ORIGINAL ARTICLE

Etiological Patterns, Liver Fibrosis Stages and Prescribing Patterns of Hepato-Protective Agents in Indian Patients with Chronic Liver Disease

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Abstract

Objective: Considering the paucity of relevant data for chronic liver disease (CLD) from India, this PAN-India study was conducted to assess the current etiologic spectrum of CLD, stage of liver fibrosis at presentation and the prescribing patterns of hepato-protective agents by gastroenterologists in Indian real-world setting. This data would aid in early detection and formulation of effective management strategies for CLD in India.

Materials and Methods: In this cross-sectional, multicentric, epidemiological study, consecutive patients (18 ≥ 65 years) diagnosed with CLD, assessed for liver fibrosis by Vibration Controlled Transient Elastography (VCTE), were evaluated for etiology by standard clinical and laboratory criteria and grouped in to alcoholic liver disease (ALD)/non-alcoholic fatty liver disease (NAFLD)/viral liver disease/ drug induced liver injury (DILI)/others. The doctors' prescription was studied in each case to note the pattern of hepatotropic medications prescribed, in addition to other specific agents.

Results: Out of 504 enrolled patients with CLD (mean age: 47.9±11.81 years; men: 67.9%), 39.7% had NAFLD, 25.6% had ALD, 17.5% had hepatitis B (HBV), 7.9% had hepatitis C (HCV), 1.6% had autoimmune hepatitis, 0.4% had DILI and 7.3% had other causes of liver disease. Diabetes (15.9%), hypertension (12.9%), hypothyroidism (3.0%), dyslipidemia (1.2%) and obesity (0.4%) were the commonly reported comorbidities. Liver stiffness corresponding to the diagnosis of F4 liver fibrosis stage was reported in 77.5% HCV, 62.0% ALD, 46.0% NAFLD and 37.5% HBV patients. About 12.5% HCV, 8.0% NAFLD, 5.4% ALD, and 1.1% HBV patients reported F3 liver fibrosis stage. About 38.3% patients were on hepatoprotective drugs; commonly prescribed drugs were ademetionine (23.8%), ursodeoxycholic acid (17.9%) and drugs of herbal origin (11.3%).

Conclusion: NAFLD is emerging as a predominant etiology of CLD in India, followed by ALD, HBV, and HCV. However, significant regional differences regarding predominant etiology was noted within the country. It was further noted that significant number of patients had advanced fibrosis based on VCTE assessment. This study emphasizes the need for appropriate risk evaluation and early assessment of severity of liver disease, for adequate disease management.

Introduction

Liver disease continues to be a significant health problem in India. According to the recently available World Health Organization data, liver disease deaths in India has reached 259,749 i.e., 2.95% of total deaths.[1,2] The age-adjusted death rate is 22.93 per 100,000 of population, ranking India 63rd in the world.[1] Liver diseases can result from a spectrum of etiologies such as alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), viral infections (hepatitis B virus [HBV] or hepatitis C virus [HCV]), autoimmune liver disease and drug-induced liver injury (DILI).

Reports of etiologic assessment of CLD published in the past 25 years indicates that hepatitis B, hepatitis C and ALD are the leading causes of liver disease in India.[3-7] However, a surge in the incidence and prevalence of NAFLD in India has been recently noted, with the global epidemic of obesity, hypertension and type-2 diabetes mellitus (T2DM).[2] NAFLD has also been recognized as one of the most important causes of CLD in western countries as well.[8,9] This recent paradigm shift in etiologic spectrum of CLD in India could be attributed to the improved access to vaccination, tests and treatment, coupled with accelerated urbanization and adaptations such as sedentary lifestyle, fatty food, uncontrolled blood sugar, obesity, smoking and high alcohol intake.

Another recent development is the decline in importance and use of liver biopsy as a primary diagnostic tool for CLD and the advent of clinically validated, quantitative, non-invasive technique such as Vibration Controlled Transient Elastography (VCTE), which provides a more realistic depiction of CLD, with much wider acceptability in staging liver fibrosis. The use of VCTE has been evaluated in CLDs and is strongly correlated to hepatic fibrosis in chronic HBV, HIV/HCV coinfection, NAFLD, ALD, cholestatic diseases and autoimmune hepatitis.[10-13] In addition, VCTE has been predictive for hepatic decompensation; rendering it useful to both help stratify cirrhotic patients into different risk categories, as recommended by the 2015 BAVENO VI guidelines for management of patients with compensated advanced

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Table 1: Liver Stiffness Cut-Offs in Chronic Liver Diseases[10-13]

	F0-F1	F1	F1-F2	F2	F2-F3	F3	F3-F4	F4
Chronic hepatitis C	1.5-7.1		7.2-8.7	8.8-9.5		9.6-12.5	12.6-14.5	>14.5
Chronic hepatitis B	1.5--7.2			7.3-8.1	8.2-10.5	10.6-11.0	11.1-18.2	>18.2
NAFLD		1.5-7		7.1-8.7		8.7-10.3		> 10.3
Alcohol liver disease		1.5-7.5		7.6-9.5		9.6-12.5		>12.5
Chronic cholestatic disease	0-7.1			7.2-11.1	11.2-14.7	14.8-15.6	15.7-17.3	>17.3
Biliary diseases	1.5-7.1			7.1-11.1	11.1-14.7	14.7-15.6	15.6-17.3	>17.3
HIV/HCV coinfection	1.5-7.2				7.2-11.9		11.9-14.6	>14.6
Chronic hepatitis C recurrence after transplantation	1.5-6.3		6.3-7.9	7.9-8.5		8.5-11.9	11.9-14.5	>14.5
Autoimmune hepatitis	<6.45			6.45		8.75		12.5
DILI	<7			7.1		9.5		12.5

Data represented in kPa; *These cut offs have been mentioned as an indication for the physicians to make a diagnosis, it shall in no case replace their judgment. This guide is based on a selection of clinical studies from the existing literature reporting use of the VCTE. This guide is not intended to be used as a conversion table from liver stiffness readings in kilopascals (kPa) to fibrosis stage. This guide can in no way replace the judgment of the physician who is ultimately responsible for the final diagnosis.*

CLD, and to screen for cirrhosis or detect undiagnosed CLD in the general population.[14,15] Moreover, VCTE has been recommended by the latest European Association for the Study of the Liver (EASL) clinical practice guidelines[16] for the management of patients with viral hepatitis infection; and has been considered as a clinically useful tool for identifying advanced fibrosis in patients with NAFLD as per the American Association for the Study of Liver Diseases (AASLD) guidelines.[17,18]

Vergniol et al. in a study in 1,457 patients with chronic HCV reported that liver stiffness measurement (LSM) by VCTE has superior diagnostic performance for predicting 5-year survival compared with biopsy.[19] In another study in patients with various conditions, Klibansky reported excellent diagnostic performance of VCTE for predicting a composite outcome including death, decompensation, and hepatocellular carcinoma.[20]

Hence considering the growing burden of CLD, recent shift in the etiologic spectrum, and the lack of relevance given to the condition, there is a need to understand the trend of CLD and its etiologies in India; to comprehend the fluctuation of its various aspects, which in turn would be helpful in strategizing the management facets of CLD in tertiary care settings. Hence this study was conducted to assess the current etiology spectrum of CLD, and stage of liver fibrosis at presentation in Indian real-world setting. The prescribing patterns of hepato-protective agents by gastroenterologists in Indian real-world setting was also ascertained in this study.

Methods

This cross sectional, multicentric, epidemiological, PAN-India study was conducted across 15 private clinics and polyclinics in India, between March to June 2017. The centres were selected across four geographically different regions: north (Delhi, Gaziabad, Lucknow Ludhiana), south (Chennai, Bangalore), west (Mumbai, Pune, Satara, Ahmedabad, Vadodara), and east (Agartala, Guwahati, Kolkata).

Consecutive patients (18 ≥ 65 years) diagnosed with CLD, assessed for liver fibrosis by VCTE, were evaluated for etiology by standard clinical and laboratory criteria, and grouped as ALD, NAFLD, viral liver disease, DILI, and others. Pregnant or lactating woman, patients with prior diagnosis of hepatitis A, hepatitis D or hepatitis E virus and patients with decompensated CLD were excluded from this study.

The study protocol was approved by local independent ethics committees. The study was conducted in accordance with the principles of Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice (ICHGCP) guidelines, and Indian regulatory guidelines (Indian Council of Medical Research and Indian GCP guidelines). All patients provided written consent in the patient authorization form to participate in the study.

Study Endpoints

The primary endpoint of this study was the percentage of CLD patients with ALD, NAFLD, VD, DILI, or any other CLDs based on history, clinical presentation, liver biochemistry or abdominal Ultrasound Sonography Test (USG) and assessment by the investigator. The secondary endpoints were the average LSM values (using VCTE) in patients with respect to different etiologies; percentage of patients with minimal fibrosis (≥F1), significant fibrosis (≥F2), advanced fibrosis (≥F3) and cirrhosis (F4); demographics and clinical profile of CLD patients; and the pattern of hepatoprotective medications prescribed, in addition to other specific agents, in patients with CLD.

Definitions used in this study

Liver Stiffness Measurement

The VCTE (FibroScan) examination was performed as per the manufacturer's recommendations. Based on the cut-offs provided in the below Table 1,[10-13] the LSM was used to categorize liver fibrosis/cirrhosis stage as minimal fibrosis (≥F1), significant fibrosis (≥F2), advanced fibrosis (≥F3), and cirrhosis (F4).

Child- Pugh score

Severity and staging of liver disease was recorded, if available. The clinical findings were used in association with laboratory studies to calculate Child-Pugh Score. The Child-Pugh score was calculated by adding the score of five factors (ascites, bilirubin, albumin, prothrombin time and encephalopathy) and ranged from 5 to 15. Child Pugh score between 5 and 6 indicated class A; 7 to 9 indicated class B and score of 10 or above indicated class C.

Statistical analysis

Continuous variables were summarized using descriptive statistics (number of observations, mean, standard deviation [SD], median, minimum and maximum inter-quartile range [IQR]). Categorical and discrete variables are presented in percentage. Tests were done at 2-sided 5% level of significance. All the statistical analyses were performed using SAS® software 9.4 (SAS Institute Inc., Cary, N.C.).

Results

Demographics and patient characteristics

A total of 504 patients were enrolled in this study. The mean age of the population was 47.9 ± 11.81 years. Majority of patients were men (342 [67.9%]) and married (470 [93.3%]).

Nearly half (247 [49.0%]) of the patients were graduates or post graduates (Table 2). Socioeconomic status showed that nearly half (248 [49.2%]) of the enrolled patients belonged to upper middle class, followed by lower middle class (120 [23.8%]).

Table 2: Baseline Demographic Characteristics

Parameters	Overall (N=504)
Age (yrs.), Mean (SD)	47.9 (11.81)
Gender n (%)	
Male	342(67.9%)
Female	162(32.1%)
BMI (Kg/m^2), Mean (SD)	25.8 (4.31)
Waist circumference (cms.)	90.5 (10.22)
Socio-economic status, n (%)	
Occupation	
Profession	103 (20.4 %)
Semi-Professional	108 (21.4 %)
Clerical, shop-owner, farmer	134 (26.6 %)
Skilled worker	48 (9.5 %)
Semi-skilled worker	12 (2.4 %)
Unskilled worker	4 (0.8 %)
Unemployed	95 (18.8 %)
Education	
Profession or honors	16 (3.2 %)
Graduate or post graduate	254 (50.4 %)
Intermediate or post high school diploma	102 (20.2 %)
High school certificate	74 (14.7 %)
Middle school certificate	43 (8.5 %)
Primary school certificate	12 (2.4 %)
Illiterate	3 (0.6 %)
Score	
Score <5 lower class	3 (0.6 %)
Score 5 – 10 upper lower class	50 (9.9 %)
Score 11–15 lower middle class	120 (23.8 %)
Score 16 – 25 upper middle class	248 (49.2 %)
Score 26 to 29 upper class	83 (16.5 %)

Table 3: Co-morbidities reported in >1% patients

Condition	N=504 n (%)
Subjects with any comorbidity	
Yes	202(40.1%)
No	302(59.9%)
Details of comorbidity	
Type 2 diabetes mellitus	80(15.9%)
Hypertension	65(12.9%)
Malnutrition	25(5.0%)
Hypothyroidism	15(3.0%)
Gastrointestinal bacterial infection	15(3.0%)
Gastrointestinal fungal infection	15(3.0%)
Constipation	14(2.8%)
Irritable bowel syndrome	12(2.4%)
Anxiety	10(2.0%)
Dyslipidaemia	6(1.2%)
Hyperchlorhydria	6(1.2%)

A total of 202 (40.1%) patients reported associated comorbidities. T2DM (80 [15.9%]), hypertension (65 [12.9%]), hypothyroidism (15 [3.0%]), dyslipidemia (6 [1.2%]) and obesity (2 [0.4%]) were the commonly reported comorbidities (Table 3). The predominant signs and symptoms associated with CLD were abdominal pain (154 [30.6%]), fatigue (103 [20.4%]), nausea (89 [17.7%]), vomiting (72 [14.3%]), ascites (65 [12.9%]), and decreased appetite (56 [11.1%]).

Etiological profile

The mean± SD age at the time of diagnosis of CLD was 46.5± 11.74 years. The mean± SD duration of CLD was 1.5± 2.26 years. Of the enrolled patients with CLD, 200 (39.7%) had NAFLD, 129 (25.6%) had ALD, 88 (17.5%) had HBV, 40 (7.9%) had HCV, 8 (1.6%) patients had autoimmune hepatitis, 2 (0.4%) patients had DILI and 37 (7.3%) had other causes.

Out of 504 CLD patients, 65 (12.9%) were newly diagnosed cases versus 439 (87.1 %) patients who were previously diagnosed. Similar pattern of CLD etiology was observed in previously and newly diagnosed patients. Summary of patient disposition by zone is depicted in Table 4.

Severity and Staging of Liver Disease

The median liver stiffness was maximum in patients with autoimmune hepatitis, followed by ALD, idiopathic diseases, HCV, HBV, NAFLD, and DILI (Table 5). Liver stiffness corresponding towards the diagnosis of F4 liver fibrosis stage was reported in 77.5% HCV (n=31), 62.0% ALD (n=80), 46.0% NAFLD (n=92) and 37.5% HBV (n=33) patients, based on VCTE. Liver fibrosis stage in patients with ALD, NAFLD, Hepatitis B, and Hepatitis C are depicted in Figure 1.

Out of 129 patients with ALD, liver stiffness values corresponding to F4 liver disease stage was reported in 62.0% patients, followed by F0-F2 in 22.5%, F2 in 10.1%, and F3 in 5.4% patients. Out of 200 patients with NAFLD, liver stiffness corresponding towards the diagnosis of F4 liver disease stage was found in 46.0% patients, followed

Table 5: Summary of severity and staging of liver disease

Category	Overall (N=504)
VCTE results median stiffness (kPa), mean (SD)	24.6 (22.54)
IQR (kPa), mean (SD)	3.2 (5.09)
IQR/Med (%), mean (SD)	13.8 (9.12)
Valid measurement, mean (SD)	10.5 (6.57)
Liver fibrosis/liver disease stage, n (%), [95% CI]	
<7kpa	120 (23.8%) [0.20 to 0.28 0.20 to 0.280.20: 0.28]
>7kpa	384 (76.2%) [0.72: 0.79]

Table 4: Summary of patient disposition by zone

Zone	ALD n (%)	NAFLD n (%)	Hepatitis B n (%)	Hepatitis C n (%)	DILI n (%)	Others n (%)
East	34 (26.4 %)	62 (31.0 %)	15 (17.0 %)	2 (5.0 %)	1 (50.0 %)	5 (11.1 %)
North	61 (47.3 %)	33 (16.5 %)	32 (36.4 %)	21 (52.5 %)	-	17 (37.8 %)
South	22 (17.1 %)	57 (28.5 %)	15 (17.0 %)	1 (2.5 %)	-	-
West	12 (9.3 %)	48 (24.0 %)	26 (29.5 %)	16 (40.0 %)	1 (50.0 %)	23 (51.1 %)

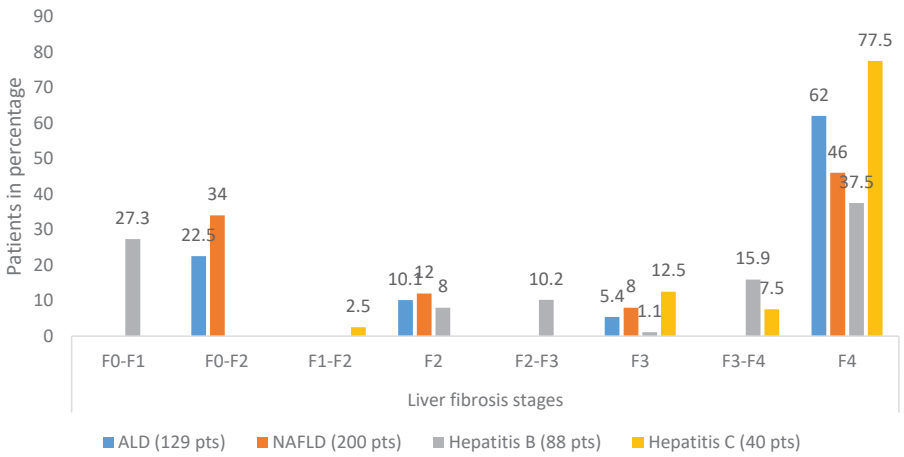

Fig. 1: Liver fibrosis stage assessed by vibration-controlled transient elastography in patients with ALD/NAFLD/Hepatitis B/Hepatitis C

Table 6: Summary of child-pugh score and abdominal ultrasound

Category	Overall (N=504)
Total Bilirubin (mg/dL)	
n	79
Mean (SD)	1.4 (0.67)
Serum albumin, g/dL	
n	79
Mean	1.6 (0.63)
Prothrombin time, prolongation (s) INR	
n	70
Mean (SD)	1.4 (0.69)
Ascites	
n	75
Mean (SD)	1.4 (0.49)
Hepatic encephalopathy	
n	75
Mean (SD)	1.1 (0.23)
Total Score, n(%)	
Grade A (5–6)	34 (6.7%)
Grade B (7–9)	33 (6.5%)
Grade C (10–15)	1 (0.2%)
Hepatic steatosis grade, n(%)	
Absent	10 (2.0%)
Mild	40 (7.9%)
Moderate	45 (8.9%)
Severe	4 (0.8%)

by F0-F2 (34.0%), F2 (12.0%), and F3 (8.0%). More than one-third of HBV patients (total=88) had liver stiffness corresponding towards the diagnosis of F4 liver disease stage (37.5%), followed by F0-F1 (27.3%), F3-F4 (15.9%), F2-F3 (10.2%), F2 (8.0%), and F3 (1.1%). More than three-fourth of HCV patients (total=40) had liver stiffness corresponding towards the diagnosis of F4 liver disease stage (77.5%), followed by F3 (12.5%), F3-F4 (7.5%), and F1-F2 (2.5%). Out of 2 DILI patients, 1 patient each had liver stiffness corresponding towards the diagnosis of F0-F1 and F4 liver disease stage. Amongst patients with autoimmune hepatitis (total=8), liver stiffness corresponding towards the diagnosis of F4 liver disease stage was found in 75.0%, followed by F2 and F3 (12.5% each). In 24 patients with idiopathic diseases, 4 (16.7%) and 20 (83.3%) patients had liver stiffness of <7 kPa and >7 kPa, respectively.

Child-Pugh score and Abdominal Ultrasound

Out of total 68 patents whose Child-Pugh's scoring was done, the proportion of patients presented with Grade A (34 [6.7%]) and Grade B (33 [6.5%]) Child-Pugh score were comparable. Only 1 (0.2%) patient was presented with Grade C. Hepatic steatosis grade was mild, moderate and severe in 7.9%, 8.9%, and 0.8% patients, respectively (Table 6).

Management of CLD patients

About 193 (38.3%) were on hepatoprotective drugs. Among hepatoprotective drugs, 120 (23.8%) patients were on ademetionine, 90 (17.9%) were on ursodeoxycholic acid, 57 (11.3%) on drugs of herbal origin (Achillea millefolium, Capparis spinosa, Cichorium intybus, Senna occidentalis, Solanum nigrum, Tamarix gallica, Terminalia arjuna), 24 (4.8%) on ornithine aspartate, and 17 (3.4%) patients on Silybum marianum. Among other drugs, majority of patients were on diuretics (95 [18.8%]), followed by vitamins (89 [17.7%]), antivirals (75 [14.9%]), beta blocking agents (67 [13.3%]), antiemetics and antinauseants (60 [11.9%]), drugs for acid related disorders (60 [11.9]), drugs for constipations (53 [10.5%]), and drugs for functional gastrointestinal disorders (53 [10.5%]).

Safety

No adverse events were reported during the study.

Discussion

The present study indicated that NAFLD (39.7%) is the commonest emerging etiology of CLD in Indian real-world setting. This is followed by ALD (25.6%), HBV (17.5%), HCV (7.9%), idiopathic disease (2.4%), autoimmune hepatitis (1.6%), cryptogenic cirrhosis (1.6%), DILI (0.4%), and Wilson disease (0.2%). Similar trend of high prevalence of NAFLD was noted amongst newly and previously diagnosed CLD cases.

However, a retrospective study on adults with CLD at the University of Calgary Liver Unit between 2008 and 2011 reported that majority of the enrolled patients had HCV (36%) or HBV (29%), while 7% had NAFLD, 5% had autoimmune liver disease, 3% had hemochromatosis, and 2% had ALD.[2121]Velosa et al from Portugal in a study of 988 CLD patients found viral etiology in 82%, alcoholic in 11%, metabolic in 2%, biliary in 2%, idiopathic in 2% and autoimmune in 1.5% of the total cohort.[22] Among viral group, HBV infection was reported in 65%, HCV in 26% and hepatitis D in 8% patients. Another prospective study from Pakistan in children (1-14 years) with suspected CLD demonstrated that 24% of the subjects had chronic HBV, 16% had autoimmune disease, and 16% had Wilson's disease.[23] However, the etiology was uncertain in 44% cases. No cases of NAFLD or ALD were observed in these children. Biopsy proven chronic hepatitis was found to be present in 354 patients out of 518 patients with CLD in a study reported by Khokhar in 2002. Out of these 86% had HCV, 10.7% HBV, 3.1% had both B and C.[24] This difference in the prevalence rate between studies could be attributed to the observed differences in CLD prevalence across countries and the contributing risk factors, which may vary based on the geographical regions.

Further, our data denoted a significant regional difference in the predominant etiology within the country. HCV, ALD and HBV were the most common cause of CLD in the northern region of India. NAFLD was found to be predominant in the east and south zone. However, Jhajharia et al in 2014 reported a high prevalence of ALD (58%), followed by HBV (19.0%), HCV (3.7%), and others (22.0%; which included autoimmune, Wilson's, NAFLD-related, and cryptogenic) in northern India. In addition, 11 patients (2.7%) had more than one etiology of CLD.[25] Chandra et al had also showed that alcohol is the most common perpetrator for CLD in central India.[26] Similarly, a study of 44 patients by Acharya et al reported that 50% of patients had chronic HBV, associated hepatitis D with HBV in 21%, HCV in 15%, and non-A, non-B other than HCV virus in 13%; 2% patients had autoimmune HBV.[7] Nevertheless, in these studies from Indian subcontinent, majority of the patients belonged to low socio-economic status.

This etiological spectrum of CLD as indicated in this study highlights the epidemiological transition within the country. Further, higher proportion of NAFLD reported in our study could be attributed to the fact that majority of patients in this study population were educated, belonging to upper middle class, making them less susceptible to alcohol dependence and abuse,[27] a factor contributing to ALD. Nevertheless, this raises concerns of access to available care for the rural, and illiterate patients, considering the Indian society as a whole.

The bidirectional association between NAFLD and components of metabolic syndrome has been strongly established.[28] Hence, the increasing

prevalence of metabolic risk factors including diabetes mellitus, obesity, etc in Indian setting could also be the contributing factor for this rapidly increasing prevalence of NAFLD in India. Considering the fact that metabolic risk factors are common in patients with NAFLD, it is postulated that NAFLD may actually be a hepatic manifestation of metabolic syndrome.[2] Moreover, NAFLD has been observed to be consistently associated with obesity,[29] type 2 diabetes mellitus,[30,31] and dyslipidemia.[32]In line with the above fact, our study also reported a high prevalence of associated comorbidities such as T2DM, hypertension, hypothyroidism, anxiety, dyslipidemia, coronary artery disease, depression and obesity.

Male predominance was observed in the present study, which is consistent to the results reported by Pal et al[33] where 79% of patients were male and Chandra et al[26] who had reported 80.6% males in the study. Jhajharia et al (2014) had also noted male predominance with a male to female ratio of 5.5:1.[25] This indicate that males are more susceptible to CLD than females, suggesting high risk of exposure to causative factors. Further, it is noted from previous literatures that the risk of a liver disease increases with age. Our study recorded a mean age of 46.5 years for CLD diagnosis which is in agreement with the finding of Jhajharia et al where the mean age of presentation was 45.6 years.[25]

Mode of presentation of patients with CLD was an important consideration taken in our study. Abdominal pain, fatigue, nausea, vomiting, ascites and decreased appetite were the major sign and symptoms associated with CLD patients in our study. These complications are markers of disease progression and depict diseases severity in its respective order. On the contrary, Pal et al has reported ascites in 52% of patients followed by jaundice in 40% and GI bleeding in 24% as the sign and symptoms associated with CLD.[33]

Liver stiffness corresponding towards the diagnosis of F4 liver fibrosis stage was reported in 77.5% HCV, 62.0% ALD, 46.0% NAFLD and 37.5% HBV patients. Moreover, 12.5% of HCV, 8.0% of NAFLD, 5.4% of ALD, and 1.1% of HBV patients had liver stiffness corresponding towards the diagnosis of F3 liver fibrosis stage. This signifies that majority of patients diagnosed in clinics with CLD seem to have F3 or F4 fibrosis at presentation.

Child-Pugh score and class, a marker of extent of liver damage, was evaluated in this study. Laboratory results of hemoglobin count, platelets count, total white blood cells count, hematocrit, red blood cells count showed elevated levels in more than half of patients, signifying ongoing injury. In a study in 91 patients, Pal et al found that 51% of patients belonged to Child-Pugh class B, followed by class C in 35% and only 14% in class A.[33] In another study by Chandra et al,[26] it was found that Child-Pugh class B and C together constituted 81.7% of the patient, which is considered as fairly advanced liver disease. In our study, out of 68 patients whose Child Pugh's scoring was done (~15% patients), approximately equal proportion of patients had Grade A and Grade B score. However, only 1 (0.2%) patient was in Grade C of Child-Pugh score. Among patients in whom USG findings were available, hepatic steatosis grade was mild, moderate and severe in 7.9%, 8.9%, and 0.8% patients, respectively. This indicate that almost half of patients of CLD were asymptomatic while remaining (constituted by Group Child-Pugh B & C) presented a remarkably advanced stage, or approached for medical care at an advanced stage. In the context of the resource restraint systems like India, this observation of a relatively late presentation of a fairly large segment of CLD patients is of particular concern. In view of this, screening and increasing awareness about liver diseases are of paramount importance. Improving liver disease awareness, risk factor detection and value-added patient education might all be considered important interventions to impact this scenario.

To the best of our knowledge, this is the first of its kind PAN-India study to report the prescribing pattern of drugs in the treatment of different etiologies of CLD. Hepatoprotective drugs were the most commonly prescribed category in our study (38.3%). Among them, ademetionine (23.8%), ursodeoxycholic acid (17.9%) and drugs of herbal origin (11.3%) were the commonly prescribed hepatoprotective drugs. Many studies have reported the effectiveness and tolerability of ademetionine in the symptomatic management of CLD.[35,36] Ursodeoxycholic acid has also been effective in reducing biochemical markers of cholestasis in patients with CLD.[37,38] Herbal medicines have also been in use in the treatment of liver diseases for a long time. As nutritional deficiency is very common in these patients, prescription of vitamin preparations was seen to be common in our study and overall they are one of the most commonly prescribed drugs after hepatoprotectives.

To conclude, this study indicate that NAFLD is emerging as an important etiology of CLD in Indian real-world setting, followed by ALD, HBV, HCV and others. Significant regional differences regarding predominant etiology within the country was also noted. CLD in India has a male preponderance, affecting mostly people of middle age group. Considerable percentage of the patients had advanced fibrosis, based on VCTE assessment. This study thus emphasizes the need for appropriate risk evaluation and early assessment of severity of liver disease, for adequate disease management. There is need for a consensus or guidelines for the management of all etiologies of CLD based on liver disease stages. However, as this was a cross-sectional study, the cause and effect of relationship could not be determined in this study. Hence further studies are warranted in larger and more representative samples to improve the generalizability of the findings to the country as a whole.

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Conflict of interest

Dr. Choudhuri and Dr. Chaudhari have received research funding from Abbott India Ltd as a consultant. Dr. Pawar and Dr. Roy are employees of Abbott India Ltd.

Data Availability

The data sets supporting the results of this article are included within the article.

References

1. World Health Rankings. World Health Organization 2017. http://www.worldlifeexpectancy.com/india-liver-disease. Accessed on 10 July 2018.
2. Duseja A, Singh SP, Saraswat VA, et al. Non-alcoholic Fatty Liver Disease and Metabolic Syndrome—Position Paper of the Indian National Association for the Study of the Liver, Endocrine Society of India, Indian College of Cardiology and Indian Society of Gastroenterology. *Journal of Clinical and Experimental Hepatology* 2015; 5:51-68.
3. Ray G. Trends of chronic liver disease in a tertiary care referral hospital in Eastern India. *Indian J Public Health* 2014; 58:186-

94.

4. SK Sarin, Chari S, Sundaram KR, et al. Young v adult cirrhotics: a prospective, comparative analysis of the clinical profile, natural course and survival. *Gut* 1988; 29:101-07.
5. Ray G, Ghoshal UC, Banerjee PK et al. Aetiological spectrum of chronic liver disease in eastern India. *Trop Gastroenterol* 2000; 21:60-62.
6. Trimukhe R, Rabi R, Narayankar SM, et al. Epidemiological spectrum of chronic liver disease in eastern Madhya Pradesh India. Data presented at 67th Annual Conference of the Association of Physicians of India, January 2012, Kolkata, India.
7. Acharya SK, Panda SK, Duphare H, et al. Chronic hepatitis in a large Indian Hospital, AIIMS, New Delhi. *Natl Med J India* 1993; 6:202-6.
8. Browning JD, Szczepaniak LS, Dobbins R, Nuremberg P, Horton JD, Cohen JC, Grundy SM, Hobbs HH. Prevalence of hepatic steatosis in an urban population in the United States: impact of ethnicity. *Hepatology* 2004; 40:1387–1395.
9. Bedogni G, Miglioli L, Masutti F, Castiglione A, Crocè LS, Tiribelli C, Bellentani S. Incidence and natural course of fatty liver in the general population: The Dionysos study. *Hepatology* 2007; 46:1387–1391.
10. Mikolasevic I, Orlic L, Franjic N, Hauser G, Stimac D, Milic S. Transient elastography (FibroScan® with controlled attenuation parameter in the assessment of liver steatosis and fibrosis in patients with nonalcoholic fatty liver disease - Where do we stand? *World J Gastroenterol* 2016; 22:7236-51.
11. Wong VW, Vergniol J, Wong GL et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology* 2010; 51:454-62.
12. Pavlov CS, Casazza G, Nikolova D et al. Transient elastography for diagnosis of stages of hepatic fibrosis and cirrhosis in people with alcoholic liver disease. Cochrane Database Syst Rev. 2015;1:CD010542.
13. Xu Q, Sheng L, Bao H, et al. Evaluation of transient elastography in assessing liver fibrosis in patients with autoimmune hepatitis. *J Gastroenterol Hepatol* 2017; 32:639-644.
14. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. *J Hepatol* 2015; 63:743-752.
15. Roulot D, Costes JL, Buyck JF, et al. Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years. *Gut* 2011; 60:977-984.
16. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015; 63:237-264.
17. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015; 62:932-54.
18. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2018; 67:328-357.
19. Vergniol J, Klibansky DA, Mehta SH et al. Transient elastography for predicting clinical outcomes in patients with chronic liver disease. *J Viral Hepat* 2012; 19:e184–e193.
20. J, Klibansky DA, Mehta SH et al. Transient elastography for predicting clinical outcomes in patients with chronic liver disease. *J Viral Hepat* 2012; 19:e184–e193.
21. Pang JX, Pradhan F, Zimmer S, et al. The feasibility and reliability of transient elastography using Fibroscan®: A practice audit of 2335 examinations. *Canadian Journal of Gastroenterology & Hepatology* 2014; 28:143-149.
22. Velosa J, Ramalho F, Serejo F, Marinho R, de Moura MC. Chronic hepatitis: The etiological spectrum, The implications for treatment. *Acta Med Port* 1993; 6:233-8.
23. Hanif M, Raza J, Qureshi H, Issani Z. Etiology of chronic liver disease in children. *J Pak Med Assoc* 2004; 54:119-22.
24. Khokhar N. Spectrum of chronic liver disease in a tertiary care hospital. *J Pak Med Assoc* 2002; 52:56-8.
25. Jhajharia A, Soni A, Pokharna R, Ashdhir P, Sharma SS, Nepalia S. Spectrum of chronic liver disease admitted to a medical college hospital in northern India: is there cause for concern? *Indian J Gastroenterol* 2014; 33:480-1.
26. Chandra KP, Singh SN, Pawah AK. Study of Clinico-etiological Profile and the Complication Pattern in Patients with Chronic Liver Disease at Tertiary Care Centre. *International Journal of Contemporary Medical Research* 2016; 3:1668-1670.
27. Crum RM, Helzer JE, Anthony JC. Level of education and alcohol abuse and dependence in adulthood: a further inquiry. *Am J Public Health* 1993; 83:830–837.
28. Wainwright P, Byrne CD. Bidirectional Relationships and Disconnects between NAFLD and Features of the Metabolic Syndrome. Lonardo A, Targher G, eds. *International Journal of Molecular Sciences* 2016; 17:367.
29. Subichin M, Clanton J, Makuszewski M, Bohon A, Zografakis JG, Dan A. Liver disease in the morbidly obese: a review of 1000 consecutive patients undergoing weight loss surgery. *Surg Obes Relat Dis* 2015; 11:137–141.
30. Prashanth M, Ganesh HK, Vima MV, John M, Bandgar T, Joshi SR, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus. *J Assoc Physicians India* 2009; 57:205–210.
31. Fan N, Zhang L, Xia Z, et al. Sex-specific association between serum uric acid and nonalcoholic fatty liver disease in type 2 diabetic patients. *J Diabetes Res* 2016; 2016:3805372.
32. Wu K-T, Kuo P-L, Su S-B, et al. Nonalcoholic fatty liver disease severity is associated with the ratios of total cholesterol and triglycerides to high-density lipoprotein cholesterol. *J Clin Lipidol* 2016; 10:420–425.
33. Pal J, Dasgupta S, Agarwal V, et al. Clinical profile of chronic liver diseases in a tertiary care center in Kolkata. *J Assoc Physicians India* 2003; 51:1173-4.
34. Pang JX, Zimmer S, Niu S, et al. Liver stiffness by transient elastography predicts liver-related complications and mortality in patients with chronic liver disease. *PLoS One* 2014; 9:e95776.
35. Frezza M and Terpin M. The Use of S-Adenosyl-L-Methionine in the Treatment of Cholestatic Disorders . A Meta-Analysis of Clinical Trials. *Drug Investigation* 1992; 4:101.108.
36. Manzillo G, Piccinino F, Surrenti C, Frezza M, Giudici GA, Le Grazie C. Multicentre double-blind placebo-controlled study of intravenous and oral s-adenosyl-L-methionine (SAMe) in cholestatic patients with liver disease. *Drug Invest* 1992; 90–100.
37. Lawate P, Rooprai R, Choudhury G, Dutta S. A prospective, multicentre, observational study of patients with chronic cholestatic liver diseases receiving Udiliv® in India: Splendid study. *Int J Basic Clin Pharmacol* 2016; 5:2621-9.
38. Qureshi H, Mehdi I, Ahmed WU, Alam SE. Role of ursodeoxycholic acid in lowering ALT in chronic liver disease. JPMA. *J Pak* Med Assoc 2006; 56:130-1.