Determinants of Chronic Liver Diseases among adult patients attending Gastroenterology clinic of Ayder Comprehensive Specialized Hospital, Mekelle, Ethiopia, 2019.

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ABSTRACT

Background: Chronic liver diseases are worldwide problems especially in the developing world. In Ethiopia, almost one-third of mortality in medical wards was due to chronic liver diseases. There is a paucity of data about determinant factors in Ethiopia, particularly in the study area. This study aimed to assess determinant factors of chronic liver diseases among patients attended in the Gastroenterology unit of Ayder comprehensive specialized hospital in Mekelle, Ethiopia, 2019.

Methods: An unmatched case-control study was conducted to include 281 participants using a pre-tested interviewer-administered questionnaire and chart review checklist systematically. Data were entered into Epi-data version 3.1 and analyzed using SPSS 20.0. Logistic regression analysis was used to assess determinant factors. The degree of association was interpreted using the Adjusted odds ratio with 95% CI and P-value <0.05.

Results: The mean (SD) age of the study participants were 41± 13 years for cases and 40± 15 years for controls. The majority, 77(81.9%) of cases and 115(61.5%) of controls were males. Fifty-two (55.3%) of cases and 118(63.1%) of controls were from urban residence; 37(39.4%) of cases and 53(28.3%) of controls were farmers. There was a significant association between alcohol consumption (AOR: 2.8; 95%CI (1.1, 7.0)), herbal medication use (AOR: 14; 95%CI (5.2, 42)), parenteral medication use [AOR: 8.7; 95%CI (3.0, 24.8)] and being Hepatitis B virus-positive (AOR: 12; 95%CI (3.0-49)) with Chronic liver diseases.

Conclusions: Alcohol consumption, herbal medication use, positive serum hepatitis B(HBV) and parenteral medication use were determinant factors of chronic liver diseases.
BACKGROUND

Chronic liver disease (CLD) is defined as a progressive disease that causes deterioration and destruction of liver cells. The connective tissue fibroids disturb the lymph and blood flow thus interferes with the normal structure and physiology of the liver (Devon). It results in scarring to the liver leads to abnormal liver function (Sanchez & Talwalkar, 2012). Chronic liver diseases can be classified as - Alcohol induced chronic liver disease, viral chronic liver disease (Hepatitis), Fatty chronic liver disease, Autoimmune chronic liver disease, Metabolic and inherited chronic liver diseases (Udell et al., 2012).

Liver disease is among the most prevalent and costly diseases with a huge human and economic burden and accounts for approximately 2 million deaths per year worldwide (Asrani, Devarbhavi, Eaton, & Kamath, 2019). According to the Global Burden of Disease study, 1.75 million deaths were attributable to (CLD) (Desai & Reau, 2016).

In the United States, Over 30 million people are likely to have some form of chronic liver disease and from 1999 to 2016 the annual deaths increased by 65% and people aged 25-34 have experienced the greatest relative increase in mortality, driven by deaths due to alcoholic chronic liver diseases (Blachier, Leleu, Peck-Radosavljevic, Valla, & Roudot-Thoraval, 2013). In Europe, it causes around 170,000 deaths per year and the burden of the disease continues to grow due to an upwards shift in obesity and type 2 DM (Mokdad et al., 2014).

In Sub-Saharan Africa chronic liver diseases-related deaths doubled between 1980 and 2010 and therefore the Central African Republic, Gabon, Malawi, Uganda, and Cote d’Ivoire were among the very best 10% of nations for these deaths in 2010 (Misganaw, Mariam, Araya, & Ayele, 2012). it had been reported that 12% of the hospital admissions and 31% of the mortality in medical wards in Ethiopian hospitals was thanks to CLD (Kooffreh-Ada, Okpara, Oku, Okonkwo, & Ihekwaba, 2015). Current epidemiological data reveals that in developing countries (like studies wiped out Nigeria in 2015 and in Addis Ababa in 2018), hepatitis B viral (HBV) infection is that the main determinant factor of CLD (Semira Abdelmenan, 2018; Younossi et al., 2011). Non-alcoholic liver disease (NAFLD) additionally plays a serious role within the etiology of CLD particularly in areas (like America) where obesity and DM may be a growing public health challenge (Setiawan et al.,...
A study wiped out America in 2016 shows that NAFLD was the foremost common determinant factors of CLD (Miquel, Clèries, Vergara, & Vela, 2018).

Globally, CLD is an important source of health and economic burden, it causes substantial health and economic burden in the US. In Spain in 2013, healthcare expenditures on patients with CLD totaled €142.1 million representing 1.8% of the total 2013 healthcare budget and hospitalization accounted for 35.1% of the total expenditure and outpatient care 22.4% (Gutteling, De Man, Busschbach, & Darlington, 2007). Studies which were done in health related quality of life of chronic liver diseases patients have shown many physical and psychological factors have been associated with CLD (Nicolas, Wang, & Nyberg, 2016).

Many studies try to decrease its burden by investing large amounts of money in funding research, vaccines and drug development to prevent new hepatitis infections (Shiferaw, Letebo, & Bane, 2016). However, the number of patients have dramatically increased because of alterations in people’s lifestyles and screening services are not widely available (Chiu et al., 2016; Sanchez & Talwalkar, 2012). The Ethiopian Health and Nutrition Research Institute, Centers for Disease Control and Prevention, World Health Organization, and Tigray Regional Health Bureau established the CLD surveillance system in 2017, but little was known about the geographical extent, trend, and epidemiology of this disease (Cainelli et al., 2016).

Although prior studies provide valuable information on the determinant factor CLD, most were conducted in highly developed countries and regions. It has an important and largely neglected health issue in low and middle income countries, like Ethiopia which carry the highest burden (Anurag et al., 2015). This paper was assessing variables which were not studied in the previous studies like variables history of herbal medication use, BMI, history of parenteral medication use. There is limited research examining the determinant factors of CLD in Ethiopia. And there is paucity information recently about determinant factors of CLD in the study area. Therefore, the aim of this study was intended to assess determinant factors of CLD in the GI unit of ACSH, Mekelle, Ethiopia, 2019

METHODS

Study population, setting and period
A Hospital -based unmatched case–control study design was conducted from March 25 to May, 2019 among chronic liver disease patients who attended in GI unit of Ayder Comprehensive
Specialized Hospital (ACSH). All CLD (cases) and non-CLD (controls) patients who were attending in the GI unit of ACSH during data collection period were the source population while All selected with confirmed CLD (cases) all selected with confirmed non-CLD (controls) patients who attended in the GI unit of ACSH during the data collection period were study population. Critically ill patients, pregnant mothers, and those patients with ascites were excluded from the study.

Sample Size Determination and sampling procedure
The sample size was 281, determined by the formula used for unmatched case control study using EPI INFO version 7.1 software.

Assumptions: Three common factors were taken from previous studies includes alcohol (David & Hamilton, 2010), personal history of liver disease (Nazzal & Sobuh, 2014) and male sex (Campos, 2004) to compute the largest sample size. After comparing the sample sizes, the factor sex (male) gave the largest sample size. Percent of exposed among controls (48.4%) & percent of exposed among cases (67.6%) & odds ratio from previous study (2.2), power of the study (1-β) to be 80%, 95% confidence level with two to one ratio among control to cases and considering 10% non-response rate, the final required sample size was 281 (94 cases and 187 controls). Sample population were selected with systematic random sampling technique by considering the data collected from September 9 to November 8, 2018, the total patient attended in the GI unit were 980 of which 190 were chronic liver diseases patients (N; (K=2)) for cases and the remained 790 were non liver diseases patients attended in GI (N; (K=4)) for control. The first sample was selected using lottery method. For every case two controls were selected (i.e. for cases, (N=190) every 2nd patient and for controls (N=790) every 4th) patient were recruited till the required sample size attained.

Data collection procedure and data quality control
Primary data were collected from eligible voluntary cases and controls using structured interviewer administered questionnaires, whereas secondary data were collected by reviewing patient medical charts using document review checklist adopted from various literatures (Semira Abdelmenan, 2018; Younossi et al., 2011). The measurement of height and weight were taken from each participants using standardized and calibrated equipment. The questionnaire was prepared primarily in English was translated to local language Tigrigna and back translated to
English by language experts. The data collection tools had four sections: -Socio-demographic characteristics related factors, behavioral related factors, socio-cultural related factors and Clinical related risk factor. Data were collected by three BSc nurses supervised with one BSc holder who were trained for one day about the research objective, eligible study subjects, data collection tools and procedures, and interview methods. To assure the quality of data, pretest was conducted on 5% of the sample size in Mekelle General Hospital two weeks before the actual data collection period. The overall activities were coordinate by supervisor and principal investigator.

**Study variables**

The dependent (outcome) variable for the study was Chronic liver diseases. The independent variables were Socio-demographic variables (such as age, sex, marital status, residency, ethnicity, educational level, monthly income, occupation); Socio-Cultural Factors (like Tattoo on the body, history of herbal medication use); Clinical Related Factors (History of blood transfusion, history of surgical procedure, history of liver diseases (family or personal), and history of parenteral medication use, Type2DM, HTN, Serum hepatitis infection (HBV&HCV), elevated liver enzyme (AST&ALT) and Thrombocytopenia) and Behavioral Factors (Alcohol consumption, cigarette smoking, Body Mass Index). Body Mass Index is defined as body mass divided by the square of the body height, and was expressed in units of kg/m$^2$, resulting from mass in kilograms and height in meters. The subjects were categorized according to BMI (kg/m$^2$): underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), and obese (≥30.0)(Kamal & Cheung, 2007).

Alcohol Consumption-was assessed by CAGE standard Screening Tool. The tool has four yes/no questions if the patient responds yes, two and above , is considered alcoholic (Afdhal et al., 2008). Thrombocytopenia- Low levels of platelets in the blood (<150,000/microliter).Was categorized as mild (>75,000/–<150,000/microliter),Moderate (50,000-75,000/microliter) and severe (<50,000/microliter)(Yang et al., 2008).

**Data management and statistical analysis**

Data were cleaned and entered using Epi-data version 3.1 and analyzed using SPSS version 20. Both descriptive and analytical statistical procedures were employed. Bi-variate and multi-variable logistic regression analyses with a 95% confidence interval were used to ascertain the association between the independent variables and the outcome variable at p-value ≤0.05. Hosmer-Lemeshow
test was used to check fitness of the model. Hosmer-Lemeshow goodness of fit test greater than 0.05 was considered as a good model fit to final prediction. Multicollinearity was checked by variance inflation factor (VIF). And variables that were statistically significant at the bi-variate level with P-value of < 0.25 were entered into a multivariable logistic regression analysis model to examine determinant factors of CLD. Statistical association in Multi variable analysis is declared at P-value <0.05.

RESULTS
Socio-Demographic Characteristics of the Study Participants
A total of 94 cases (CLD) and 187 controls (Non-CLD) were participated in the study making a response rate of 100%. Majority, 77(81.9%) of cases and 115(61.5%) of controls were males while, 17(18.1%) of cases and 72(38.5%) of controls were females. The mean (SD) age was 41±13 years for cases, ranging from 18-75 years and 40±15 years for controls, ranging from 18-92 years. The age distribution showed that 35(37.2%) of cases and 56 (29.9%) of controls were between age group of 30-41 years. Fifty-two (55.3%) of cases and 118(63.1%) of controls were from urban residence; 37(39.4%) of cases and 53(28.3%) of controls were farmers and, 67(71.3%) of cases and 113(60.4%) of controls were married. (Table-1)

Behavioral and Socio-cultural Characteristics of the Study Participants
Among the total respondents 53(56.4%) of cases and 51(27.3%) of controls were alcohol consumers (CAGE score ≥2) and 33(62.3%) of cases and 21(41.2%) of controls were consuming alcohol for ≥10 year. The mean(SD) baseline BMI of cases were 22±3 kg/m² with the minimum of 17.5 kg/m² and maximum 29.1kg/m² and 21.7±3 kg/m² for controls with the minimum of 17.5 kg/m² and maximum 28.2 kg/m². Of the total respondents 34(36.2%) of cases and 24(12.8%) of controls had tattoo on their body and also 77(81.9%) of cases and 42(22.5%) controls had history of herbal medication use (Table-2)

Clinical Characteristics of the Study Participants
In the current study, 78(83.0%) of cases and 56(29.9%) of controls had history of parenteral medication use. The mean (SD) of AST level was 66±74 IU/L and ranging from 12.6 to 368.0IU/L for cases and 48± 58 IU/L and ranging from 9 to 462IU/L for controls and of 28(29.8%) of cases and 34(18.2%) of controls had mild thrombocytopenia (75,000-150,000/microliter) (Table- 3).
Out of the total respondents 73(77.7%) of cases and 28(15.0%) of controls were positive for serum HBV and 21(22.3%) of cases and 159(85.0%) of controls were HBV negative (figure2).

**Determinant Factors of Chronic Liver Diseases**

During the bi-variate logistic regression analysis being alcohol drinkers, history of herbal medication and parenteral medication use and serum HBV status had statistically significant at P-value <0.05 while being sex, residence, educational status, tattoo on the body, history of Type2DM, family history of liver diseases, personal(individual) history of liver diseases, and HCV status were significant at P-value <0.25 and were included in multi-variable logistic regression. However, the multivariable logistic regression analysis showed that the odds of being alcohol consumer (CAGE score ≥2) were 2.8 times higher risk of acquiring liver disease (AOR: 2.8; 95% CI (1.1, 7.0)) compared to nondrinkers. The result revealed that those who had history of herbal medication use had nearly 14 time higher odds of risk of acquiring liver disease (AOR: 14; 95% CI (5.2, 42.0)) compared to non-users. Hepatitis B-positive participants were more likely to (AOR: 0.09; 95% CI (0.03, 0.30)) have liver disease as compared to those who had negative test result. Moreover, the odd of developing liver disease was higher among who had history of parental medication use (Table -4).

**DISCUSSIONS**

The aim of the study was to assess the determinants of chronic liver diseases among adult patients attending in the GI unit of ACSH, Mekelle, and Tigray, Ethiopia

This study revealed that, alcohol drinkers (CAGE score ≥2) were more likely to develop CLD compared to non-drinkers; this is in line with the study conducted in Addis Ababa, Iran, Taiwan, USA, Europe and Italy, (Afdhal et al., 2008; David & Hamilton, 2010; Meng et al., 2012; Trichopoulos et al., 2011), (Stroffolini et al., 2018). This is due to that over ninety percent of consumed alcohol is processed in liver while the rest (less than ten percent) exits the body via urine, sweat and breathing. Chronic alcohol drinking causes destruction of liver cells which results in scarring of the liver (cirrhosis), alcoholic hepatitis and cellular mutation that lead to CLD as well as liver cancer (HCC) (Hong et al., 2015).

On the contrary, the result of this study is inconsistent with study conducted in Nigeria (Error! Reference source not found.) the difference might be due to the criteria used to classify drinker and non-drinker (in this study CAGE standard tool is used similarly with the study done in U.S.A
(Navarro et al., 2017) but in the study conducted in Nigeria duration year of drinking and amount of gram of alcohol ingested was used to classify drinker vs non-drinker. As it was been shown that the amount of alcohol ingested (irrespective of the type of alcohol consumed) was the most important determinant factors for CLD with the risk of developing the diseases increasing with the ingestion of >60-80g/day of alcohol for ten years for male and >20g/day for female. CAGE standard tool can’t consider the amount of alcohol ingested so the variation might be due to this reason. Community participation as seen in other programs and health interventions also reported an effective tool in the prevention of harmful alcohol use. Supported and empowered communities can use their local knowledge and cultural experiences and values to change behaviors.

Herbal medication use is common practice all over the country. In the present study, the risk of developing CLD had nearly 14 times higher among clients who had history of herbal medication use as compared with who hadn’t history of herbal medication use. Studies have revealed that history of herbal medication use was at increased risk of CLD. This study also reveals the same result with the study conducted in Nigeria and China (David & Hamilton, 2010; Meng et al., 2012; Navarro et al., 2017). This is due to Herbal products are not tested with the scientific rigor required of conventional drugs and also cannot be marketed for the diagnosis, treatment, cure or prevention of the diseases so using such kind of medicine for health is risky because such kind of drugs hadn’t common dose and frequency since they aren’t scientifically approved. One of the major roles of liver is to act as a filter for toxins. It does this through a complex metabolic process by taking the medicine we ingest and breaking them down into non-toxic components and flushing them out of the body so herbs can damage the liver during this process. Certain herbs can form toxic metabolites that can damage liver cells and as a result the liver can became so damaged that it can’t function well as usual. Attention should be given to minimize the use of herbal medication in the community (David & Hamilton, 2010).

In this study, the likelihood of developing CLD in clients with history of parenteral medication use (injectable drug use (IDU) were higher compared with their counterparts. This result is consistent with the study conducted in Nigeria and Iran (Misganaw et al., 2012; Semira Abdelmenan, 2018). This is due to drug induced chronic liver diseases due to the result of direct toxicity from the administered drug or their metabolites, injury may result from immune-mediated mechanisms. Initial hepatocyte destruction due to direct drug toxicity may be further enhanced by the
subsequent inflammatory reaction. The first step of drug metabolism is known as phase I reaction and is mediated by enzymes of the hepatic cytochrome p450 system. Intermediate bioactive products generated in this step may interact with various cellular organelles (e.g. mitochondria) leading to hepatocyte dysfunction and cellular demise (Jahangirnezhad, Hajiani, Makvandi, & Jalali, 2011). But the result of this study is not supported by another study done in Iran (Bapna, Tripathi, & Tekur, 1996). This variation might be related with the sample size used. Other reason might be the use of parental medication is more common in developing countries and many patients self-medicate because most drugs are available without a prescription from a doctor (Kawaguchi et al., 2015).

In the current study, the risk of developing CLD among clients who were HBV positive is more likely as compared to their counter parts. This result is consistent with the study conducted in Addis Ababa, Europe, Japan, China and North Africa respectively (Bahri et al., 2011; Schölmerich & Holstege, 1990; Stroffolini et al., 2018; Younossi et al., 2011; Zhang, Wang, Han, & Zhuang, 1998). This is due to the histological end points of chronic active HBV leading liver cell necrosis, inflammation, cytokine production and liver scarring (fibrosis). Hepatocyte cytolysis due to T lymphocytes-mediated cytotoxicity probably directed against Hepatitis B antigen on the hepatocellular membrane has a leading role in liver damage. In an early stage, active viral replication takes place; HBV-DNA is not integrated into the host cells. Liver cell necrosis is due to cytotoxic T lymphocytes. In a second phase, often after many years, HBV-DNA is integrated into hepatocyte clones and autoimmune-like reactions lead to further liver cell damage (Schölmerich & Holstege, 1990).

**List of abbreviations and acronyms**

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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACSH</td>
<td>Ayder Comprehensive Specialized Hospital</td>
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<tr>
<td>ALT</td>
<td>Alanine aminotransferase</td>
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<td>AST</td>
<td>Aspartate aminotransferase</td>
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<td>CLD</td>
<td>Chronic Liver Diseases</td>
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<td>EPI</td>
<td>Epidemiological Information</td>
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<td>GI</td>
<td>Gastro Intestinal</td>
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<td>HBV</td>
<td>Hepatitis B Virus</td>
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<td>HCV</td>
<td>Hepatitis C Virus</td>
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<td>IU</td>
<td>International Unit</td>
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NAFLD  Non-Alcoholic Fatty Liver Disease
SGOT  Serum Glutamic-Oxalo acetic Transaminase
SGPT  Serum Glutamic Pyruvic Transaminase
USA  United States of America

Authors’ contributions

All authors contributed to the design of the study and the interpretation of data. Tadesse Kebede performed the data analysis and Woldemichael Tadesse drafted the manuscript. The authors read and approved final manuscript.

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Competing interests: The authors declare that they have no competing interests.

Ethics and consent

Ethical clearance was obtained from Ethical Review Committee (ERC) of Mekelle University dated March 25, 2019, and numbered ERC 1279/2019. Letter of permission was obtained from chief clinical director of ACSH. Moreover, prior to conducting the study, the purpose and objective of the study was described to the study participants and a written informed consent was obtained. Respondents were allowed to refuse or discontinue participation at any time they want. Information was collected anonymously and confidentiality was assured and maintained throughout the study period. Beneficence of the participants was maintained throughout the study period.

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Availability of data and material: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request

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