 95% efficacy of DAAs- Study from Egypt

d = standard error = 0.05

The calculated sample was = 73

Taking 10% for contingency which is 7, the final total sample size was = 80

During conduction of the pilot study, there was incomplete data on many of the patient's documents that were retrieved using the HMIS and pharmacy log books as well as missing charts and wrong diagnosis. Taking this into consideration, the study period was extended from one year to two years based on estimation of the available patient MRNs that fulfill the eligibility criteria to get the minimum sample size. All the patients treated with DAAs during this time period having a complete data were included in the final analysis.

4.9. Data collection Procedures

4.9.1. Data collection instruments

Structured questionnaire was used to reach the objectives. It was developed and adapted from other related researches in a way that will address the objectives of the study.

4.9.2. Data quality measurements

Questionnaire was prepared in English version adopted and modified from different literatures. Then It was used to collect data from patients' chart and electronic records. Patient MRN was taken from HMIS books and pharmacy registries, which was then given to chart room staffs to get patients charts. For some of the patients who had follow up via I care system data was directly acquired from I care system. Data was collected by the principal investigator and interns. Date collectors were trained to make them familiar with the study objectives. Patient chart, electronic medical recording and pharmacy registries were used for data completeness. During data collection, continuous follow up and supervision was done by the principal investigator. In order to check if the questionnaire is clear and addressing the objective, questionnaire was pre-

tested on a 5% of samples. Finally, the collected data was checked for completeness before execution of any data entry process.

4.9.3. Data Analysis and presentation

Data was entered into the latest SPSS version 26 manually. Data was analyzed and result summarized by using descriptive statics. Continuous variables are reported as mean and standard deviation. fisher's exact test was used to check for any association between the categorical variables and considered to be statistically significant when the p value is below 0.05. logistic regression model was used to assess for any association between continuous independent variables and the dependent variable. Confidence interval and power are set at 95% and 80% respectively.

5. ETHICAL CONSIDERATION

Before conducting the study, the study proposal was submitted to the department of internal medicine and ethical clearance was issued by the department of internal medicine and college of medicine and health sciences. Before data collection, a brief explanation about the objective and significance of the study was given for the data collectors.

6. DISSEMINATION OF RESULTS

The results of the study will be presented to Addis Ababa University, college of medicine and health science, department of Internal Medicine. After thesis defense the manuscript will be sent for publication.

7. RESULT

7.1 Study population and demographic data

A total number of 517 patient MRNs with a diagnosis of HCV were collected from HMIS log book and pharmacy registries at both TASH and Adera specialty clinic. Among thus patient card numbers, 67 medical records went missing whereas 450 patient medical records were retrieved. From the 450 medical records, 136 were incomplete, 58 were not having the diagnosis of interest and patients were not treated with DAAs on 172 medical records. So proper data was collected and analyzed only from 84 medical records retrieved using HMIS and pharmacy logbooks.

Among the 84 patients, 47 (56%) were females and the mean age was 49 ±10.6 years. Forty-five (53%) of patients enrolled in this Study, were treated at Adera Specialty clinic. The rest 39 (46.4%) took their treatment at Tikur Anbessa Specialized Hospital.

More than one third (n=31,36.9%) of patients have one or more medical comorbidities. diabetes mellitus and hypertension were diagnosed in 14(16.7%) and 18(21.4%) of patients. Seven (8.3%) and 3(3.6%) of the participants have Human Immunodeficiency Virus (HIV) and Chronic Hepatitis B Virus (CHB) Coinfection respectively. Nine (10.7%) patients had concomitant diagnosis of Fatty liver disease.

Seventy-seven (90%) of patients enrolled in this study were treatment naïve patients. While 7 (8.3%) patients had previous treatment history, 4 patients with SOF/LED regimen, 1 with IFN + ribavirin, 1 with SOF/DCL regimen and 1 patient with both direct acting antiviral and interferon based regimens.

Figure1: Patient medical record selection and eligibility for the study

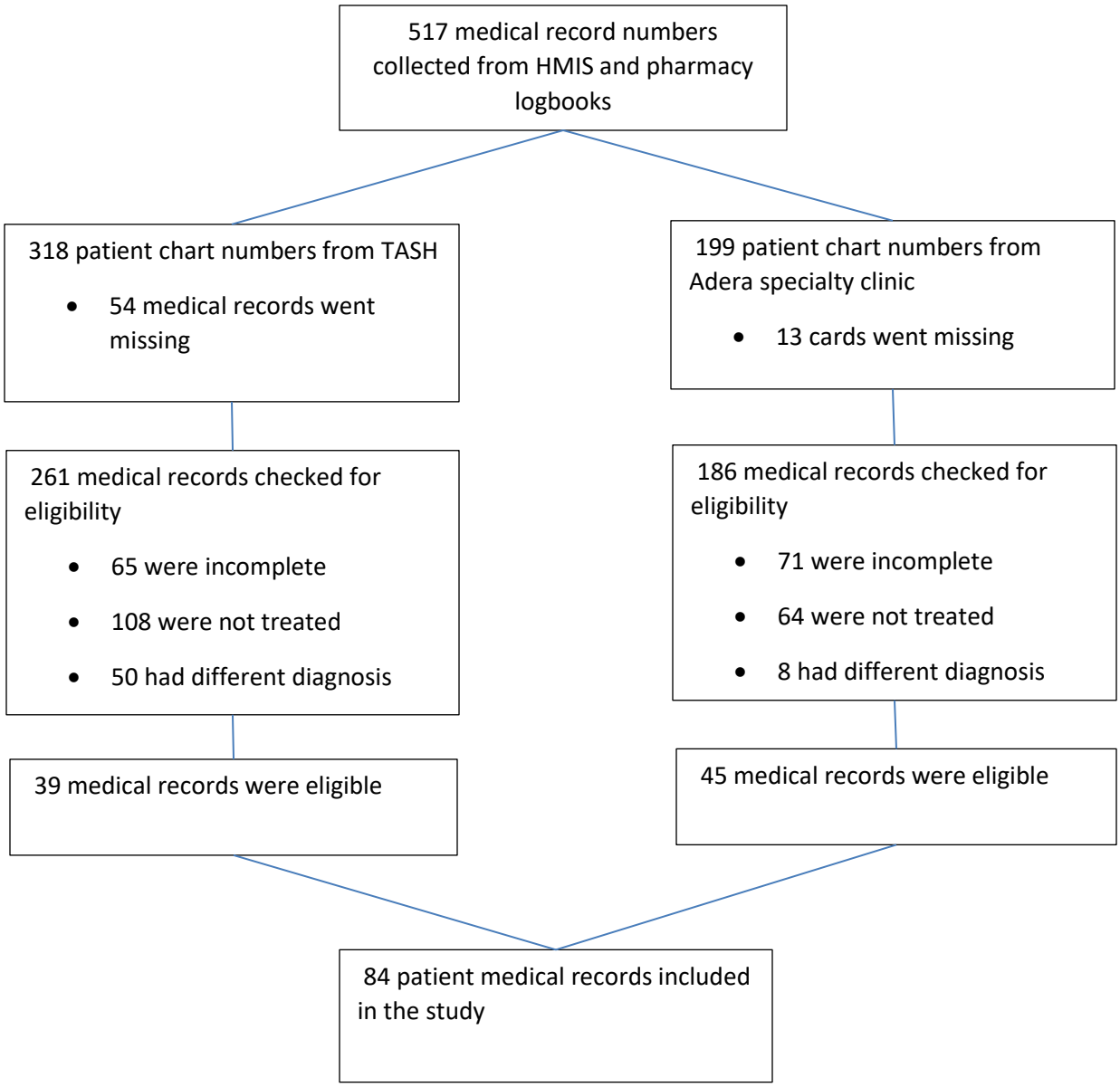
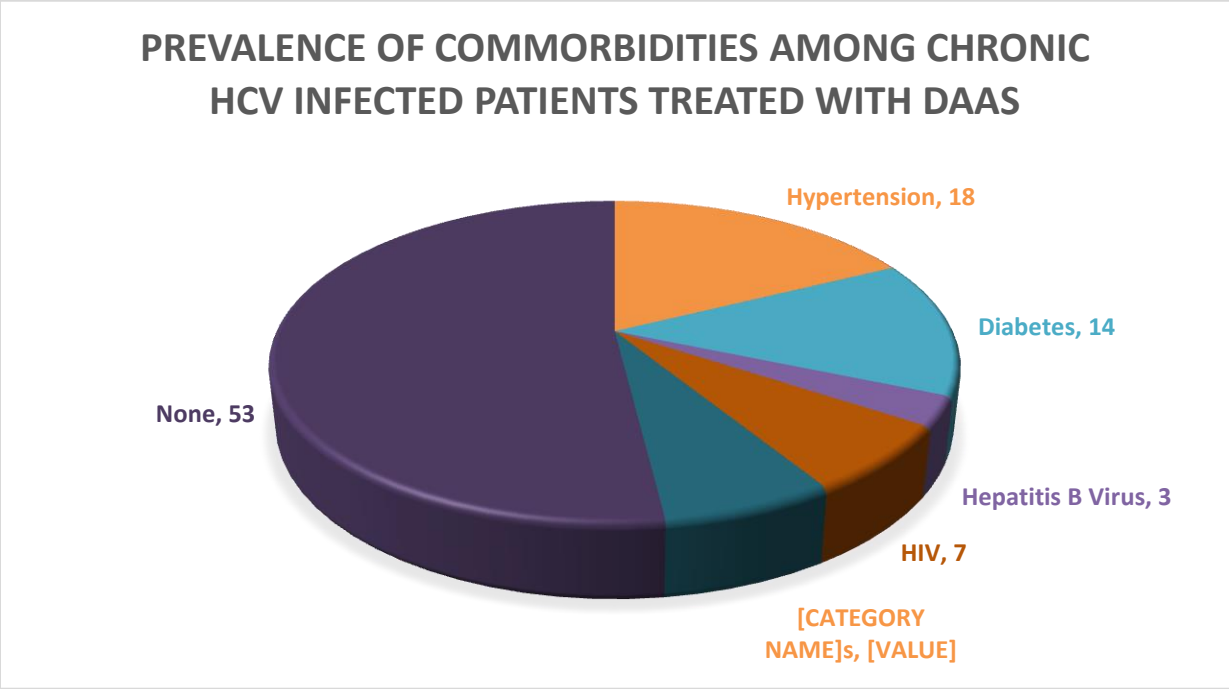


Table 1: Sociodemographic characteristics of chronic HCV infected patients treated with DAAs at TASH and Adera specialty clinic.

Variables		Frequency	Percent(%)
Age in Years	20-35	9	10.7
	36-50	35	41.7
	51-65	34	40.5
	>65	6	7.1
Gender	Male	37	44.0
	Female	47	56.0
Treatment Center	Tikur Anbessa	39	46.4
	Adera	45	53.6
Address	Addis Ababa	66	78.6
	Oromia	4	4.8
	Amhara	7	8.3
	SNNRP	4	4.8
	Others	3	3.6
Medical Comorbidities	Diabetes	14	16.7
	Hypertension	18	21.4
	Hepatitis B Virus	3	3.6
	HIV	7	8.3
	Other	7	8.3
Previous Antiviral Treatment	Naïve	77	91.7
	Experienced	7	8.3

Figure 2: Prevalence of medical comorbidities among chronic HCV infected patients treated with DAAs at TASH and Adera specialty clinic.



7.2 Baseline laboratory, virologic and imaging characteristics

Noninvasive assessment of liver fibrosis using APRI (AST to Platelet ratio) score was done for 74 patients before initiation of therapy. Of these patients, 45 had value ≤1 and 29 had value >1 which is reported to fairly correlate with cirrhosis based on previous studies. Forty-three (51.2%) of the 74 patients had APRI score more than 0.7 which correlates with F2- F4 fibrosis in patients with Chronic HCV infection(45).

Fifty-one (60.7%) of the 84 patients enrolled in this study have their hepatitis C virus genotype known before administration of DAAs. The most frequently found genotype was genotype 4; detected in 39(76.4%) patients, followed by Genotype 1(n= 7, 13.7%) and Genotype 2(n= 3, 5.9%) genotype 3 and 5 accounted for 1(1.9%) patient each. Viral subtype was documented for 13 patients, of these, 5 had subtype 4e, 2 had subtype 4a/c/d, 2 had subtype 2a/c, one patient subtype 2c and 3 patients with subtype 1a/b, 1b and 1g each. Pretreatment HCV Viral load value ranges from 450 to 17 million, the mean being 2.7 million.

Abdominal Ultrasound was documented for (n=80, 95%) patients, and 39 (46%) had normal abdominal sonography report, features of early or late cirrhosis was documented in (n=34, 40%)

of patients. Only 6 patients had documented fibro scan of whom, F1, F2 and F3 Fibrosis was diagnosed on one patient each, and 3 other patients had F4 Fibrosis. Sixteen (19%) patients had Upper GI endoscopy, of whom 13(15.5%) had different grades of esophageal varices, and 3 had normal endoscopy report.

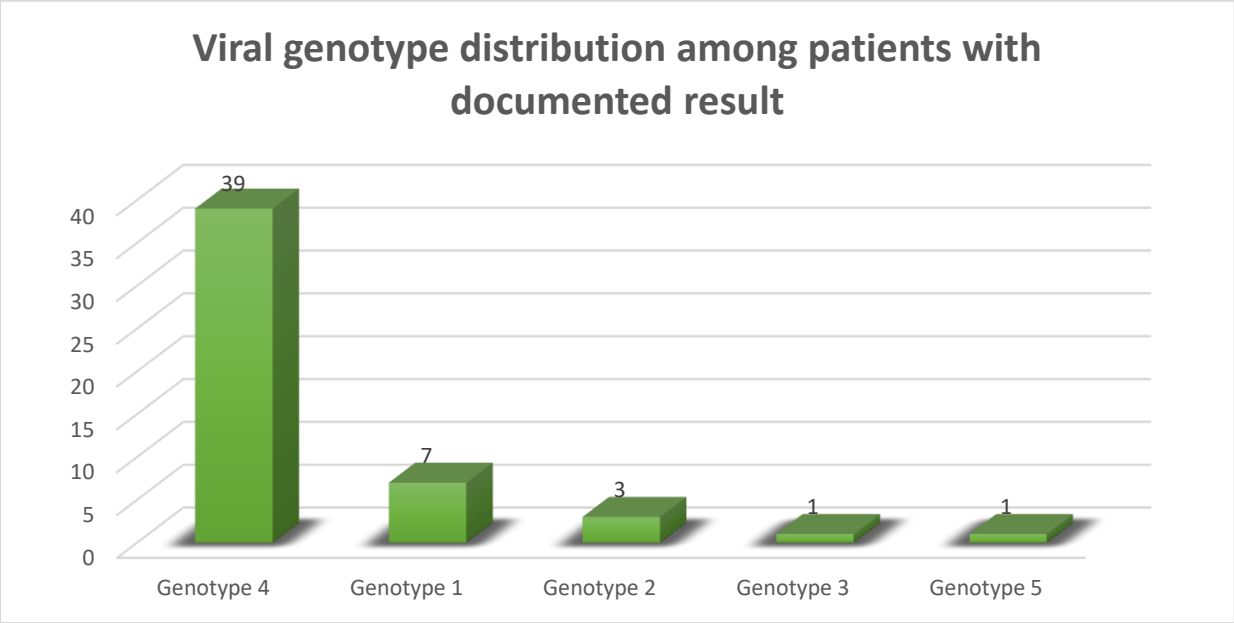
Table 2: Laboratory profile of chronic HCV infected patients treated with DAAs at TASH and Adera specialty clinic**.**

Variables	Mean (SD)
WBC (n=74)	5,570 (1945) /mcl
Hgb (n=74)	15.3 (2.1) g/dl
Platelet (n=74)	173,757 (78,791)/ mcl
Creatinine (n=60)	0.86 (0.21) mg/dl
ALT (n= 77)	61.2 (47.8) Iu/l
AST (n=77)	64.2 (50.3) Iu/l
ALP (n=68)	238 (114) Iu/l
TBILI (n=57)	0.9 (0.8) mg/dl
DBILI (n=53)	0.3(0.2) mg/dl
INR (n=22)	1.3(0.35)
Albumin (n=32)	3.8(0.6) g/dl
Viral RNA level (n=84)	2,776737 (3,997416) Iu/ml

Table 3: Laboratory and Imaging characteristics of chronic HCV infected patients treated with DAAs at TASH and Adera specialty clinic.

Variables		Frequency	Percentage
APRI Score	APRI score < 0.7	31	36.9
	APRI score 0.7 to 1	14	16.7
	APRI score 1.01 to 2	17	20.2
	APRI score >2	12	14.3
	Not Available	10	11.9
HCV Genotype	Genotype 1	7	8.3
	Genotype 2	3	3.6
	Genotype 3	1	1.2
	Genotype 4	39	46.4
	Genotype 5	1	1.2
	Not available	33	39.3
Abdominal Ultrasound	Normal scan	39	46.4
	Portal hypertension with no cirrhosis	1	1.2
	Features of cirrhosis	34	40.5
	Only Splenomegaly	1	1.2
	Fatty liver	5	6.0
	Not documented	4	4.8

Figure 3: Viral genotypic distribution among chronic HCV infected patients treated at TASH and Adera clinic.



7.3 Treatment regimen and duration

SOF/LED combination was the most commonly used regimen in this study, accounting for 50(59.9%) patients. Majority (n=79, 94%) were treated with a 12 week course regimen, 3(3.6%) patients with 24 course regimen and one patient each (2.4%) were treated with 16 and 20-week course regimen.

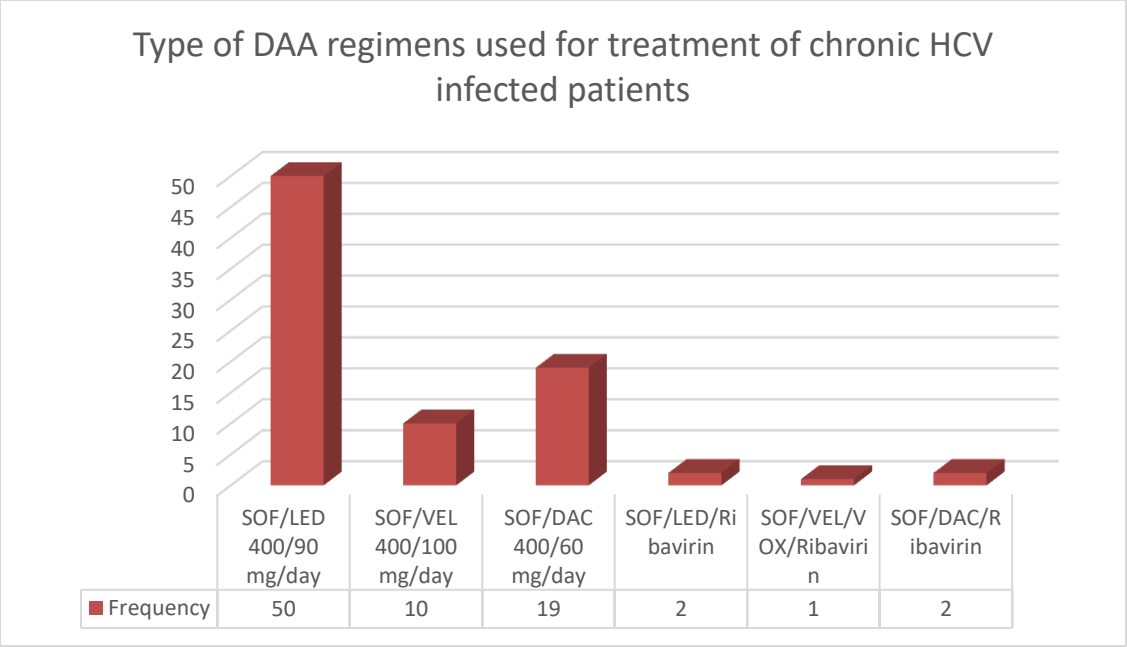
2 patients were hospitalized for Upper GI bleeding during the course of Direct acting antiviral agent and discharged improved after 1 week of hospital stay. DAA associated side effects were reported in 16 (19.1%) patients, 15 (17.9%) had fatigue and nausea where as one patient had headache.

Forty (47.6%) patients were taking concomitant medication while on DAAs, beta blockers and diuretics were the commonest followed by PPI, other antihypertensive agents, antidiabetic agents, statins, HAART, PTU, thyroxine and different anticoagulants.

Table 4: Type of DAA regimens used for treatment of chronic HCV infected patients treated at TASH and Adera specialty clinics.

DAA regimen	Frequency	Percent
SOF/LED 400/90 mg/day	50	59.5
SOF/VEL 400/100 mg/day	10	11.9
SOF/DAC 400/60 mg/day	19	22.6
SOF/LED/Ribavirin	2	2.4
SOF/VEL/VOX/Ribavirin	1	1.2
SOF/DAC/Ribavirin	2	2.4

Figure 4: Types of DAA regimes used for treatment of chronic HCV infected patients treated at TASH and Adera specialty clinic.



7.4 Treatment outcome

Viral load was determined 12 weeks after completion of therapy for all patients. Viral RNA was undetectable in 76(90.5%) patients and detectable in 8(9.5%) patients. SVR12 was achieved in 92.2% of treatment naïve and 71.5% of treatment experienced patients. Based on imaging

findings, 93.5% of patients Among those who have no liver cirrhosis and 85.3% of patients among those who have liver cirrhosis achieved SVR12.

Table 5: Outcome of chronic HCV infected Patients treated with DAAs at TASH and Adera specialty clinics

HCV RNA 12Week after DAA Completion	Frequency	Percent
Detectable	8	9.5
Undetectable	76	90.5

7.5 Factors Affecting Treatment outcome

Since there is a low event rate of failed SVR (n=8, 90.5%), fisher's exact test was used to see for any association between the categorical independent variables and treatment outcome.

Using this model, the degree of liver injury was found to have significant association with treatment outcome. none of the 31 patients with APRI Score of <0.7 had treatment failure, while 7 of the 43 patients with APRI Score ≥0.7 had treatment failure with P value of 0.037.

No significant association was observed using other parameters like gender, presence or absence of liver cirrhosis based on imaging findings, previous treatment history, presence or absence of comorbidities, viral genotype, type of DAAs used and duration of therapy.

Table 6: Fisher's Exact test of correlation showing the association between independent variables and treatment outcome of chronic HCV infected patients treated with DAAs.

Factors		HCV RNA 12 weeks after completion of DAA				P Value
		Detectable		Undetectable		
		Frequency	Percent(%)	Frequency	Percent(%)	
Gender	Male	5	(13.6)	32	(86.4)	0.29
	Female	3	(6.3)	44	(93.7)	
Treatment Center	Adera	3	(6.6)	42	(93.4)	0.46
	TASH	5	(12.8)	34	(87.2)	
Comorbidity	Present	3	(9.3)	28	(90.7)	1.00
	Absent	5	(9.4)	48	(90.6)	
Previous HCV Treatment	Present	2	(28.5)	5	(71.5)	0.13
	Absent	6	(7.7)	71	(92.2)	
APRI Score	<0.7	0	(0)	31	(100)	**0.037**
	≥ 0.7	7	(16.2)	36	(83.7)	
HCV Genotype	G-1	2	(28.6)	5	(71.4)	0.45
	G-2	0	(0)	3	(100)	
	G-3	0	(0)	1	(100)	
	G-4	4	(10.3)	35	(89.7)	
	G-5	0	(0)	1	(100)	
Liver status	Non cirrhotic	3	(6.5)	43	(93.5)	0.27
	Cirrhotic	5	(14.7)	29	(85.3)	
DAA Regimen	SOF/LED	4	(8.0)	46	(92)	0.19
	SOF/VEL	1	(10)	9	(90)	
	SOF/DAC	2	(10.5)	17	(89.5)	
	SOF/LED/ Ribavirin	0	(0)	2	(100)	
	SOF/DAC/ Ribavirin	1	(50)	1	(50)	
	SOF/VEL/VOX/ Ribavirin	0	(0)	1	(100)	
Duration of treatment	12 weeks	7	(8.9)	72	(91.1)	0.402
	16 weeks	0	(0)	1	(100)	
	20 weeks	0	(0)	1	(100)	
	24 weeks	1	(33.3)	2	(66.7)	

Using binary logistic regression, there was no statistically significant association between continuous variables and treatment outcome. However, baseline serum viral RNA and direct bilirubin levels were found to have p values close to the level of significance (P-value:0.05)

Table 7: Bivariate logistic regression showing the association of independent variables with the outcome of chronic HCV infected patients treated with DAAs at TASH and Adera clinic.

Variables	Mean ± SD		COR (95%, CI)	P- Value
	Detectable	Undetectable		
Age	52.25±7.4 years	48.6±10.9 years	0.968(0.901-1.039)	0.366
WBC	6645±2811/mcl	5474±1849/mcl	1.00(0.999-1.000)	0.167
Hemoglobin	15.7±1.9 g/dl	15.2±2.0 g/dl	0.867(0.540-01.392	0.554
Platelet	135,666±40,202/mcl	177,117±80,634/mcl	1.000(1.000-1.000)	0.213
ALT	58.1±22.5 Iu/l	61.4±49.4 Iu/l	1.002(0.983-1.020)	0.871
AST	72.1±30.9 Iu/l	63.5±51.6 Iu/l	0.997(0.983-1.012)	0.685
ALP	267±104.8 Iu/ml	235±114.8 Iu/l	0.998(0.990-1.005)	0.548
Total Bilirubin	1.3±0.76 mg/dl	0.8±0.83 mg/dl	0.659(0.318-1.366)	0.262
Direct Bilirubin	0.45±0.23 mg/dl	0.24±0.22 mg/dl	0.043(0.002-1.173)	**0.062**
INR	1.61±0.49	1.26±0.34	0.081(0.001-4.694)	0.225)
Creatinine	0.82±0.06 mg/dl	0.86±0.23 mg/dl	2.324(0.028-193.121)	0.709
Serum Albumin	3.85±0.91 g/dl	3.82±0.59 g/dl	0.920(0.126-6.739)	0.935
Viral Load	5,431,474.75± 5,988,634 Iu/ml	2,497,290.88± 3,675,001 Iu/ml	1.000(1.000-1.000)	**0.066**

8. DISCUSSION

In this study a total of 84 patients with chronic HCV infection were included. Mean age is 49±10.6 years and females accounted for 47(56%) cases. Previous studies from Egypt(42) and Rwanda(40) had mean age of 49.7 and 64 years respectively. Females accounted for 40.67% in the study from Egypt and 62% in the study from Rwanda. The difference in sex proportion could be due to epidemiologic factors or methodological differences. Thirty-four (40.5%) patients in this study were found to have liver cirrhosis based on imaging parameters which was 19% on a recent study conducted in Ethiopia(44) and 77 (91.7%) patients were treatment naïve. Concomitant medical comorbidities were diagnosed in more than one third of patients (n=31, 36.9%), diabetes and hypertension being the commonest ones.

Among the 51(60.7%) patients with Documented chronic HCV infection, Genotype 4 accounted for 39 (76.5%) patients followed by genotype 1 and 2. this result is in agreement with previous studies conducted in Ethiopia which reported similar finding. In one of the studies genotype 4 accounted for 35(77.6%) of the 46 study participants followed by genotype 2 and 1 respectively(4). In another prospective study conducted in Ethiopia, genotype 4 accounted for 120(60%) of the 200 study participants while genotype 1, 2 and 3 accounted for the remaining patients respectively(3). A recent prospective study done among Ethiopian chronic HCV infected patients also showed similar genotypic distribution(44).

Out of the 84 patients, 76(90.5%) achieved successful eradication of HCV. SVR was 93.5% among non-cirrhotic and 85.3% among those who were diagnosed with cirrhosis based on imaging features (P value: 0.25). SVR12 was achieved in 92.2% of treatment naïve and 71.5% of treatment experienced patients but the difference was not statistically significant (P value: 0.13).

In this study, APRI score was used to assess the degree of liver fibrosis based on reports from previous studies(45). There was a statistically significant difference in achieving SVR12 between patients with significant liver fibrosis (F2-F4) assessed by using APRI score cut point of 0.7. All of the patients with APRI score of < 0.7 achieved SVR while only 83.7% of the patients with APRI score of ≥0.7 achieved SVR (P- value: 0.037). There was no statistically significant difference in outcome using APRI score cut points of 1 and 2.

The result of this study is in accordance with other studies done in Africa. One study done in Rwanda on patients with Genotype 4 and 1 infection showed an overall SVR of 87%. The regimen used for this study was SOF/LED for 12 weeks. In this study, APRI score of ≥1 and genotype 4r were found to have significant association with non-response(40).

Another study done on Patients of African origin using several combinations of DAAs showed an overall SVR rate of 89%. In this study majority of the patients were infected with genotype 1 and 4. They reported that the use of NS5A based regimens and infection with unusual genotype 1 subtypes were found to have significant association with lack of SVR(39). In our study there was no observed association between treatment outcome and the type of DAAs used as well as viral subtype patients had. However, there were few documented viral subtypes in our study and it is difficult to conclude.

A Prospective study from Egypt using SOF/DCL and SOF/LED regimens for 12 weeks reported an overall SVR of 96% and 98% respectively. This outcome seems a little bit higher than our study but their study participants were only non-cirrhotic, treatment naïve genotype 4 infected patients(43).

A recently published prospective study conducted on 164 Ethiopian patients showed an overall SVR rate of 98.8%. In this study, 19% of patients had evidence of cirrhosis and SVR was 93.5% among cirrhotic and 100% among non-cirrhotic patients. Although the result of our study is almost comparable with this study, the slight difference in outcome could be due to difference in methodology(44). The other possible explanations for lower SVR rate in our study could be due to higher number of patients with cirrhosis, differences in types of regimens used and duration of treatment.

In this study, we found out that patients who failed to achieve SVR had a higher baseline mean viral RNA level compared to patients who achieved SVR with P value of 0.66 which is close to the level of significance. Few studies reported association between higher viral RNA level and failure to achieve SVR. However, differences in SVR rates were observed between patients with higher and lower baseline viral RNA level(34).

With regard to the predictive factors associated with non-response to therapy, our result revealed that higher degree of liver fibrosis (F2-F4) assessed using APRI score is associated with failure

to achieve SVR. Several studies have reported association of SVR rate with the degree of liver injury. Higher SVR rates were reported in patients with chronic hepatitis or child A liver cirrhosis than in those with child B or C liver cirrhosis(40,42,46).

9. CONCLUSION

Based on this study majority of the patients were found to be infected with genotype 4 HCV. The most commonly used regimen was SOF/LED followed by SOF/DCL and SOF/VEL. These regimens appear to have favorable outcome with high rate of SVR and good safety profile in the treatment of chronic HCV infected patients. Presence of F2-F4 liver fibrosis assessed by using APRI score cut point of 0.7 was found to be associated with non-response to treatment.

10. RECOMMENDATION

To conduct a large multicenter prospective study in order to extensively look for predictors of outcome and degree of association including assessment of viral subtypes.

Recommend for the government, policy makers and the medical community to all work together towards further capacity building, diagnosis and treatment of chronic HCV infected patients in order to achieve the goal of HCV elimination.

11. LIMITATIONS OF THE STUDY

Even though TASH and Adera specialty clinic are centers where patients are referred and managed from all over the country, majority of the patients (78.6%) in this study are from Addis Ababa. This might have an impact on the generalizability of the study.

There are few number of patients with failed SVR which makes it difficult to assess the type and degree of association between some of the variables and the outcome.

This is a retrospective study and there was incomplete data for some of the parameters like laboratory profiles, imaging reports and patient reported medication side effects. These and other factors may affect the study as some of the parameters may have association with the treatment outcome.

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Annex:

QUESTIONNAIRE

This is a questionnaire which is prepared to undergo retrospective study on treatment outcome of chronic HCV patients treated with DAAs at 2 centers in Addis Ababa, Ethiopia over a period of 2 years. The data will be collected from patient charts, electronic medical recording systems and HMIS.

Date _____ MRN/ICARE ID_____

Treatment Center: _____

1. SOCIODEMOGRAPHIC CHARACTERSTICS

1.1 Age _____

1.2 sex

1.2.1 M 1.2.2. F

1.3 Address

A) Addis Ababa B) Oromia

C) Amhara D) SNNRP

E) others (specify) _____

2. Comorbidities

A. HBV
B. HIV
C. DM
D. IHD
E. HTN

F. Others_____

3. other liver diseases

A. Alcoholic liver disease
B. HCC
C. Fatty Liver
D. AIH
E. Hemochromatosis
F. Wilsons
G. Others

4. Previous HCV treatment history

A. Yes
B. No

5. If Yes for Q4, type of previous treatment regimen_____

6. HCV Genotype and subtype_____

7. Baseline Viral RNA level_____

8. Hematologic and Laboratory profiles

A. CBC

	Baseline (date_____	End of treatment (date_____
WBC		
Hgb		
Platelet		

	Baseline (date_____	End of Treatment (date_____
Creatinine		
BUN		

B. Renal function test

C. Liver chemistries and tests

	Baseline (date_____	End of Treatment (date_____
ALT		
AST		
ALP		
Total Bilirubin		
Direct Bilirubin		
PT		
INR		
Albumin		

D. **APRI** score at Treatment initiation _____

9. Fibro scan at treatment initiation

A. Done (finding) _____

B. No done

10. Abdominal Ultrasound

A. Normal
B. Portal HTN
C. Features of Cirrhosis
D. Per portal fibrosis
E. Splenomegaly

11. Endoscopy

A. Esophageal Varices
B. Gastric Varices
C. Both Esophageal and Gastric varices
D. Portal Hypertensive gastropathy
E. Not done

11. Current Treatment

A. current DAA treatment regimen and dose_____
B. duration of treatment_____
C. Viral RNA level

	Baseline Date_____	12 weeks after end of therapy
RNA Level		

12. Hospitalization during treatment period

A. Yes
B. No

13. If yes, reason for Hospitalization (Specify) _____

14. Outcome of Hospitalization

A. Discharged improved
B. Death

15. length of hospital stay (in days) _____

16. Concomitant Medication intake during DAA treatment period

A. PPIs_____
B. HAART_____
C. Statins_____
D. Anticonvulsants_____
E. Antidepressants_____
F. Beta blockers_____
G. Others _____
H. None

13. Drug induced (DAAs) side effects

A. Headache
B. Nausea
C. Fatigue
D. Diarrhea
E. Insomnia
F. Anemia
G. Others_____
H. None

Data Collector Name _____

Date collector Signature _____

DECLARATION

I, the undersigned, declare that this postgraduate thesis is my original work, has not been presented for a degree in this or any other university and that all sources of material used for the thesis have been duly acknowledged.

Postgraduate Candidate: Yonatan Habtamu (MD, Internal Medicine Resident)

Signature: …….

Date of Submission: December 29, 2020

This thesis has been submitted with my approval as advisor.

Advisor: Rezene Berhe (MD, Internist, Consultant gastroenterologist and hepatologist)

Signature: …….

Date: …….

Place: Addis Ababa, Ethiopia