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Risk factors of Cirrhosis of liver - a tertiary care hospital 0based case control study

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ABSTRACT

Background: Cirrhosis of Liver is an end result of a variety of liver diseases characterized by fibrosis and architectural distortion of the liver with formation of regenerative nodules and can have varied clinical manifestations and complications.
Objective:To identify the risk factors of Cirrhosis of Liver among patients attended in Gastro enterology department in a tertiary care hospital.
Methods:A total of 118 participants, 59 cases of Liver Cirrhosis and 59 controls were selected by convenience sampling technique. Data collected by using socio demographic performa and disease related questionnaire. Socio demographic data was presented in terms of frequency and percentage for both case and control groups which determined the significant variables. Logistic regression with odds ratio (OR) was used to identify the relationship between the presence or absence of Liver Cirrhosis with presence or absence of risk factors.
Results: Among the selected risk factors, Alcoholism (OR- 15.700, P value- 2.54^{e-09}), Smoking(OR- 4.38, P value- 0.001) and Hepatotoxic Medications(OR- 2.170, P value- 0.109) were statistically significant after Univariate Logistic Regression. After Multivariate Logistic Regression, Alcoholism was found to be a risk factor for Cirrhosis of Liver (OR - 20.7, P value< 0.001).

Conclusion:There is a significant relationship between the risk factors and Cirrhosis of Liver.

Key Words: Cirrhosis of Liver, Case control study, Risk factors

1. Introduction

Global prevalence of Cirrhosis of Liver from autopsy studies ranges from 4.5% to 9.5% of the general population, and its rates have been steadily increasing over the years.[1] Cirrhosis is ranked as the 11th important cause of death worldwide and within the 20 leading causes of disability-adjusted life years(1.6%) and years of life lost(2.1%) of the world over burden. Approximately 2 billion people are alcoholics throughout the world and 75 million are vulnerable for alcohol-related liver disease. However, its prevalence is underestimated as almost a third of the patients remain asymptomatic.[2]

In Kerala, 60% of Liver Cirrhosis is caused by alcohol and viral hepatits.[3] Kerala has the highest per capita consumption of alcohol than other states in India, at over 8 litres per person per year which is above the national average alcohol consumption that is 5.7 litres per person per year and mortality related to liver diseases is on the rise in Kerala.[4]

Previous literatures notify various risk factors for Cirrhosis in different countries.[5-7] For instance, Among viral infections, hepatitis B virus(HBV) and hepatitis C virus(HCV) are main contributing factors worldwide. Among people in Himachal Pradesh Alcohol (62.9%) and Hepatitis B (10.1%); and in high risk areas of China and Africa Chronic HBV infection whereas in developed countries chronic HCV infection[8] meanwhile in the Cirrhotic State Peshavar in Pakistan, Hepatitis C specifically through prick by contaminated syringes or blades or blood transfusion; are the predominant causes of Liver Cirrhosis.[9-10]

Cirrhosis is more prevalent in overweight persons and smokers as well. Furthermore, it develops as a result of an exogenous/toxic/infectious/autoimmune/vascular process or an inborn error of metabolism.[11] Individuals with multiple risk factors (Hepatitis, obesity or alcoholism)[12]or cigarette smoking, high serum T Bil and AST/ALT ratio, prolonged duration or family history of hepatitis B, Non alcoholic fatty liver disease (NAFLD) associated with host factors like Non alcoholic steatohepatitis (NASH), metabolic factors, genetic polymorphism, male gender and older age also accelerate the risk for Liver cirrhosis.[12-14]

In view of the etiologies of Liver Cirrhosis reportedly varying across the world, the study aims to analyse the impact of crucial factors like alcoholism, smoking, Body Mass Index, comorbidities, viral infections, genetics and hepatotoxic medications in the occurrence of Liver Cirrhosis among Keralites in a selected setting.

High mortality and morbidity rates of Liver cirrhosis across the world emphasize the need to appraise the knowledge of people about its causes, clinical features, prognosis and

treatment. Lack of knowledge about risk factors and prevention was observed among patients, family and medical community as the single greatest cause of Liver Cirrhosis.[15] So, this study equips health professionals with evidence to impart health awareness about risk factors of Liver Cirrhosis to the public. Future qualitative and quantitative studies including interventions are essential to enhance the livelihoods of patients with Cirrhosis of Liver.[15]

2. Materials and Methods

2.1. Operational Definition

In this study, Risk Factors are the variables like alcoholism, viral infections(Hepatitis B or C), obesity, comorbidities and medications that result in an increased risk for cirrhosis of Liver in an individual. Cases are the patients who are clinically diagnosed with Cirrhosis of Liver after undergoing ultrasound and Liver Function Test; and Controls are patients not diagnosed to have Cirrhosis of Liver but have the same symptoms as that of the cases.

2.2. Study Design

Case Control Study

2.3. Study Setting

The study was conducted in Gastro enterology in-patient and out-patient departments of Malankara Orthodox Syrian Church(MOSC) Medical College Hospital, Kolenchery in Ernakulam district, Kerala, India .

2.4. Study Population

Population in this study include patients seeking treatment for cirrhosis of liver and allied symptoms from Gastroenterology department in a tertiary care hospital. Sample size was 118, n=59 for case and control group each which was estimated based on testing of odds ratio.The study enrolled 118 cooperative patients, above 18 years of age, of both genders, with clinical symptoms of Cirrhosis of Liver receiving treatment from Gastroenterology department. As per the Exclusion Criteria, patients who have not undergone specific diagnostic tests for liver Cirrhosis, un conscious patients or with memory /cognitive impairment were excluded from the study. The conceptual frame work for this study was developed on the basis of Betty Neuman’s Health Care systems Model(1972).

2.5. Ethics & Data

Ethical clearance obtained from Institutional review board of MOSC Medical College Hospital, Kolenchery. Data collection was completed in 3 weeks, from 12/11/18 to 02/12/18. Convenience sampling technique was used to select desired number of samples from the selected wards. Those subjects who fulfilled the inclusion criteria were identified; participant

information sheets provided and informed written consent was obtained after explaining the purpose of the study; anonymity and confidentiality was assured; and questionnaire provided to collect the data.

The first part of questionnaire Socio-Demographic profile, gathered relevant sample characteristics and the second part yielded clinical information such as 1.clinical manifestations of Cirrhosis of Liver presented by the selected participants, 2.diagnostic tests for Cirrhosis of Liver underwent by the participants and 3. Risk factors of Cirrhosis of Liver. The variables of Risk factor related Questionnaire comprise alcoholism, smoking, infections like Viral infections or hepatitis, Diet (fast food), Obesity/ Body Mass Index, Comorbidities, liver diseases, genetics, and hepatotoxic medications; to assess its significant association with Cirrhosis of Liver. Variable Genetics comprised family history of liver cirrhosis and genetic disorders leading to cirrhosis such as Hemochromatosis, Wilson's disease, Cystic fibrosis and Alpha-1 antitrypsin deficiency. Additional data on alcoholism like duration, starting age, amount, frequency, type of drinks, addiction were collected. Also analysed prevalence of other comorbidities among study participants and duration of use of drugs with hepatotoxic nature for such ailments.

2.6. Statistical Analysis

The collected data were coded in Microsoft Excel and based on the objectives and hypothesis of the study, data were analysed using R software. Descriptive and Inferential statistics were used to analyse the data. Socio demographic data was presented in frequency and percentage for both case and control groups. The categorical variables recorded in frequency and percentage followed by continuous variable in mean and standard deviation as data follows normal distribution. Statistical analysis using discrete variables, Logistic Regression with odds ratio (OR) was used to identify the risk factors of Cirrhosis of Liver and the relationship between the presence or absence of Cirrhosis of liver with presence or absence of risk factors. The p value <0.05 was considered as statistically significant. Univariate logistic regression identified the statistically significant variables of Cirrhosis of Liver from which risk factors of Cirrhosis of Liver were identified using Multivariate logistic regression.

3. Results

3.1. Distribution of Socio demographic variables

Frequency and percentage distribution of study participants based on socio demographic variables is summarised in (Table 1).The study revealed that majority of study participants

are above 61 years of age(51.69%), males(70.34%), married(93.22%), belonged to nuclear family system(94.92%), with a mixed diet pattern(93.22%), having primary or high school education(44.07%), and pursuing an occupation which requires moderate physical activities(42.37%).

Table 1 : Frequency and percentage distribution of subjects based on socio demographic variables

(n=118)

Sl No	Variables	Frequency (F)	Percentage (%)
1	**Age in Years**		
	20-40 years	16	13.56
	41-60 years	41	34.75
	Above 61 years	61	51.69
2	**Gender**		
	Male	83	70.34
	Female	35	29.66
3	**Religion**		
	Christian	54	45.76
	Hindu	50	42.37
	Muslim	14	11.86
	Others	0	0
4	**Marital status**		
	Single	5	4.24
	Married	110	93.22
	Divorced	1	.85
	Widower	2	1.69
5	**Family Pattern**		
	Nuclear Family	112	94.92
	Joint Family	6	5.08
6	**Education**		
	Primary School	52	44.07

	High School- 12 th	52	44.07
	College Graduate	11	9.32
	Professional	3	2.54
	PG & Above	0	0
7	**Occupation**		
	Heavy Worker	35	29.66
	Moderate Worker	50	42.37
	Sedentary Worker	8	6.78
	Unemployed	24	20.34
	Retired	1	0.85
8	**Income**		
	<Rs.10,000/month	50	42.37
	Rs.10,000-Rs.20,000/month	53	44.92
	Rs.20,000-Rs.50,000/month	9	7.63
	Rs.50,000-Rs.1 Lakh/month	4	3.39
	>Rs.1Lakh /month	2	1.69
9	**Diet Pattern**		
	Vegetarian	8	6.78
	Mixed	110	93.22

3.2. Clinical symptoms of Cirrhosis of Liver

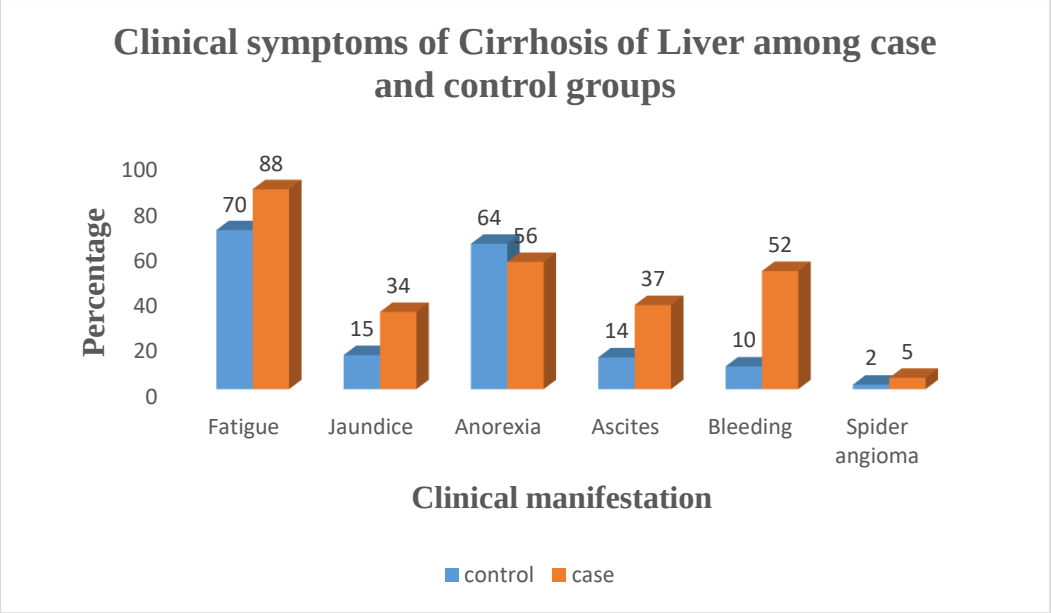
As per Frequency and percentage distribution of subjects based on clinical symptoms of Cirrhosis of Liver shown in (Table 2) (Fig1), Fatigue(78.81%) constitutes most commonly manifested symptom followed by Insomnia(61.02%) and Anorexia(60.17%). Even though a significant percentage progressed to severe form of complications like bleeding problems(31.36%), pedal edema(38.98%) and ascites(25.42%), the typical manifestations Spider angioma(3.39%) and Palmar Erythema(0.85%) were rarely reported by the patients.

Table 2: Frequency and percentage distribution of subjects based on clinical symptoms of Cirrhosis of Liver .

(n=118)

Sl No	Variables	Frequency (f)	Percentage (%)
1	Fatigue	93	78.81%
2	Jaundice	30	25.42%
3	Bleeding problems	37	31.36%
4	Nausea or vomiting	50	42.37%
5	Anorexia	71	60.17%
6	Insomnia	72	61.02%
7	Confusion/altered sensorium	41	34.75%
8	Spider angioma	4	3.39%
9	Palmar erythema	1	0.85%
10	Ascites	30	25.42%
11	Pedal edema	46	38.98%
12	Itching of skin	33	27.97%
13	Weight loss	33	27.97%
14	Stomachache	26	22.03%

Figure 1 : **Bar diagram showing comparison in Percentage distribution of clinical symptoms of Cirrhosis of Liver among the case and control groups, in a tertiary care hospital, Kerala, India.**



3.3. Analysis as per objectives- To identify the risk factors of Cirrhosis of Liver

(Table 3) shows Univariate and Multi variate Logistic Regression on Risk Factors of Cirrhosis of Liver. After (Univariate)Simple Logistic Regression, the obtained results were Alcoholism (OR-15.700, P value- 2.54^{e-09}), Smoking (OR- 4.38, P value- 0.001), Infections (OR-0.726, P value- 0.425), Fastfood (OR-1.380, P value- 0.425), Comorbidities (OR-1.520, P value- 0.349), Liver Diseses (OR-1.16^{e+09}, P value- 0.99), Hepatotoxic Medications(OR- 2.170 , P value- 0.109). After Univariate analysis , 3 variables alcoholism, smoking and medications were found to be statistically significant and were included into Multivariate Analysis(Multiple Logistic Regression). The results of Multivariate Analysis shows Alcoholism (OR- 20.7, P value <0.001), Smoking (OR- 0.61, P value- 0.43) and Medications (OR- 2.07, P value- 0.23). Thus, by doing Multiple logistic Regression, it is found that alcoholism (OR- 20.7, Pvalue<0.001) is a risk factor for Cirrhosis of Liver. On testing the hypotheses, there is significant relationship between the risk factors and Cirrhosis of Liver.

Table 3: Univariate Logistic Regression and Multi variate Logistic Regression on Risk Factors of Cirrhosis of Liver

(n =118)

Variable		Cirrhosis of Liver		Univariate		Multi Variate	
		Present	**Absent**	**OR**	**P value**	**OR**	**P value**
Alcoholism	No	10	45	15.700	2.54 $^{e-09}$ *	20.7	P<0.001*
	Yes	49	14				
Smoking	No	26	9				
	Yes	33	50	4.38	0.001*	0.61	.43
Infections	No	43	39				
	Yes	16	20	0.726	0.425	-	-
Fastfood	No	39	43				
	Yes	20	16	1.380	0.425	-	-
Comorbidities	No	11	15				
	Yes	48	43	1.520	.349	-	-
Liver disease	No	0	43				
	Yes	59	16	1.16e+09	.99	-	-
Medications	No	8	15				
	Yes	51	44	2.170	0.109*	2.07	.23
Genetics	No	-	-				
	Yes	-	-				

P < 0.05 is significant

BMI

(n= 118)

	Mean	**S D**
Mean & SD	23.75	3.44

With respect to years of drinking, among the 63 alcoholic study participants35 (29.66%) were chronic alcoholics for more than 20 years(Table 4) and among them 25% cases and 10% controls have been alcoholics for more than 20 years(Fig.2)Comparatively a higher percentage (26.27%) had started consuming alcohol at a very early age of before 20 years and just 1.69% started their drinking habit after 40 years of age(Table 5) and almost half of them showed symptoms of addiction.

Table 4 : Frequency and Percentage distribution of Years of drinking .

(n= 63)

Sl No	**Variables (Drinking Years)**	**Frequency (F)**	**Percentage (%)**
a.	Non alcoholic	55	46.61%
b.	Alcoholics since 5-10 Years	6	5.08%
c.	10-20 Years	22	18.64%
d.	More than 20 Years	35	29.66%

Figure 2 : **Bar diagram Showing comparison of percentage distribution of years of drinking among alcoholic subjects in case and control groups .**

Table 5 : Frequency and Percentage distribution of starting age of drinking

(n = 63)

Sl No	Variables (Starting Age)	Frequency (F)	Percentage (%)
1.	Before 20 Years	31	26.27%
2.	20-40 Years	30	25.42%
3.	After 40 Years	2	1.69%
4.	Non alcoholic	55	46.61%

Referring to the frequency of alcohol consumption, majority of 52 participants(44.07%) were daily drinkers, 2.54% drink 1-2 days/week, while remaining were occasional drinkers. Regarding the amount of alcohol consumed, 37 patients (31.36%) used to consume more than 500 ml (8 pegs) alcohol per day meanwhile 11.02% drink 240 ml to

480ml(4-8 pegs) and 8.47% patients drink 60 ml to 180 ml(1-3 pegs) per day. In an attempt to identify the most preferred drink, it was found that Brandy is the first choice (43.22%)of alcoholic patients in this study while a combination of Brandy and Toddy 4.24 % of preference; Brandy and Rum 2.54%; Brandy, Rum and Toddy constitute 1.69% and only 0.85% preferred to take Toddy alone.

As concerns viral infections, 30 participants had history of Jaundice and 18 had Hepatitis(16 HBV,1 HAV,1HCV). A notable percentage had comorbidities like Diabetes, Hypertension, Hyperlipidemia and were on Antidiabetics/Insulin, Antihyperlipidemics and Antihypertensives treatment; plus comparatively a higher percentage(56.78%) were on long term hepatotoxic drugs like Oral Hypoglycemics, Lipid lowering agents, Analgesics(Diclofenac), Hormonal, Ayurveda/herbal medicines, Calcium or Vitamin supplements, Anti cardiac and De addiction/Antipsychotic drugs (Table 6).

Table 6 : Frequency and Percentage distribution of duration of intake of hepatotoxic medications.

(n=94)

Sl No	Variables (Duration Of Drug Intake)	Frequency (F)	Percentage(%)
1	Since 1 year	6	5.08%
2	2-5 Years	21	17.80%
3	More than 5 Years	67	56.78%
4	Not on medications	24	20.33%

4. Discussion

The study observed that most of subjects are male gender above 61 years, having only primary or high school education. Similar results on higher incidences of Liver Cirrhosis with regard to age and gender were reported in Pakistan as well. As per a study conducted at medical

wards of Khyber Teaching Hospital and Lady Reading Hospital Peshawar, Pakistan in 2009, the prevalence of Liver Cirrhosis were higher in male patients (79.7%) above 45 years of age (68.9%), low in intermediate age group (29.7%) and in frequent in young age group (1.4%). These results signify that the male gender and old age groups are most affected population of Liver Cirrhosis compared to females and younger age groups in the Asian region. Older age is crucial for the progression to cirrhosis in patients with Non Alcoholic Fatty Liver Disease (NAFLD) along with other risk factors like Non Alcoholic Steato Hepatitis (NASH), metabolic factors and genetic polymorphisms.[15]

Lack of higher education in study subjects suggests the importance of education in eliminating the risks for Liver Cirrhosis. Younger population often have high level education and good awareness about cirrhosis of liver. [16]

Findings on clinical manifestations of cirrhosis are supported by previous studies where a wide range of clinical features are reported in Cirrhosis patients worldwide such as Jaundice(90.5%), anorexia, weightloss(100%), ascites(97.3%)and peripheral edema(73%),Spider angioma, Splenomegaly, Palmar erythema(<20%), gynecomastia, foetor hepaticus, elevated Serum ALT(80%) and total Bilirubin(90.7%) and muscle wasting.[17] Similarly, the risk for variceal bleeding, hepatic encephalopathy, [18]Tuberculosis[19],intracerebral haemorrhage,[20] sepsis,[21]portal vein thrombosis and intestinal infarction[22] is more with Liver Cirrhosis. 50% cases result in Cirrhotic cardiomyopathy[23] or also at risk for renal dysfunction [24] .

The study reveals alcoholism as a major Risk factor for Cirrhosis of Liver. Alcoholism, even moderate, is a risk factor for cirrhosis.[25] In UK and Himachal Pradesh (62.9%) drinking alcohol at harmful levels and in United States chronic excessive alcohol use, are the main causes of cirrhosis of Liver. [26] Similarly, a large prospective study among UK women, also found an increased incidence of liver Cirrhosis with quantity of alcohol consumed; therefore, for a specific amount of alcohol consumed, daily alcohol consumption not with meals has greater than a doubling of cirrhosis incidence. Excess risk of cirrhosis was lower, by about a third, if alcohol was usually consumed with meals than without meals (RR 0.69).The excess risk of cirrhosis was about two-thirds higher with daily than with less frequent consumption (RR 1.61).[27]

Among alcoholic participants, many were chronic alcoholics drinking alcohol daily while others were occasional drinkers; mostly prefer brandy than toddy, rum or wine. Brandy, Rum and beer are the most preferred drinks by Keralites. The amount and duration of alcohol

are directly related to Cirrhosis.[28,29] Supporting these findings, another study conducted on the Patterns of drinking and liver cirrhosis revealed a significant association between daily drinking and highest risk for Cirrhosis; likewise from a lifetime perspective, recent drinking in the last decade was further relevant than earlier drinking. Potential discrepancies in mortality risk for various types of beverages were notified where wine is linked with lower risk given the same quantity of alcohol compared to beer or spirits.[30] The dose-dependent relationship between alcohol and LC may be mediated by the degree of individual susceptibility to the detrimental effect of alcohol to the liver.

However, a weak correlation exists between the amount of alcohol consumed and incidence of Alcoholic Liver Cirrhosis, so as some develop severe liver disease with moderate levels of alcohol consumption while in others extreme levels of alcohol use only progressed to a mild liver Injury. Genetic risk factors for alcoholic cirrhosis- genome-wide case-control study, was intended with a focus on 'Why do only a minority of alcoholics develop liver cirrhosis?'. Thus far, genetic polymorphism (in PNPLA3) solely has been prioritized replicable positive result as a risk factor for ALC.[31] In contrast to alcoholism, a case control study to assess the risk factors for primary biliary cirrhosis in United Kingdom, showed significant association with smoking (OR=1.63(95%CI, 1.27 to 2.09)) while a negative association with Alcohol consumption.[32]

Consequently, people with misuse of alcohol, age above 50 years, male gender, hepatitis B virus / hepatitis C virus infection, older age obesity (BMI of 30 kg/m^2 or higher) , insulin resistance/type 2 diabetes, hypertension and hyperlipidemia in NASH need to be aware of their high risk to develop cirrhosis .

The limitation of study is that it was conducted among patients receiving treatment in a hospital setting where most of them were above 61 years of age; therefore, risk factors of Liver Cirrhosis is likely to be different for other age groups.

5. Conclusion

Cirrhosis of Liver is a global concern due to alarmingly rising consumption of alcohol and lifestyle changes. Proving the common belief in Kerala that liver diseases are caused by alcohol consumption, alcoholism is found to be the greatest significant risk factor for Liver Cirrhosis in the present study as well. Early detection followed by individually tailored, risk-adapted treatment, weight reduction, prohibiting drinking,[33] prolonged abstinence,dietary modification(Low-fat diet), hepatitis vaccination, avoidance of NSAIDs(nonsteroidal anti-inflammatory drugs)[34], and managing risk factors[35] are basic treatment options ,which can

either stabilize or reverse cirrhosis. In short, awareness about risk factors is crucial for prevention and control of Cirrhosis of Liver in global population. Also, further interventions are required from policy makers to restrict alcohol consumption at detrimental levels. Hence, It is the need of the hour for the public to be more aware of this menace and strive towards optimum health by eliminating the risk factors and adopting healthy lifestyles for a healthy society.

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