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Original Article

Internal Medicine Section

Sexual Dimorphism in Decompensated Non Ethanol-related Chronic Liver Disease: A Retrospective Cohort Study

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ABSTRACT

Introduction: Women exhibit a distinct natural history of chronic liver disease compared to men, particularly regarding progression and outcomes. Although liver disease prevalence is generally higher in men, the incidence of non ethanol-related liver disease is increasing among females. Metabolic syndromes and their consequences are less recognised in the female population until they develop end-stage cirrhosis. Limited studies have explored the differences between male and female cirrhosis. The present study aimed to address the knowledge gap in female Decompensated Chronic Liver Disease (DCLD).

Aim: To identify the differences in presentation and outcomes between females and males with non ethanol-related cirrhosis.

Materials and Methods: The present retrospective cohort study was conducted in the Department of Medical Gastroenterology and Hepatology,Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India, involving 27 males and 33 females with non ethanol-related decompensated cirrhosis. A comparison was made between the aetiologies, presenting symptoms, complications, laboratory values, Model for End-stage Liver Disease (MELD) score, and in-hospital mortality during the first decompensation. Data analysis was performed using Statistical Packages for Social Sciences (SPSS) version 24.0 Quantitative variables were expressed as mean and Standard Deviation, while qualitative variables were expressed as frequency and percentage. The association between categorical variables was analysed using the Chi-square test, and the comparison of continuous variables between the two groups was analysed using independent sample t-test. A p-value of <0.05 was considered statistically significant.

Results: The mean age of decompensation was 56.5 years for men and 50.9 years for women. The most common aetiology in men was Non Alcoholic Fatty Liver Disease (NAFLD) (63%), while in females, it was NAFLD (45%) and cryptogenic cirrhosis (45%) (p=0.020). Diabetes Mellitus (DM) was more prevalent in males (55.6% versus 33.3%). Variceal bleed was more common in females (66.7% versus 48.1%). Jaundice was more frequently observed in males (44.4% versus 21.2%) (p=0.05). Ascites was more prominent in males (70.4% versus 45.5%) (p=0.05). Hepatic Encephalopathy (HE) was more prevalent in males (22.2% versus 15.2%). Females had a lower MELD scores compared to males (12.4±6.1 versus 15.2±6.4). Mortality was higher in males (22.2% versus 12.1%).

Conclusion: Women with Decompensated Chronic Liver Disease tend to decompensate at a younger age compared to males and have a higher risk of Upper Gastrointestinal (UGI) bleeding. NAFLD was the most common aetiology in both groups. Ascites and HE were more commonly observed in men. Females had lower MELD scores, resulting in a longer waiting period on the transplant list compared to males. Mortality was higher in males.

Keywords: Cirrhosis, Diabetes, Gender, Varicies

INTRODUCTION

Sexual dimorphism is evident in the pathophysiology, disease manifestations, and treatment response of chronic liver disease. Possible causes include differences in immune response, the effect of sex hormones on metabolic pathways, and variations in gene transcription [1,2]. The liver is a sexually dimorphic organ, with more than 1000 genes expressed differently between males and females [3]. Liver fibrosis, which is the precursor to cirrhosis, also exhibits gender disparity across all aetiologies [4-6].

Hepatic decompensation, or Decompensated Chronic Liver Disease (DCLD), represents the end stage of liver diseases, characterised by the full manifestation of symptoms and the identification of the underlying liver disease. It is interesting to note that most chronic liver diseases, such as Alcoholic Liver Disease (ALD), Metabolic Dysfunction Associated Fatty Liver Disease (MAFLD), and Chronic viral hepatitis, often go unnoticed due to their subclinical nature, until the decompensation stage [7,8]. These diseases have a different natural histories in males and females. During the premenopausal period, women are generally protected from fibrosis progression compared to men. This observation has been linked to oestrogen, as circulating estradiol seems to suppress lipid accumulation, inflammation, and fibrosis progression [9].

In a large population-based multicentre study from India, the incidence of chronic liver disease was found to be 1.28%, with alcohol-related liver disease being the most common aetiology [10]. A meta-analysis study reported a community prevalence of 28.2% for Non Alcoholic Fatty Liver Disease (NAFLD), which increased to 40.8% in hospital-based data [11]. However, there is a lack of studies from India investigating gender disparity in the diagnosis and treatment of non ethanol-related chronic liver disease. This knowledge gap will become problematic in the future when MAFLD becomes the leading cause of cirrhosis in India, especially if women at risk remain unidentified. A recent large retrospective study from the United States comparing gender differences in hospitalised cirrhosis patients found that women had a lower incidence of decompensating events but higher co-morbidities [12]. However, similar studies have not been conducted in India. Despite the limitations of a small sample size due to the short-term period and being a single-centre study, the present research aimed to serve as a stepping stone for future prospective studies, filling the knowledge gap in understanding the sexual dimorphism exhibited by Indian cirrhotics. The present hospital-based study compares non ethanol-related decompensated cirrhosis in men and women to explore their diverse presentations and prognoses.

MATERIALS AND METHODS

The present retrospective cohort study was conducted at the Department of Medical Gastroenterology and Hepatology, Tirunelveli Medical College, Tirunelveli, Tamil Nadu, India. Data collection was carried out from January 2022 to January 2023, and data analysis, interpretation, and manuscript drafting were completed from March 2023 to May 2023. The study was approved by the Institutional Ethics Committee (TVMC/IEC/SS/8, dated 6/12/21), and informed consent was obtained from all patients. A total of 27 males and 33 females were included.

Inclusion criteria: The study included patients with new-onset ascites, acute variceal bleeding, Hepatic Encephalopathy (HE), or combinations of these conditions. Patients presenting with acute-on-chronic liver failure and/or hepatorenal syndrome were also included

Exclusion criteria: Patients with a previous history of decompensation, alcoholics, pregnant women, and those who went against medical advice were excluded from the study.

Study Procedure

Data were obtained from inpatient records. The study compared decompensation events, complications, and laboratory values including haemoglobin, platelet count, bilirubin levels, serum albumin, International Normalised Ratio (INR), urea, creatinine, and prognostic scores such as Model for End-stage Liver Disease (MELD) [13] and Child-Pugh scores [14]. The presence of Diabetes Mellitus (DM), decompensation events, and mortality were considered qualitative variables. The grading of esophageal varices was done using the Westaby classification [15].

STATISTICAL ANALYSIS

Data analysis was conducted using SPSS version 24.0 Quantitative variables were expressed as mean and standard deviation, while qualitative variables were expressed as frequency and percentage. The association between categorical variables was analysed using the Chi-square test, and the comparison of continuous variables between the two groups was analysed using independent sample t-test. A p-value less than 0.05 was considered statistically significant.

RESULTS

The mean age of decompensation was 56.6 years for males and 50.9 years for females [Table/Fig-1]. For the same level of decompensation, males had a higher MELD score than females [Table/Fig-1]. Diabetes was more prevalent in males and likely contributed to metabolic dysfunction leading to cirrhosis [Table/Fig-2]. The most common decompensating event in females was haematemesis, while ascites was the most common in males [Table/Fig-3]. Jaundice was a predominant sign in males. The most common aetiology of liver disease in both males and females was NAFLD [Table/Fig-4]. In females, a significant proportion had no known aetiology due to the inability to perform liver biopsy and the absence of metabolic dysfunction features. Whether these cases are still classified as burned out NAFLD or cryptogenic cirrhosis remains inconclusive. There was no statistically significant difference between males and females in terms of laboratory values. In both groups, the majority of patients had large, grade 3 varices on endoscopy [Table/Fig-5]. Mortality was higher in the male group [Table/Fig-6].

DISCUSSION

In present study of non alcohol-related cirrhosis, NAFLD was found to be the most common aetiology in both males and females with DCLD. This contradicts a previous study where Hepatitis B Virus infection (HBV) was the most common aetiology in chronic liver disease in India, with NAFLD being more prevalent in western parts and HBV-related cirrhosis more prevalent in South India. These variations in observations are significant because NAFLD-related cirrhosis is rising in India, while it is already the leading cause of cirrhosis in the developed world.

Variables	Gender	n	Mean±SD	Range	Median	IQR	p-value
Age (years)	Male	27	56.5±12.1	24-75	56	51-68	0.133
	Female	33	50.9±15.4	17-82	50	43.5-65	
Haemoglobin (g/dL)	Male	27	9.3±2.3	5.2-13.7	9	7.9-10.7	0.153
	Female	33	8.4±2.5	3.5-13.4	9.1	6.7-10.15	
Platelet (count/mm^3)	Male	27	109629.6±58196.7	26000-269000	100000	68000-122000	0.388
	Female	33	94727.4±71670.3	1.12-352000	78000	49500-111000	
Bilirubin (mg/dL)	Male	27	2.63±2.3	0.4-9.8	1.7	0.8-4.4	0.391
	Female	33	2.09±2.46	0.5-11.6	1.1	0.8-2.25	
Albumin (g/dL)	Male	27	3.34±0.77	2-4.6	3.4	2.7-4.1	0.856
	Female	33	3.38±0.75	1.8-4.9	3.2	2.85-4	
INR	Male	27	1.41±0.36	0.76-2.1	1.31	1.15-1.79	0.51
	Female	33	1.35±0.34	0.62-1.94	1.31	1.1-1.65	
Urea (mg/dL)	Male	27	39.3±29.4	15-145	30	20-43	0.08
	Female	33	28.8±15.1	14-81	25	17.5-34	
Creatinine (mg/dL)	Male	27	1.13±0.48	0.6-2.5	1	0.8-1.3	0.101
	Female	33	0.91±0.52	0.5-3.3	0.8	0.7-0.9	
Sodium (meq/L)	Male	27	136.9±3.2	131-142	137	134-140	0.611
	Female	33	137.3±3.5	131-146	138	135-140	
MELD	Male	27	15.2±6.4	7-28	13	10-20	0.09
	Female	33	12.4±6.1	6-28	10	7.5-15	
Child-Pugh	Male	27	8.41±2.41	5-13	8	7-10	0.149
	Female	33	7.58±2	5-11	7	6-9.5	

[Table/Fig-1]: Patient baseline characteristics.
INR: International normalisation ratio; MELD: Model for end-stage liver disease; IQR: Interquantile range; p>0.05 non significant

DM	Gender				Total		χ^2	df	p-value
	Male		Female						
	n	%	n	%	n	%			
Yes	15	55.6	11	33.3	26	43.3	2.99	1	0.084
No	12	44.4	22	66.7	34	56.7			
Total	27	100	33	100	60	100			

[Table/Fig-2]: Diabetes Mellitus (DM) and DCLD.
p>0.05 non significant; DCLD: Decompensated chronic liver disease

Parameters	Gender				Total		χ^2	df	p-value
	Male		Female						
	n	%	n	%	n	%			
Variceal bleed	13	48.1	22	66.7	35	58.3	2.10	1	0.148
Jaundice	12	44.4	7	21.2	19	31.6	3.70	1	0.054
Ascites	19	70.4	15	45.5	34	56.7	3.75	1	0.053
Hepatic encephalopathy	6	22.2	5	15.2	11	18.3	0.50	1	0.481

[Table/Fig-3]: Decompensation events in males and females.
p>0.05 non significant

Aetiology	Gender				Total		χ^2	df	p-value
	Male		Female						
	n	%	n	%	n	%			
AIH	0	0	2	6.1	2	3.3	11.68	4	0.020
Chr BCS	1	3.7	0	0	1	1.7			
HBV	5	18.5	1	3	6	10			
NAFLD	17	63	15	45.5	32	53.3			
Unknown	4	14.8	15	45.5	19	31.7			
Total	27	100	33	100	60	100			

[Table/Fig-4]: Aetiology of liver disease.
AIH: Autoimmune hepatitis; Chr BCS: Chronic Budd-Chiari syndrome; HBV: Hepatitis B virus infection; NAFLD: Non alcoholic associated fatty liver disease; p<0.05 significant

Oesophageal varices	Gender				Total		χ^2	df	p-value
	Male		Female						
	n	%	n	%	n	%			
No varices	1	3.7	1	3	2	3.3	2.21	3	0.530
Grade 1	3	11.1	3	9.1	6	10			
Grade 2	9	33.3	6	18.2	15	25			
Grade 3	14	51.9	23	69.7	37	61.7			
Total	27	100	33	100	60	100			

[Table/Fig-5]: Oesophagealvarices grading.
p>0.05 non significant

Death	Gender				Total		χ^2	df	p-value
	Male		Female						
	n	%	n	%	n	%			
Yes	6	22.2	4	12.1	10	16.7	1.09	1	0.296
No	21	77.8	29	87.9	50	83.3			
Total	27	100	33	100	60	100			

[Table/Fig-6]: Mortality in the study subjects.
p>0.05 non significant

It is important to implement screening programs to identify at-risk populations with obesity and metabolic syndromes, allowing for the early detection of hepatic fibrosis or compensated cirrhosis [16]. This would enable effective interventions to reverse the condition.

The study found that females in the group decompensated at a younger age than males. Premenopausal women have protective factors, such as oestrogen, that slow down hepatic fibrosis. However, these factors decrease in postmenopausal women, putting them at an increased risk of cirrhosis [17-19]. Early decompensation in females could have been delayed if they had undergone cirrhosis screening earlier.

Cirrhosis attributed to NAFLD-related cirrhosis is becoming a significant public health burden, leading to significant Disability Adjusted Life Years (DALY). In the past 10 years, there has been a rising trend in the contribution of NAFLD-related cirrhosis to DALY [20].

Mortality was higher in the male population. A recent study from China showed a declining Age Standardised Mortality Rate (ASMR) in their patients, but the ASMR in males was up to 3.65 times higher [21]. In India, the death rate for liver cirrhosis and DALY reduced by 12.3% for cirrhosis in India [22]. However, according to present study liver cancer-related mortality is increasing. The reduction in the mortality rate of cirrhosis is likely due to better healthcare and decreased alcohol consumption. However, NAFLD is showing an increasing trend in incidence and mortality. NAFLD is associated with significantly higher mortality from hepatocellular cancer and an increased risk of non-liver-related deaths, particularly cardiovascular-related deaths [23,24].

The most common decompensating event in females was variceal bleeding, while in males, it was ascites. This contradicts another study where ascites was the index decompensating event in most of the study population [25]. Variceal bleeding is a complication of cirrhosis with a mortality rate of 10% [26] with an increased crude death rate for the female population [27]. It is a sequela. It occurs due to portal hypertension, leading to the rupture of oesophageal and gastric varices. Fibrosis screening and upper gastrointestinal endoscopy could have prevented variceal bleeding if conducted as advised by the Baveno committee [28].

The MELD score was higher in male patients than in females, possibly due to higher creatinine levels associated with higher muscle mass in men. This disparity has implications in MELD-dependent transplant enlisting, where females are less likely to receive a liver transplant due to lower MELD scores [29]. The modified MELD 3.0 score aims to address this disparity and provide equal opportunities for liver transplants to females [30]. Gender-based treatment strategies, such as hormonal replacement therapies for female NAFLD patients, are also being studied [31,32]. Alongside screening programs, these interventions may help prevent the progression of cirrhosis in female patients.

Overall, the present study highlights the importance of understanding the etiological variations, implementing screening programs, and addressing gender disparities in the management of cirrhosis to improve outcomes and reduce the burden of the disease.

Limitation(s)

The present study had the drawback of a low sample size, and the data was collected retrospectively from in-hospital records. It is important to note that this was a single-centre study. Several additional factors, such as sepsis, sarcopenia, functional status, and causes of mortality, could have been included in the study variables for more effective comparisons.

CONCLUSION(S)

The present study clearly demonstrates gender differences in non alcohol-related chronic liver disease, particularly in terms of age of decompensation, decompensation events, and mortality. These findings have important clinical implications for both preventive clinics and advanced liver clinics. They highlight the need to identify high-risk groups and implement preventive measures to avoid decompensation and treat specific complications. The study also emphasises the necessity for special screening programs targeting women, especially during the perimenopausal period when they are at a high-risk for fibrosis progression and cirrhosis. While gender-specific hormonal therapies are still being investigated, there is promising research being conducted in the field of NAFLD. Overall, the present study contributes valuable insights into the understanding and management of gender-specific differences in

chronic liver disease, offering a foundation for future research and the development of targeted interventions.

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