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Metabolic Syndrome and Associated Factors among Patients with Chronic Liver Disease

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ABSTRACT

Introduction: Metabolic syndrome, one of the manifestations of chronic liver disease have become emerging problems of both low and middle-income countries and it is becoming the leading cause of morbidity and mortality both with the individual risk factors of dyslipidemia, hyperglycemia, hypertension and central obesity. Currently there is no accepted central underling mechanism and researches have shown a link between metabolic syndrome and liver disease. Further studies are important to manage these risks of cardiovascular disease.

Objective: This study was conducted to assess the magnitude of metabolic syndrome and associated factors among chronic liver patients attending at the gastroenterology clinic of Jimma medical center.

Materials and Methods: 83 patients with chronic liver disease were included and Hospital based cross sectional study was used in the study. National cholesterol education program adult treatment panel III and international diabetic federation criteria was used to assess metabolic syndrome. Socio demographic characteristics were collected through interviewer-administrated questionnaire adapted from world health organization stepwise tools. Measurements for anthropometric characteristics and blood pressure were taken using aneroid sphygmomanometer and standard anthropometric measuring instruments respectively. Clinical history of patients was also reviewed from their chart. Laboratory test was done to assess biochemical parameters by taking blood sample of patients. Data were analyzed by SPSS software version 20. Ethical clearance from Jimma University institute of review board and formal written consent from study participants was obtained.

Result: Out of the total 83 participants metabolic syndrome was found in 26(31.3%) and 32(38.6%) according to the NCEP ATP III and IDF criteria respectively. Body mass index AOR (95% CI): 6.2(1.7-22.25) P-value = 0.005, Total cholesterol AOR (95% CI): 3.9(1.2-13.27), P-value = 0.024, Very low-density lipoprotein AOR (95% CI): 6.04(1.58-23.09), P-value =0.008 were the variables that become associated with metabolic syndrome in the multivariate analysis.

Conclusion and Recommendation: Metabolic syndrome is prevalent in patients with liver disease. A comprehensive medical care approach to liver patients is important to adequately assess and address the additional components of metabolic syndrome, which has known to potentiate cardiovascular disease.

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Abbreviations
SBP: Systolic Blood Pressure
DBP: Diastolic Blood Pressure
WC: Waist Circumference
HDL: High Density Lipoprotein
LDL: Low Density Lipoprotein
VLDL: Very Low-Density Lipoprotein
TC: Total Cholesterol
BMI: Body Mass Index
WHR: Waist to Hip Ratio

Introduction

The first description of patients with clustering of various metabolic abnormalities was as early as 1923 but it was more than fifty years later, in 1988, that Reaven gave the term 'syndrome X' for this entity. The last two decades have brought different a number of definitions and criteria to identify this condition. Various studies have demonstrated differences in these definitions and a few researchers have questioned the utility of these criteria and even the existence of such a syndrome [1]. Numerous factors are involved in metabolic syndrome (MetS) disorder. The syndrome has been given several names such as insulin resistance (IR) syndrome, pluri-metabolic syndrome, and syndrome-X [2].

MetS is a recent concept in medicine because it was thirty years ago when it started to group the different MetS components as a common pathology. MetS currently becomes a global issue since it affects many of people. Numerous factors are involved in MetS development. As it, have negative consequences on health a lot of treatments have been proposed to palliate it such as drugs, surgery

or life style changes where nutritional habits have shown to be an important point in its management [3].

Chronic liver disease can affect plasma lipid level in different ways. Among its the plasma triglyceride and cholesterol level are disturbed due to reduced lipoprotein biosynthetic capacity, and increase in connective tissue result in disorganization of the lobular architecture which is characterized by replacement of liver tissue by fibrosis (scar tissue) [4,5].

Metabolic syndrome is a condition characterized by the co-existence of three or more of the five components, which are hyperglycemia, hypertension, central obesity abnormally high triglyceride and lower high-density lipoprotein that are risk factors for cardiovascular disease [6-9].

Conditions such as visceral fat accumulation, obesity, and diabetes mellitus underlie the pathologic actors of MetS. In liver, MetS may accompany fatty liver or steatohepatitis, with possible progression to liver cirrhosis in some cases [10].

Prevalence of metabolic syndrome varies drastically around the globe, both on a country-by-country basis and at smaller regional levels such as rural, suburban, and urban. Since the 20th century, most countries have seen an increase in the prevalence of MetS in the population. Prevalence of MetS is 34.7% in United States in 2012, 24.5% in China in 2015. Other countries, such as Malaysia, India, Philippines, Nigeria, Brazil, and Iran have also observed metabolic syndrome in greater than 25% of the population. Turkey has the highest prevalence of metabolic syndrome in the world, with 44.0% of the population diagnosed according to IDF criteria. metabolic syndrome rate is higher in females compared to males and increased with age [11].

MetS and obesity are associated with NAFLD. A study including 356 patients in Washington indicates 71% of them are obese and 67% have metabolic syndrome according to NCEP ATPIII criteria. It is also associated with higher insulin resistance, hepatic steatosis, and portal inflammation Interestingly, ethnic differences may be important in this relationship and require further study [7-12].

Across sectional study in thirty-nine subjects with NAFLD and eighty-two controls in India show that MetS is manifested in 41% of the cases and 19.5 % in controls ($P<0.01$) by using the NCEP ATPIII criteria. The Subjects had significantly higher values of Body mass index, hip circumference, Fasting blood glucose, total cholesterol and serum triglycerides [8].

Twenty years follow-up retrospective cohort study in Shanghai indicates there is a positive association between HBV infection and MetS [13]. Since liver lesions can accompany fatty liver, necrotizing inflammation of the parenchyma, and fibrosis, MetS and NAFLD and/or non-alcoholic steatohepatitis are considered to be closely correlated and represent certain phenotypes of MetS in the liver [10].

Other study in china assesses the prevalence of MetS in patients with abnormal liver function and it becomes 31.8% and 39.0% in women and in men respectively [14]. In Africa, the prevalence of MetS is increasing, and it tends to increase with age. This increase in the prevalence of metabolic syndrome in the continent thought to be due to departure from traditional African to western lifestyles. Though the use of different criteria is a limitation to compare these findings, they are still informative about the burden of metabolic syndrome [15].

The prevalence of metabolic syndrome in adults of Ethiopia was 12.5% according to a study done in Addis Ababa city [16]. Another study showed 4.8% prevalence in the general population of Ethiopia and 16.7% was indicated in Jimma town [17,18]. However, prevalence of metabolic syndrome in association to chronic liver disease has not reported in Ethiopia.

WHO report showed a link between metabolic syndrome and liver disease. It also indicated that our understanding of this complex set of risk factors is limited, and that further research is needed [19]. Therefore, these indicated problems and the current worldwide increase in non-communicable disease with risk of mortality initiate us to carry out such study. This may have a role in the management and exposing and adding insight for researchers and other responsible organs about metabolic syndrome.

Material and Methods

Study Area and Period

The study was conducted in Jimma Medical Center (JMC) from March to June of 2019. Jimma, one of the towns in Oromia regional state is located at 352km from the capital city, Addis Ababa, Ethiopia. JMC is one of the largest teaching referral hospitals in the country, providing the health service at inpatient and outpatient level for about 15 million populations living in and around the area. Specialists, medical residents, medical interns and other health professionals deliver the health service. Study participants were chronic liver patients attending at the gastroenterology clinic of Jimma Medical Center during the study period who meets the inclusion criteria.

Inclusion Criteria

All chronic liver patients attending at the gastroenterology clinic of JMC with in the period of data collection aged ≥18years, with duration of liver disease onset ≥ 6 months were included in the study.

Exclusion Criteria

Patients with medical history or treatments for the following diseases:

- Renal failure
- Cardiovascular disease
- Pregnant woman and those that come after the start of data collection for follow up were excluded.

Sampling Technique and Sample Size Determination

Simple random sampling technique was used to select the study participants. A total of 105 chronic liver patients were in follow up during the time of data collection in the gastroenterology clinic of Jimma Medical Center. This list of patients was our frame to select the sample size and lottery method was used to select the final sample size. By considering those 105 patients as target population (N), the total sample size (n) of 83 patients was obtained using Yamane Taro, 1967equation as follows [20].

$$n = \frac{N}{1+N\,(e)\,2}$$

$$n = \frac{105}{1+105(0.05)2}$$

n =83, which is the final sample size of our study.
Where: - n =sample size

N =population size =105
e = sampling error (at 95% confidence interval, it is 0.05).

Instruments and Data Collection Procedures
Data Collection Technique
Two BSc nurses employed at the gastroenterology clinic of Jimma medical center collected the data and another one-laboratory technician assigned to analyze the biochemical parameters. Data collectors were briefly oriented about the objectives and purpose of the study and took formal written consent from the study participants and Ethical clearance from the institution before data collection. Ethical approval to conduct this study was obtained from Jimma University institutional review board committee (IRB committee, reference number IHRPGY/521/2019) and an official latter of cooperation and clearance was obtained from Jimma Medical Center (study site) of the Gastroenterology clinic and Department of Biomedical Sciences. Similarly, the entire data management process including the interviewing of participants and sample taking process, were done according to the important guidelines and regulations pertaining to research processes involving human subjects (for example- Declarations of Helsinki, Finland, June 1964).

Questionnaire adapted from world health organization stepwise instrument, was used to record all valuable information about the socio-demographic characteristics and their medical history was reviewed from their chart [21].

Standardized instruments like digital balance, stadia meter, tape meter, aneroid sphygmomanometer, was used to measure weight, height, waist, hip and blood pressure respectively. Auto analyzer (human star 80) machine also used to measure biochemical parameters.

Procedures of Testing and Measurement
Blood Sample Collection and Analysis
Five milliliter of venous blood was drawn from each participant using a disposable plastic syringe by following all the safety measures. The blood was poured into serum separator tube (SST) and then centrifuged before it clots. Serum was kept at - 80°c in refrigerator until biochemical analysis was carried out. Participants were instructed to come for laboratory examination after 12 hours of fasting, which is morning before breakfast. Biochemical analysis (Lipid profile, total protein and amino acids, fasting blood glucose) was performed from the serum of each patient by auto analyzer (human star model 80) machine. Manufacturer instruction of reagents was strictly followed [22,23].

Fasting Blood Glucose Measurement
Blood glucose analysis was done to measure the amount of glucose in the blood. It was used to detect both hyperglycemia and hypoglycemia for diagnosis of diabetes. Glucose oxidase is highly specific for glucose and does not react with other saccharides. Glucose oxidase catalyzes the oxidation of ß-D- glucose present in the plasma to D-glucono-1, 5-lactone with the formation of H2O2 [24]. In this study, fasting blood sugar was determined using human star 80-analyzer machine from serum.

Blood Pressure Measurement
Blood pressure was measured using aneroid sphygmomanometer. The measurement protocol is as follows. After a supine rest of five minutes, three measurements in the sitting position at 5-minute intervals on the left hand were done. The mean of all the three measurements was used as the systolic and diastolic Blood pressures [25,26]. Participants were instructed not to take any blood pressure lowering medications 24 hours prior to the tests.

Anthropometric Measurements
Weight was measured in kilograms (Kg) using digital weighing machine at a precision of 0.1Kg with the study subjects minimally dressed. Height was measured in centimeter (cm) in erect position at a precision of 0.1 cm with shoes removed using height scale (stadia meter).

Waist circumference (WC) was measured in cm at the midpoint of the line between the lowest border of the thoracic cage and anterior superior iliac spine using a measuring tape. Hip circumference was also measure using tape meter just below the iliac crust. Body mass index (BMI) also calculated as weight in Kg/height in meter square. WHR was used as measurement of central obesity, which intern is a possible indicator of other more serious health conditions. It was calculated as waist divided by hip. According to WHO, WHR of above 0.9 for Male and 0.8 for female was considered as abdominal obesity but this study was used country specific cut points for WHR when the IDF criteria was used. WHR were calculated as waist circumference divided by hip circumference [27]. All anthropometric measurements were performed after ordering the patients to be with light cloths and shoes removed.

Assessment of Metabolic Syndrome
Patients were classified as having metabolic syndrome according to NCEP ATPIII Criteria 2001, if He or She has three or more of the following components [28].

- Abdominal obesity: - WC ≥102 cm in men and ≥88 cm in women.
- Hypertriglyceridemia: - ≥150 mg/dl (1.695 mmol/L)
- Low HDL-C: <40 mg/dl in men and <50 mg/dl in women
- High blood pressure (BP): - ≥ 130/85 mmHg
- High fasting glucose: - ≥110 mg/dl.

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have central obesity defined as waist circumference (central obesity) ≥80 cm in women and ≥94 cm in men and additional two of the following abnormalities.

- Raised triglyceride: ≥150mg/dl or specific treatment for this lipid abnormality
- Reduced HDL cholesterol: <40mg/dl (1.03mmol/L) in males, < 50mg/dl (1.29mmol/L in Females, or specific treatment for this Lipid abnormality.
- Raised Blood Pressure: Systolic BP≥130 or diastolic BP≥85 mmHg
- Raised Fasting Plasma Glucose: (FPG) ≥100 mg/dl (5.6mmol/L) or Previously diagnosed Type II Diabetes

If BMI is >30kg/m², central obesity can be assumed and waist circumference does not need to be measured [29]. These "consensus criteria" again included the same five components in all the different organizations, but did not designate any component as required. It however still recommended the use of ethnic or country-specific cutoff points for central obesity [30].

Therefore, this study was incorporated the cut-off points of 83.7 cm for males and 78.0 cm for females for waist circumference. The optimal cut-offs for defining obesity using BMI in the study area were as follow:

- >22.2 kg/m^2 Obese
- 21.6–22.2Kg/m^2 Overweight
- 18.3–21.5 Kg/m^2 Normal
- <18.2 Kg/m^2 Underweight for Males., and
- >24.5 kg/m^2 Obese
- 23.1-24.5Kg/m^2 Over weight
- 21.9-23.0Kg/m^2 Normal
- < 21.8 Kg/m^2 Underweight was also the cut- off point for females; while the cut-offs for diagnosing obesity using waist to hip circumference ratio was taken as 0.88 for males and 0.82 for females [31].

Operational Definitions

Chronic liver patient: - When the duration of liver disease onset persists for at least six months [32,33].

Alcoholic Intake

More than 30 grams per day in males and more than 20 grams per day in females, or drinking alcohol for at least three days per week (5% alcoholic content) for six consecutive months previously (average of 2 bottles of beer per day) and two days per week for local drinks [34].

Khat Chewing

chewing of khat two or more days per week for more than six months.

Smoking: smoking average of 10 stick of cigarette per week

Data Processing and Analysis Procedures

The collected data were checked for completeness and missing values. It was then be coded and entered in to Epi- Data manger version 4.4.2 and then exported to Statistical package for social science (SPSS) program version 20 for analysis. Continuous variables were presented as the means, standard deviation, and frequencies. Descriptive statistics and Binary logistic regression (including multivariable binary logistic regression) was used in the analysis of the data. P-value <0.05 was considered as significant in the final model.

Data Quality Assurance

The English version of the questionnaire was translated in to Amharic and Afaan Oromo languages and back to English to check its consistency. Two BSc nurses working at the gastroenterology clinic of Jimma medical center collected the data. Data collectors were briefly oriented about the objectives and purpose of the study to respondents and took written consent from the study participants prior to data collection. Then, face-to-face interview using semi- structured questionnaire was used to assess the medical history and socio-demographic and life style characteristics of study participants.

The blood sample was taken under aseptic techniques with standard operational procedures and lipid profile, fasting glucose level, total protein, albumin and bilirubin was analyzed from serum using auto analyzer (human star model 80) by following the manufacturer instructions of reagents.

At all times of data collection, the principal investigators supervise and works with the data collectors to ensure proper data collection. At the end of each day of data collection, the principal investigator crosschecked data to assure completeness of the information and ensure proper storage of the collected sample. The auto analyzer machine was checked for its consistency by the laboratory technician during the biochemical analysis. Great attention was given in data insertion to software on computer.

Results

Socio-Demographic Characteristics of the Study Participants

Out of the total 83 sampled patients there was 100% response rate and 27 (32.53%) of them were males and 56 (67.46%) were females. The mean (±SD) age of the study participants was 42.36 (± 12.93) years. Most, 67(80.7%) of the study participants were married, 12(14.5%) were single and 4(4.8%) were divorced.

About 51(61.4%) of them were housewives, 13(15.6%) were government employees and work in office and 19(22.89%) have other works (cleaners, and farmers). 29 (34.9%) of the patients have no formal education, 17(20.5%) have diploma and above, 20(24.1%) complete primary education and 17(20.5%) complete their secondary education. From the total participants 19(22.9%) have monthly income of <1000, 30(36.1%) of the participants have monthly income of (1001-2000), 24(28.9%) of them have an income of 2001-3000 and the rest have an in income of >3000 birr (See Table 1).

Table 1: Socio Demographic Characteristics of Patients with Chronic Liver Disease Attending at Jimma Medical Center, South West Ethiopia from March to June 2019

Variable		Total Freq.(%)	Male Freq.(%)	Female Freq. (%)
Age	18-30	17(20.5)	6(7.2)	11(13.3)
	31-40	26(31.3)	9(10.8)	17(20.5)
	41-50	11(13.3)	3(3.6)	8(9.6)
	>51	29(34.9)	9(10.8)	20(24.1)
	Total	83(100)	27(32.5)	56(67.5)
Marital status	Married	67(80.7)	23(27.7)	44(53)
	Single	12(14.5)	4(4.8)	8(9.6)
	Divorced	4(4.8)	0	4(4.8)
	Total	83(100)	27(32.5)	56(67.5)
Employment status	In office	13(15.6)	3(3.6)	10(12.04)
	In kitchen with smocks	51(61.4)	1(1.2)	50(60.2)
	Others	19(22.89)	9(10.8)	10(12.04)
	Total	83(100)	27(32.5)	56(67.5)

Educational level	No formal Educ.	29(34.9)	5(6)	24(28.9)
	Primary	20(24.1)	8(9.6)	12(14.5)
	Secondary	17(20.5)	9(10.8)	8(9.6)
	Diploma & above	17(20.5)	5(6)	12(14.5)
	Total	83(100)	27(32.5)	56(67.5)
Monthly income (ETB)	<1000	19(22.9)	11(13.3)	8(9.6)
	1001-2000	30(36.1)	6(7.2)	24(28.9)
	2001-3000	24(28.9)	9(10.8)	15(18.1)
	>3001	10(12)	1(1.2)	9(10.8)
	Total	83(100)	27(32.5)	56(67.5)

In the employment category others refers to farmers and cleaners, Freq - frequency and ETB - Ethiopian birr.

Life style and clinical characteristics of the study participants

From the study participants only 14(16.9%) drink alcohol. In addition, 4(4.8%) and 33(39.8%) of them smoke cigarette and chew Khat respectively. About 98.8% of them have no family history of thyroid disease. About 73(86.7%) have ascites and 9(10.8%) have visceral hemorrhage, not shown in table 2. The cause for liver disease was hepatitis virus (HBV and HCV), which accounts 65(78.3%) of the total sample size and for 18(21.7%) of the patients the causes was alcohol, autoimmune disease, medication and adult bile ductopenia (See Table 2).

Table 2: Life style and Clinical Characteristics of Chronic Liver Disease Patients on Follow up at Jimma Medical Center, South West Ethiopia from March to June 2019

Variables		Total: Freq.(%)	Male: Freq. (%)	Female: Freq.(%)
Alcoholic intake	Yes	14(16.9)	12(14.5)	2(2.4)
	No	69(83.1)	15(18.1)	54(65.1)
	Total	83(100)	27(32.5)	56(67.5)
Smoking	Yes	4(4.8)	4(4.8)	0(0%)
	No	79(95.2)	23(27.7)	56(67.5)
	Total	83(100)	27(32.5)	56(67.5)
Khat	Yes	33(39.8)	18(21.7)	15(18.1)
	No	50(60.2)	9(10.8)	41(49.4)
	Total	83(100)	27(32.5)	56(67.5)
Reason for visiting the clinic	Liver related	58(69.9)	21(25.3)	37(44.6)
	Cold/Flue	3(3.6)	1(1.2)	2(2.4)
	Abdominal pain	22(26.5)	5(6)	17(20.5)
	Total	83(100)	27(32.5)	56(67.5)
	Yes	1(1.2)	0(0%)	1(1.2)
Family history of thyroid Disease	No	82(98.8)	27(32.5)	55(66.3)
	Total	83(100)	27(32.5)	56(67.5)
Causes of liver disease	Hepatitis Virus(B&C)	65(78.3)	16(19.3)	49(75.4)
	Alcohol and others	18(21.7)	11(13.3)	7(8.4)
	Total	83(100)	27(32.5)	56(67.5)
Duration of Liver disease	≤12 Year	31(37.3)	8(9.6)	23(27.7)
	>12 Years	52(62.7)	19(22.9)	33(39.8)

In the cause of liver disease category others refers to - medication, autoimmune disease, adult bile ductopenia and hepatic steatosis.

Biochemical and Anthropometric Levels of Patients with Chronic Liver Disease

The mean and standard deviation of anthropometric and biochemical measurements of the study participants were incorporated in table 3. The mean systolic blood pressure and diastolic blood pressure of the study population was 120 (±16) and 78 (±12) respectively.

Mean waist circumference was 82 (±12) and, mean fasting glucose level and HDL-cholesterol level was 89.8 (±25.4) and 62.40 (±24.3) respectively. The mean BMI of patients was also 21.94 (±3.73). Dyslipidemia is the main determinant of MetS and according to the result of the study, triglyceride was higher which becomes 188.07 (±84.45), mean LDL–cholesterol was 76.8 (±48.45), and mean total cholesterol was 210 (±57.10). Mean total protein become 8.79 (±1.27), mean hemoglobin was 9.75 (±2.94) which was

very less than normal in both males and females. The result also showed mean albumin and bilirubin levels of 4.23 (±1.01) and 0.70 (±0.55) respectively (See Table 3).

Table 3: Biochemical and Anthropometric Characteristics of Chronic Liver Patients on Follow up at Jimma Medical Center, outhwest Ethiopia from March to June 2019

Variables	Total Mean(±SD)	Male Mean (±SD)	Female Mean (±SD)
SBP(mmHg)	120.02(16)	1 12(16)	124(16)
DBP(mmHg)	78.47(12.2)	77(11)	79(13)
Glucose(mg/dl)	89.80(25.4)	89.79(29.72)	89.81(23.41)
HDL(mg/dl)	62.04(24.34)	54.91(23.87)	65.49(24.02)
Triglyceride(mg/dl)	188.07(84.45)	164(78)	199(86)
LDL(mg/dl)	76.8(48.07)	67.39(40.42)	81.37(51.08)
VLDL(mg/dl)	37.6(16.89)	32.89(15.69)	39.89(17.11)
TC(mg/dl)	210.48(57.10)	178(47)	226(55)
Total Protein(g/dl)	8.79(1.27)	8.87(1.25)	8.76(1.30)
Albumin(g/dl)	4.23(1.01)	3.84(1.05)	4.43(0.95)
Bilirubin(mg/dl)	0.70(0.55)	0.79(0.61)	0.66(0.53)
Hemoglobin(g/dl)	9.75(2.94)	9.30(3.27)	9.97(2.78)
BMI(weight/height2)	21.94(3.73)	20.59(3.15)	22.60(3.85)
WHR	0.94(0.32)	0.98(0.08)	0.92(0.15)
WC(cm)	82.06(12.16)	80(15)	83(11)

Components of Metabolic Syndrome in the Study Participants

According to the NCEP ATPIII criteria 18 (22.9%) and 7 (8.4%) of the patients with MetS have systolic and diastolic blood pressure of ≥130 and ≥85 mmHg respectively.

Out of the total 13(15.7%) of the patients with metabolic syndrome have abnormal waist circumference and 24(28.4%) of them have abnormal TG level. The result also showed abnormal HDL in 15(18.1%) of the patients with metabolic syndrome. Normal triglyceride (<150mg/dl) was observed only in 5(6%) of the patients with MetS. About 11(13.3%) of the Patients with metabolic syndrome also have normal levels of high-density lipoprotein and a total of 13(15.7%) patients with metabolic syndrome was also showed values of fasting glucose ≤ 110mg/dl and also 13(15.7%) of them showed fasting glucose level of >110mg/dl (See Table 4).

Table 4: Components of Metabolic Syndrome Among Chronic Liver Disease Patients on Follow up at Jimma Medical Center, Southwest of Ethiopia from March to June 2019

Variables		Metabolic syndrome (NCEP ATP III)	
		Present: Frequency (%)	Absent: Frequency (%)
SBP	<130	8(9.6)	49(59)
	≥130	18(22.9)	8(9.6)
DBP	<85	19(21.7)	53(63.9)
	≥85	7(8.4)	4(4.8)
WC	Normal	13(15.7)	49(59)
	Abnormal	13(15.7)	8(9.6)
TG	<150	2(2.4)	30(36.1)
	≥150	24(28.4)	27(32.5)
HDL	Normal	11(13.3)	45(54.2)
	Abnormal	15(18.1)	12(14.5)
Fasting	< 110mg/dl	13(15.7)	53(63.9)
Glucose	≥110mg/dl	13(15.7)	4(4.8)

Waist circumference (WC): Normal <102 for males and <88 for females according to the NCEP ATP III and abnormal is above these values.; High-density lipoprotein (HDL): Normal = ≥40mg/dl for males and ≥50 mg/dl for females, SBP-systolic blood pressure, DBP- diastolic blood pressure and TG- triglyceride.

Number of MetS Components in Males and Females of the Study Participants

In the current study, 11 (13.3%) males and 23 (27.7%) females found to have at least one component of metabolic syndrome and 4 (4.8%) of Males and 6 (7.2%) of females have at least two components. At least three components of metabolic syndrome were also showed in 4 (4.8%) of males and 17 (20.5%) of females. Four and above components were present in 2 (2.4%) of males and 3 (3.5%) of females using the NCEP ATP III. In addition, 6 (7.2%) Males and 20(24.1%) females were found to have metabolic syndrome using the National cholesterol program adult treatment panel III and, 7 (8.4%) of males and 25 (30.1%) of females were found to have metabolic syndrome using the international diabetic federation criteria (See Table 5).

Table 5: Number of MetS Components Using the NCEP ATP III and IDF Criteria of Patients with Chronic Liver Disease on Follow up at Jimma Medical Center, Southwest of Ethiopia from March to June 2019

Number of Metabolic Syndrome criteria	NCEP ATPIII criteria		IDF criteria	
	Male	Female	Male	Female
0	6(7.2%)	7(8.4%)	3(3.6%)	5(6%)
At least 1	11(13.3%)	23(27.7%)	5(6%)	11(13.3%)
At least 2	4(4.8%)	6(7.2%)	10(12%)	17(20.5%)
At least 3	4(4.8%)	17(20.5%)	5(6%)	12(14.5%)
4 and above	2(2.4%)	3(3.5%)	4(4.8%)	11(13.3%)

NCEP ATPIII: National cholesterol education program adult treatment III, IDF: International diabetic federation.

Predictors of Metabolic Syndrome in the Study Population

In the bivariate analysis variables having p-value ≤ 0.25 were selected as candidates for the final multivariate analysis. Accordingly, nine variables (gender, age, monthly income, total cholesterol, total protein, hemoglobin, BMI, VLDL and duration of liver disease) were identified as the expected associated factors for the presence of MetS with their specific COR (95% CI) and p-values as described in table 6.

Further multivariate analysis (binary logistic regression with backward LR method) was used to identify the main associated risk factors for the development of MetS by controlling confounders with AOR. Based on this BMI, Total cholesterol and VLDL were identified as the main associated factors with P-value <0.05.

By controlling all other variables constant the likelihood of developing MetS was six times higher among patients with higher body mass index than patients with normal or lower. The likelihood of developing metabolic syndrome was also four times higher among higher cholesterol level than those with normal level and six times higher among patients with abnormal VLDL- cholesterol than patients with normal or lower (See Table 6)

Table 6: Logistic Regression Model of Variables Associated with MetS Using the NCEP ATP III Criteria of Patients with Chronic Liver Disease on Follow up at Jimma Medical Center, Southwest Ethiopia from March to June 2019

Variables		Metabolic syndrome		COR(95% CI)	P-value	AOR(95% CI)	P-value
		Present: freq. (%)	Absent: freq. (%)				
Gender	Male	6(7.2)	21(25.3)	1			0.115
	Female	20(24.1)	36(43.4)	0.5(0.17-1.48)	0.219*	0.35 (0.09 -1.28)	
Kaht chewing	No	14(16.9)	36(43.3)	1			
	Yes	12(14.5)	21(25.3)	1.4(0.57-3.76)	0.422		
Age	18-40	11(13.3)	32(38.6)	1			0.086
	≥41	15(18.1)	25(30.1)	0.57(0.22-1.46)	0.244*	0.35 (0.10 -1.16)	
Alcohol intake	No	23(27.7)	45(54.2)	1			
	Yes	3(3.6)	12(14.5)	0.48(0.12-1.90)	0.303		
Smoking	No	25(30.1)	50(60.2)	1			
	Yes	1(1.2)	7(8.4)	0.43(0.05-3.2)	0.421		
Visceral hemorrhage	No	22(26.5)	52(62.7)	1			
	Yes	4(4.8)	5(6)	0.52(0.13-2.1)	0.375		
Ascites	No	5(6)	6(7.2)	1			
	Yes	21((25.3)	51(61.4)	2(0.55-7.3)	0.285		

Marital status	Married	16(19.3)	41(49.4)	1			
	Other	10(12)	16(19.3)	0.62(0.23-1.66)	0.346		
Employment	In office	14(16.9)	34(41)	1			
	Other	12(14.5)	23(27.7)	0.78(0.31-2.01)	0.620		
Income	<3000	21(25.3)	52(62.7)	1			0.688
	≥3001	5(6)	5(6)	0.4(0.1-1.5)	0.184*	0.71 (0.13 -3.78)	
Educational status	Educated all	7(8.4)	22(26.5)	1			
	No formal Education	19(22.9)	35(42.2)	0.58(0.2-1.6)	0.303		
Duration of disease onset	6-12 months	14(16.9)	17(20.5)	1			0.194
	≥13 months	12(23.1)	40(48.2)	2.7(1-7.1)	0.039*	2.2(0.66 -7.3)	
Cause of liver disease	Hepatitis virus(B&C)	21(25.3)	44(53)	1			
	Other	5(6)	13(15.7)	1.2(0.39-3.9)	0.714		
Hemoglobin (g/dl)	Normal	10(12)	13(15.7)	1			0.472
	Abnormal	16(19.3)	44(53)	2.1(0.77-5.7)	0.143*	1.6(0.4-6.2)	
Albumin (g/dl)	Normal	9(10.8)	26(31.3)	1			
	Abnormal	17(20.5)	31(37.3)	0.63(0.24-1.6)	0.348		
Bilirubin (mg/dl)	Normal	10(12)	13(15.7)	1			
	Abnormal	16(19.3)	44(53)	0.73(0.28-1.87)	0.517		
Total protein (g/dl)	Normal	12(14.5)	16(19.3)	1			0.820
	Abnormal	14(16.9)	41(49.4)	2.1(0.83-5.7)	0.109*	0.867(0.25-2.9)	
T.cholestrol (mg/dl)	Normal	11(13.3)	11(13.3)	1			0.024**
	Abnormal	15(18.1)	46(55.4)	3(1.1-8.4)	0.031*	3.9(1.2-13.27)	
VLDL (mg/dl)	Normal	11(13.3)	11(13.3)	1			0.008**
	Abnormal	15(18.1)	46(55.4)	3.06(1.1-8.4)	0.031*	6.04(1.6-23.09)	
LDL(mg/dl)	Normal	23(27.7)	46(55.4)	1			
	Abnormal	3(3.6)	11(13.3)	1.8(0.46-7.2)	0.386		
BMI	Normal and underweight	11(13.3)	9(10.8)	1			0.005**
	Overweight and obese	15(18.1)	48(57.8)	3.9(1.36-11.2)	0.011*	6.2(1.7-22.25)	
WHR	Normal	6(7.2)	16(19.3)	1			
	Abnormal	20(24.1)	41(49.4)	0.76(0.26-2.26)	0.633		

Freq. (%) refers to frequency (%), COR - crude odds ratio; AOR - adjusted odds ratio; CI - confidence interval, Very low density lipoprotein (VLDL) - normal <30 mg/dl, abnormal ≥30 High density lipoprotein (LDL) - normal <130 mg/dl, abnormal ≥130 mg/dl; total protein - normal 6-8.3 g/dl, abnormal is both higher and lower from the normal cut point; bilirubin - Normal 0.3 -1.2g/dl and abnormal is below and above of this normal value. Albumin: Normal is 3.5-5g/dl and abnormal is above and below this point;

T. cholestrol indicates Total cholesterol: normal <200 mg/dl, abnormal ≥200; Triglyceride: normal <150mg/dl and abnormal is ≥150mg/dl; Hemoglobin: normal is 13.8-17.2g/dl for males and 12.1-15.1g/dl for females, abnormal is different from this normal value. In employment status category - others include housewives, cleaners and farmers;

In marital status category - others include single, divorced and widowed, In cause of liver disease - others include alcohol, medication, adult bile ductopenia, hepatic steatosis, and autoimmune disease. P-value ≤ 0.05 was considered as statistically significant in the multivariate analysis.

Discussion

The current study was conducted to assess the prevalence of metabolic syndrome and associated factors among chronic liver patients. It has well understood that the international anthropometric cutoff points for detection of body fatness and risk of MetS are not appropriate for Ethiopians. Ethiopians have higher body fat at a relatively low BMI because of the slender body frame which predisposes them to very higher risk of MetS and type2 DM [23]. The prevalence of the MetS is strongly dependent on the different cut-off points, the population sample studied and sets of criteria used by different definitions. So using the IDF criteria is important because it allows using ethnic or country specific cut points for waist circumference to assess MetS [9].

The prevalence of metabolic syndrome in the current study was 31.3% and 38.6% according to NCEP ATP III and IDF criteria respectively. This prevalence is slightly higher than the prevalence of 21.6% conducted in India using IDF criteria [35]. Indeed, their study was done on chronic Hepatitis C Virus patients. It is also higher than the prevalence indicated by a cross -sectional study done in Pakistan which shows 17.78% from 90 HCV cases using the same NCEP ATP III criteria [36]. This difference may be due to the socio-demographic differences and their study uses the Asian-American cut points for the metabolic syndrome components.

Another study done in Nepal among NAFLD showed lower prevalence of MetS (13.6%) using NCEP ATP III criteria. In addition, other criteria (IDF) in their study showed a prevalence (30.1%) [37]. This difference with the current study may be due to socio- demographic characteristics and using of different cut points for waist circumference. Their study showed a significant high level of waist circumference, systolic blood pressure, and diastolic blood pressure in patients as compared to control population ($p < 0.001$). In addition, lipid profile parameters showed significant statistical elevation among the cases. This is in agreement with our study, which showed increased levels of the individual components of the MetS mainly systolic Blood pressure, Triglyceride and Waist circumference.

Our study showed higher prevalence of metabolic syndrome in females (24.1%) than males (7.2%) and old age even if it does not show a significant association in the statistical analysis. A study done in Iran showed a higher prevalence of MetS (65.2%) by using the NCEP ATPIII criteria and pointed out higher prevalence in males than females, and metabolic syndrome is higher at ages greater than 40 [9,13,38]. This may be due to the occupational status of females in our study population in which most of them were housewives and have lack of regular physical exercise and WC cut point differences in the two study areas. This may also be due to increase in arteriosclerotic effect of blood vessels with age. A cross-sectional study done in Shanghai showed higher prevalence of metabolic syndrome in the overweight and obese than people with normal body weight. Analyses of their study revealed that increased BMI in patients with fatty liver was associated with significant increases in the prevalence of abdominal obesity and hypertension [38]. This is in agreement with our study, which showed 13.3% of metabolic syndrome in the normal and underweight together and 18.1% prevalence in the overweight and obese. WC, Fasting Glucose level, VLDL, TG, TC was highly increased among the overweight and obese patients than those with normal BMI. HDL-cholesterol and blood pressure only show slight increase in patients with higher BMI. The increase in most lipid profiles may be due to the failure to inhibit gluconeogenesis and glucose output which result in hyperglycemia and hyperinsulinemia. This initiates lipogenesis and accumulation of triglycerides in Liver of chronic liver patients. This increases the fat content of our body leads to obesity.

Other studies also show an increased level of lipid profile in chronic liver patients, but some studies indicated an inverse relationship between severity of liver disease and level of lipid profile [39-43].

According to the current study, the following were the determined associated factors of metabolic syndrome among patients with chronic liver disease using 95% CI.

The odds of developing MetS were six times higher among patients with higher BMI than those patients with normal or lower BMI, (AOR (95% CI): 6.2(1.7-22.25), P-value = 0.005. This is in lined with the result of the study done in china AOR (95% CI) 7.4(4.5-12.09), p-value <0.001. Larger numbers of people with MetS have raised BMI among adults [2,44,45]. This may be due to the increase in free fatty acid level which results from accumulation of excess lipid. This further leads to cardiovascular abnormalities like vascular plaque formation and myocardial infraction. In obesity leptin secretion increases, which have vaso-contractile, effect related to sympathetic nervous system and non-esterified fatty acid production also increased. This has inverse correlation with insulin sensitivity. Insulin resistance also increases which have direct anti natriuretic effect and stimulates sympathetic nervous system.

The odds of developing MetS were three times more likely among patients with abnormally higher total cholesterol than those with lower total cholesterol, AOR (95% CI): 3.9(1.2-13.27), P-value = 0.024. This is supported by a study done in Japan which showed an increase in total cholesterol in those patients who develop MetS [46]. This may be due to the reason that increased levels of cholesterol for prolonged periods will favor deposits in the sub-intimal region of arteries. Aorta, coronary arteries and cerebral vessels predominantly affected by the atherosclerotic effect. Macrophages in the sub-intimal regions of arteries try to degrade this LDL cholesterol but if over production of cholesterol persists the macrophages become over loaded with cholesterol and form foam cells. Various growth factors liberated by these macrophages enhance accumulation of platelets, lipoproteins, glycosamino glycans and collagen and forms atherosclerotic plaques and stiffness. An increased level of di-acyl glycerol, an intermediate of lipid metabolism, which activates protein kinase Cε (PK Cε) also, impairs the tyrosine kinase activity of the insulin receptor by inhibiting phosphorylation of the insulin receptor. Under this condition, lipogenesis occurs that causes fatty liver, further inflammation, fibrosis, lastly portal hypertension and cardiovascular abnormalities. Liver is the only organ that can excrete cholesterol through bile. Most of the cholesterol in our body incorporates in to LDL, which have correlation with the incidence of cardiovascular disease. Oxidized and glycated LDL, creates a pro-coagulant surface on the endothelium, causing blood clot formation. Abnormal level of cholesterol in blood and the Beta cells so leads to defect in glucose homeostasis and insulin resistance.

The odds of having MetS was also six times more likely in patients with higher VLDL than those with lower VLDL levels, AOR (95% CI): 6.04(1.58-23.09), P-value = 0.008. This may be due to the activation of TNF-α and other proinflamatory cytokines and over production of di-acyl-glycerol that inhibit the function of insulin receptor substrate (IRS) proteins, which contribute to insulin resistance by decreasing glucose transporter (GLUT-4) expression and lipoprotein lipase in peripheral tissue.

Recent evidence from review articles suggests that a diabetic dyslipidemia is a cluster of potentially atherogenic lipid and lipoprotein abnormalities that are metabolically interrelated. Fundamental defect is an overproduction of large very low–density lipoprotein (VLDL) particles, which initiates a sequence of lipoprotein changes, resulting in higher levels of remnant particles, smaller LDL, and lower levels of high-density lipoprotein (HDL) cholesterol. Due to this effect higher level of VLDL is associated with MetS [47]. A cross-sectional study on eighty-two HBV patients in Ghana showed elevated serum total cholesterol, LDL and VLDL levels, and contributed to high risk of MetS and cardiovascular diseases [48].

Differently other cross-sectional studies showed significantly reduced levels of cholesterol, LDL, HDL and VLDL in cases of chronic liver patients (P<0.000) (49–51). Also, inverse association was observed between MetS and chronic hepatitis B AOR: 0.32, 95% CI (0.12–0.84) in a cohort study consisting of 594 HBV patients in India according to the NCEP ATP III criteria [49-52].

The difference may be due to differences in temperature used for serum storage until the analysis of biochemical parameters that may cause differences in the result of the biochemical analysis.

Conclusion and Recommendations

Metabolic syndrome is prevalent among chronic liver patients. Patients with BMI higher than normal, higher total cholesterol and those with increased VLDL-cholesterol have higher chance to develop MetS in chronic liver disease.

Therefore, this finding shows the need for prevention, diagnosis and management of the individual components of metabolic syndrome. Patients having or at risk of metabolic abnormalities should be advised to be screened for dyslipidemia and diabetes.

Study Limitation

The present study was employed small size and we recommend interested researchers to involve large sample size to ensure representativeness and consistency of the study. Prospective type of study is also important to see temporal relationship of variables.

Ethics Approval and Consent to Participate

Ethical approval to conduct this study was obtained from Jimma University institutional review board committee (IRB committee, reference number IHRPGY/521/2019) and an official latter of cooperation and clearance was obtained from Jimma Medical Center (study site) of the Gastroenterology clinic and Department of Biomedical Sciences.

Formal informed written and oral consent to participate was obtained from each study participants (age of > 18) before data collection. Data were collected after informed written consent and agreement from each individual of the study subjects was obtained. The study participants were agreed to participate after they know the possible risks benefits of the study. Diagnostic results of the patients were informed to them by communicating with their doctors. Confidentiality of responses was given to participants. Any abnormal finding of their laboratory result was required consultation of physicians of Gastroenterology clinic for further interventions.

All methods were performed according to the important guidelines and regulations pertaining to research processes involving human subjects (for example- Declarations of Helsinki, Finland, June 1964).

Consent for Publication

Not applicable

Availability of Data and Materials

Supporting files for this study is available and shall be provided in a separate file upload by the corresponding outer on request.

Declarations

All the information shared in the resume is correct, and I take full responsibility for its correctness. I solemnly declare that the information in this resume is true to the best of my knowledge and belief.

Availability of Data

all the data are available and submitted on request by the corresponding outer.

Conflict of Interest

We declared that we had no financial, material or any other competing interest

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Authors Contribution

Mr. Hadush Tinsiae Kahsay controls the overall work and writes the proposal, the result and discussion. He also analysis the data and writes the manuscript. Also follows over all processes of the work. Also identifies the problem.

Mr. Tewodros Gebremariam (Assistant prof.), and Dr. Dagmawi Tewelde commented all the work of the research. They also participated in asking fund for reagents for the laboratory process from Jimma University. They also help in problem identification.

Mr. Iyassu Taddesse constructed the questionnaire and commented the process of the work.

Mr. Zeray Mulaw, Mr. Kibrom Alemu participated in the thesis editorial process and Data Analysis process. They also participated in manuscript edition and commenting the whole work.

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