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**Original Research Article**

# Epidemiology and treatment practices of chronic cholestatic liver disease in India: a physician survey-based study

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## ABSTRACT

**Background:** Chronic cholestatic liver disease (CCLD) constitutes an intricate array of liver diseases in India. A physician-based survey was conducted to understand the prevalence, current treatment approaches, and gaps in the management of CCLD in India.
**Methods:** A total of 215 physicians participated to complete a questionnaire comprising 35 questions related to the prevalence and current treatment of CCLD and assess gaps in its management.
**Results:** Most physicians (53.5%) reported liver disorders with cholestasis to be prevalent in 10-20% of patients, while 34.9% reported their prevalence in 21-30% of patients. Alcoholic liver disease with cholestasis (CCLD [ALD]) was reported in 10-20% of patients and 21-30% of patients by 33.5% and 37.2% of physicians, respectively. Drug-induced liver disease with cholestasis (CCLD [DILI]) was reported to be present in 5-10% of patients by 34.9% of physicians. Ursodeoxycholic acid (UDCA) was found to be used by 60% physicians in >50% of patients with CCLD (ALD), commonly for a period of 4-12 weeks (48.4% physicians), while it was used for 12-24 weeks by 38.1% physicians in CCLD (DILI); for both conditions, the preferred dose was 10-15 mg/kg body weight. UDCA was reported to have good tolerability and efficacy by most physicians for both conditions.
**Conclusions:** In light of scarce data on CCLD prevalence and management approaches in India, the present survey findings provide useful insights on its prevalence in India and support the use of UDCA therapy for the management of its symptoms.

**Keywords:** CCLD, Ursodeoxycholic acid, Alcoholic liver disease, Drug-induced liver disease, Liver function test

## INTRODUCTION

Chronic cholestatic liver disease (CCLD) comprises a complex spectrum of hereditary and acquired hepatobiliary disorders, resulting in impaired bile secretion or diminished bile formation.[1,2] The disease course is heterogenous most likely involving genetic predisposition and exposure to environmental factors.[2,3] CCLD increases the risk for several complications and rising morbidity and mortality rates associated with the underlying condition and poses a significant healthcare burden. Cholestatic liver disorders manifest from infancy to childhood with clinical signs of fatigue, pruritis, and jaundice. Pruritis is seen in around 80% of CCLD patients, and evidence suggests the signs of metabolic bone disease, fat-soluble vitamin deficiencies, and dyslipidemia in CCLD patients.[4,5] It may also lead to hepatocellular carcinoma or cholangiocarcinoma and eventually death.[6]

CCLD is a primary pathological component of diverse diseases, the most common being primary biliary

cholangitis (PBC), primary sclerosing cholangitis (PSC), and biliary atresia (BA).[2] Globally, the incidence of PBC ranges between 0.33 and 5.8 per 100,000 inhabitants/year and prevalence ranges between 1.91 and 40.2 per 100,000 inhabitants. Further, the incidence rates for PSC range between 0 and 1.3 per 100,000 inhabitants/year and prevalence rates range between 0 and 16.2 per 100,000 inhabitants.[7] Although robust epidemiologic statistics have been presented across the West, the reported incidence and prevalence of CCLD appear to be lacking from India as well as the must be quantified by leveraging population-based data from the existing registries.

CCLD can be frequently seen among people with excess alcohol abuse leading to alcoholic liver disease (ALD).[8] In rare instances, CCLD can occur due to the usage of certain drugs, alternative medicines, or some toxic substance, referred to as drug-induced liver injury (DILI).[9] Data related to DILI in India is quite limited; however, it is one of the important causes of liver failure resulting in significant morbidity and mortality.[10,11] Ursodeoxycholic acid (UDCA) is the primary bile acid used in the treatment of CCLD.[4] This hydrophilic bile acid works by membrane stabilization, cytoprotection, and immunomodulation of affected liver cells.[1] The American Association for the study of liver diseases (AASLD) and the European association for the study of the liver (EASL) recommend UDCA as the life-long treatment of choice for PBC, with a recommended dose of 13-15 mg/kg/day.[12,13] Treatment with UDCA prevents further progression of PBC, such that duration of survival can be improved by 16-20 years.[4,14]

Similarly, UDCA is the most common treatment prescribed for PSC, although long-term results in disease improvement are unclear.[4] Moreover, poor long-term outcomes and no improvement in survival time were reported with a high dose of UDCA (>28 mg/kg/day) in patients with PSC, and guidelines regarding the use of UDCA in PSC have not been formulated yet.[4,15] In India, there remains lack of data on physicians' perspectives about the efficacy, tolerance and compliance with UDCA in the treatment of CCLD. Additionally, data in relation to the basis of physicians' decisions while commencing the treatment with UDCA is also scarce.[1] Therefore, the aim of this physician-survey-based survey was to assess the epidemiology, current treatment strategies, as well as gaps in the management of patients with CCLD in the India.

## METHODS

### *Survey design*

This was a cross-sectional, questionnaire-based survey designed to assess the epidemiology, diagnosis, and treatment options for CCLD (ALD) and CCLD (DILI), and the role of UDCA in the management of both across India. A total of 215 physicians involved in the clinical practice of CCLD participated in the survey. Ad board with clinical experts was conducted to develop and validate the questionnaire. Participants were invited to complete the internet-based validated structured survey questionnaire. The survey questionnaire comprised 34 questions, including questions on understanding CCLD prevalence, diagnosis, and current treatment options (Table 1). This survey was performed in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) and national guidelines. Informed consent was obtained from the participating physicians. Because this survey did not involve direct patient intervention, ethical clearance by an external ethics review board was not obtained. The confidentiality and identity of the participating physicians were preserved throughout the survey and data processing.

### *Study period*

The study period was between May 2022 to September 2022.

### *Data analysis*

Physician responses were gathered and summarized using counts/percentages, as appropriate. The procedure for data quality check was performed along with the query resolution. Data analysis was done post-data lock approval. The rank data were calculated by the weighted linear combination method, in which for each question, the most preferred choice as an answer can be determined. were analyzed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA) and Microsoft excel (Microsoft Corporation 2019).

## RESULTS

### *Epidemiological patterns and burden of CCLD*

A total of 215 physicians responded to the survey. Liver disorders with cholestasis (alanine aminotransferase [ALT]/alkaline phosphatase [ALP] ratio <2 with or without pruritus) were found to be prevalent in 10%-20% of patients by 53.5% physicians, in 21%-30% of patients by 34.9% physicians, in 31%-50% of patients by 8.8% physicians and in >50% of patients by 2.8% physicians (Figure 1). CCLD was found to be more common among males as reported by 52.5% respondents, and 32.6% respondents claimed that the proportion of CCLD was highest among patients aged 41-60 years.

ALD with cholestasis was reported to be prevalent in 10-20%, 21-30%, 31-50% and >50% of patients by 33.5%, 37.2%, 24.2% and 5.1% of physicians, respectively. Additionally, DILI with cholestasis was reported to be prevalent in <5%, 5-10%, 11-20%, and >20% of patients by 13.5%, 34.9%, 29.8%, and 21.9% of physicians, respectively (Figure 1).

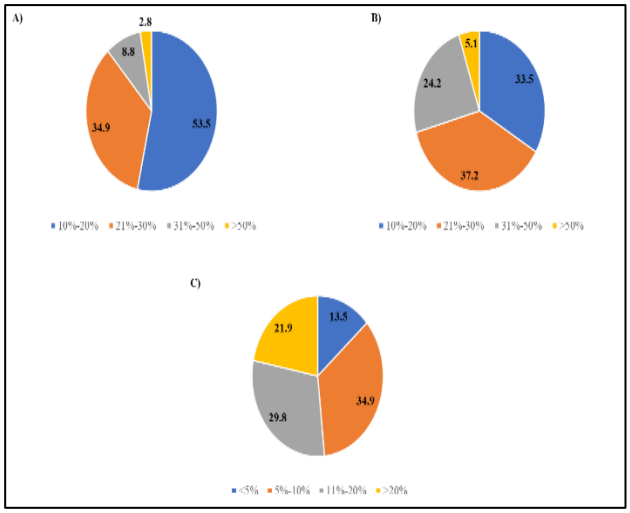


**Figure 1: Epidemiological burden of CCLD.**

Prevalence of A) liver disorders with cholestasis, B) ALD with cholestasis, and C) DILI with cholestasis in the Indian population. *Cholestasis defined as ALT/ALP ratio <2 with or without pruritus. ALD-alcoholic liver disease, ALP-alkaline phosphatase, ALT-alanine transaminase, CCLD-chronic cholestatic liver disease, DILI-drug-induced liver injury, CCLD- chronic cholestatic liver disease.

***Comorbidities, complications, diagnosis, and management of CCLD (ALD)***

The survey also assessed physicians' perspectives regarding the symptom burden, comorbidities, diagnosis and treatment of in patients with CCLD (ALD). Typically, patients were found to suffer from CCLD (ALD) symptoms for 1-3 months by 34.9% of physicians. Of the surveyed physicians, >50% stated that <20% of patients who present with CCLD (ALD) discontinue alcohol consumption before consultation, while 29.3%, 18.6%, and 0.9% stated that this proportion was 21-30%, 31-50%, and >50% of patients, respectively (Table 2).

Most physicians (57.2%) reported that multiple comorbidities, including cardiac conditions, diabetes, hypertension, hypertriglyceridemia, or hyperuricemia, are commonly seen in patients with CCLD (ALD). The second most common comorbidity reported was hypertriglyceridemia and hyperuricemia (23.3%), followed by diabetes (14.4%), hypertension (2.3%), and cardiac conditions (1.9%; Table 2). A large number of physicians (75.8%) reported that multiple complications including ascites, gastrointestinal bleeding, hepatic encephalopathy, or hepatorenal syndrome, can be seen among patients with CCLD (ALD) in the Indian population. Ascites (10.7%) was reported to be the second most frequent complication, followed by hepatic encephalopathy (7.4%), and gastrointestinal bleeding (5.1%; Table 2).

Multiple diagnostic techniques, including detailed history taking with clinical features, laboratory investigations, or abdominal ultrasonography, were employed by majority of the participating physicians (83.7%) for diagnosis of CCLD (ALD) investigations included checking for deranged liver function tests (LFTs) including ALT/ALP ratio <2, prothrombin time, and international normalized ratio. Fibroscan was preferred by majority of the physicians (80.9%), while fibrotouch was preferred by approximately half (49.3%) of the physicians (Table 3).

Clinical practices for the management of CCLD (ALD) varied considerably among the surveyed physicians (Table 3). Multiple pharmacological approaches were the most preferred among the majority of the physicians (70.2%), while hepatoprotective agent like UDCA was preferred by 23.7% of physicians. More than half the physicians (68.4%) prescribed corticosteroids to 10%-20% of patients. For patients with alcohol-induced severe hepatitis with cholestasis, 45.1% of physicians prescribed nutritional supplements in >50% of patients, while approximately half the physicians (49.8%) did not prefer to use herbal hepatoprotectives (sylimarin, *Capparis spinosa* [Himsara], and *Cichorium intybus*). According to 80% of physicians, herbal hepatoprotective supplements helped in the improvement of LFTs in 10%-20% of patients with CCLD (ALD), while only 1.0% agreed that they show improvement in >50% of patients (Table 3).

***Prevalence, complications, diagnosis and management of CCLD (DILI)***

Physicians' perspectives on complications, diagnosis and treatment approaches in relation to DILI-induced CCLD are summarized in Table 4. According to 34.9% of physicians, herbal DILI was observed in 5-10% of patients in their clinical practice, while 15.8% of physicians found it to be observed in <5% of patients.

Association between herbal drug use and CCLD (DILI) was suggested by 31.2% of the physicians in >20% of patients, 29.3% of physicians in 5%-10% of patients, and 28.8% in 11%-20% of patients (Table 4). More than half the physicians (58.6%) reported that patients with CCLD (DILI) experience multiple complications including acute liver failure, acute on chronic liver failure, or drug-induced autoimmune hepatitis.

As per the surveyed physicians, 81.9% used multiple methods for the diagnosis of CCLD (DILI), including detailed history taking with clinical features, laboratory investigations, liver biopsy, or abdominal ultrasonography. Similarly, most participants (71.6%) relied on multiple pharmacological approaches in the management of CCLD (DILI), including N-acetyl cysteine, hepatoprotective like UDCA, corticosteroids, or S-adenosyl methionine (Table 4).

***Role of UDCA in the management of CCLD (ALD) and CCLD (DILI)***

Table 5 summarizes physicians' experience with UDCA in management of alcohol-induced and drug-induced

CCLD. According to survey, majority of physicians (60.0%) prescribed UDCA for >50% patients with CCLD (ALD), 22.8% physicians prescribed to 31-50% patients; 9.8%, to 21-30% patients, and 6.0%, to 10-20% of patients.

Nearly half they physicians (48.4%) prescribed UDCA for 4-12 weeks in patients with CCLD (ALD), while 12-24 weeks was the most preferred duration for CCLD (DILI; (38.1% physicians). For both the conditions, the recommended UDCA dose was 10-15 mg/kg body weight by most of the survey participants (93.0% for CCLD [ALD] as well as 95.4% for the CCLD [DILI]; Table 5).

There mixed opinion among the participating physicians about improvement in LFTs following treatment with UDCA. Overall, 40.5% and 34.9% of physicians found UDCA to improve LFTs in >50% of patients with CCLD (ALD) and CCLD (DILI), respectively. Only 1.4% and 0.9% physicians opined that UDCA didn't improve LFTs in patients with CCLD (ALD) and CCLD (DILI), respectively (Table 5). Properties considered by survey physicians when prescribing UDCA for CCLD (ALD) were anti-inflammatory effect alone (6.1% physicians), choleretic effect alone (9.3%), immunomodulatory effect alone (3.3%)/ all 3 effects (81.4%).

Tolerability and efficacy of UDCA in patients with CCLD (ALD) were reported to be good by 87.0% and 69.8% of survey participants, respectively. Likewise, for patients with CCLD (DILI), the tolerability and efficacy of UDCA were found to be good by 85.6% and 69.8%, of physicians, respectively (Figure 2). Majority of the physicians (84.7%) prescribed UDCA for multiple indications (Figure 3).

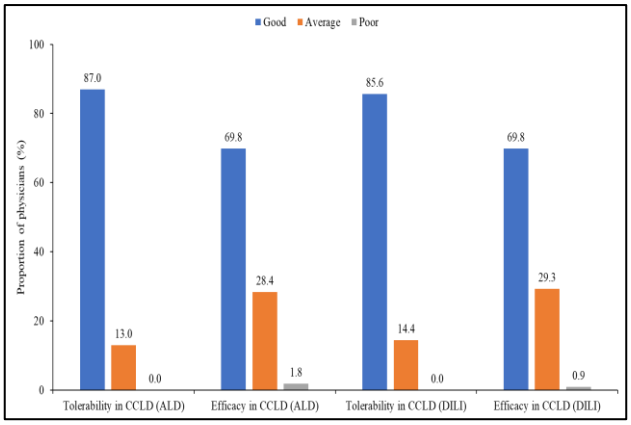


**Figure 2: Tolerability and efficacy of UDCA in CCLD (ALD) and CCLD (DILI).**

ALD-alcoholic liver disease, CCLD-chronic cholestatic liver disease, DILI-drug-induced liver injury.

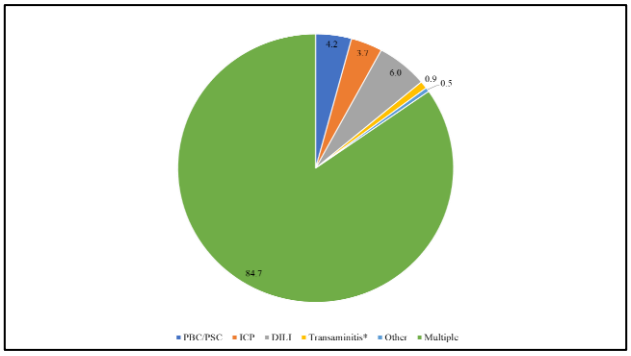


**Figure 3: Indications for prescribing UDCA.**

*of any origin. ICP-intrahepatic cholestasis of pregnancy, PBC-primary biliary cholangitis, PSC-primary sclerosing cholangitis, UDCA-ursodeoxycholic acid.

**Table 1: Survey questionnaire.**

| S. no. | Questionnaire | | | | |
|---|---|---|---|---|---|
| **Section 1: Epidemiology of CCLD in the Indian population** | | | | | |
| **Q1** | How common are liver disorders with cholestasis (ALT/ALP ratio <with/without pruritus) in Indian population? | | | | |
| | 10-20% | 21%-30% | 31%-50% | >50% | |
| **Q2** | What is proportional percentage split of CCLD with cholestasis patients across age groups? (Total to be 100%) | | | | |
| | <20 years: ___% | 21-40 years: ___% | 41-60 years: ____% | >60 years: ____% | |
| **Q3** | What is the gender-wise percentage breakup of CCLD with cholestasis patients? | | | | |
| | Male: ___% | | Female: ___% | | |
| **Section 2: Epidemiology of CCLD (ALD) in the Indian population** | | | | | |
| **Q4** | Among various types of liver disorders, how common is ALD with cholestasis (ALT/ALP ratio <2 with or without pruritus) in the Indian population? | | | | |
| | 10%-20% | 21%-30% | 31%-50% | >50% | |
| **Q5** | How long are the patients typically suffering from ALD with CCLD symptoms before consultation? | | | | |
| | >1 month | 1-3 months | 3-6 months | >6 months | |
| **Q6** | How common are the patients with ALD who have stopped consuming Alcohol? | | | | |
| | <20% | 21%-30% | 31%-50% | >50% | |
| **Q7** | Which comorbidity is commonly seen with ALD? (Tick all which is applicable) | | | | |
| | Hypertension | Diabetes mellitus | Hypertriglyceridemia and hyperuricemia | Cardiac conditions | Others (please specify) |
| **Q8** | How many patients of ALD with cholestasis in Indian population present with complications? (Tick all apply) | | | | |
| | Ascites | GI bleeding | Hepatic encephalopathy | Hepatorenal syndrome | |

Continued.

| S. no. | Questionnaire | | | | |
|---|---|---|---|---|---|
| **3a: Diagnosis and treatment options for CCLD (ALD)** | | | | | |
| **Q9** | How do you diagnose ALD with cholestasis? (Tick all that apply) | | | | |
| | Detailed history taking with clinical features | Lab investigations (LFT deranged including ALT/ ALP ratio <2) PT and INR values | USG abdomen | Liver biopsy | |
| **Q10** | Do you prefer fibroscan in ALD with cholestasis? | | | | |
| | Yes | | No | | |
| **Q11** | Do you prefer fibrotouch in ALD with cholestasis? | | | | |
| | a) Yes | | b) No | | |
| **Q12** | What pharmacological approach is used in the managing patients of ALD with the cholestasis? (Tick all that apply) | | | | |
| | Hepatoprotective like UDCA | SAMe | Pentoxifylline | Corticosteroids | Others (Please specify) |
| **Q13** | To what % of patients of ALD with cholestasis do you use corticosteroids? | | | | |
| | 10%-20% | 21%-30% | 31%-50% | >50% | |
| **Q14** | To what % of ALD patients (severe hepatitis) with Cholestasis do you use Nutritional supplements? | | | | |
| | 10-20% | 21%-30% | 31%-50% | >50% | |
| **Q15** | Among various types of drugs used in liver disorders, how often are herbal hepatoprotective (sylimarin, *Capparis spinosa* [Himsara], *Cichorium intybus*) is used in patients of ALD with cholestasis? | | | | |
| | 10%-20% | 21%-30% | 31%-50% | >50% | Do not use |
| **Q16** | Based on clinical practice, do you agree that herbal hepatoprotective helps in the improvement of LFT in ALD with cholestasis? | | | | |
| | 10%-20% | 21%-30% | 31%-50% | >50% | |
| **Section 3b: Role of UDCA in the management of CCLD (ALD)** | | | | | |
| **Q17** | To what % of patients of ALD with cholestasis do you use UDCA? | | | | |
| | 10%-20% | 21%-30% | 31%-50% | >50% | Do not use |
| **Q18** | Which properties do you consider while using UDCA in ALD with cholestasis? | | | | |
| | Choleretic effect | Anti-inflammatory effect | Immunomodulatory effect | All the above | |
| **Q19** | What is the average duration of therapy with UDCA given to an ALD patient with cholestasis in clinical practice? | | | | |
| | 2-4 weeks | 4-12 weeks | 12-24 weeks | >24 weeks | |
| **Q20** | In your clinical practice, do you use UDCA with a dose of 10-15 mg/kg body weight in patients of ALD with cholestasis? | | | | |
| | Yes | | No (Please specify the dose you use) | | |
| **Q21** | Based on clinical practice, do you agree UDCA helps in the improvement of LFT in the ALD with the cholestasis? | | | | |
| | 10%-20% | 21%-30% | 31%-50% | >50% | Does not improve |
| **Q22** | How would you rate the tolerability of UDCA in ALD with cholestasis? | | | | |
| | Good | Average | Poor | | |
| **Q23** | How would you rate the efficacy of UDCA in ALD with cholestasis? | | | | |
| | Good | Average | Poor | | |
| **Section 4: Epidemiology of CCLD (DILI) in the Indian population** | | | | | |
| **Q24** | Among various types of liver disorders, how common is DILI with cholestasis (ALT/ALP ratio <2 with or without pruritus) in the Indian population? | | | | |
| | <5% | 5%-10% | 11%-20% | >20% | |
| **Q25** | Do you see cases of herbal DILI in your clinical practice? | | | | |
| | <5% | 5%-10% | 11%-20% | >20% | |
| **Q26** | Whether herbal DILI is associated with cholestasis? | | | | |
| | <5% | 5%-10% | 11%-20% | >20% | |
| **Q27** | How many patients with DILI with cholestasis present with complications in the Indian population? (Tick all that apply) | | | | |
| | Acute liver failure | Acute chronic liver failure | Drug-induced autoimmune hepatitis | Others | |

Continued.

| S. no. | Questionnaire | | | | |
|---|---|---|---|---|---|
| **Section 5a: Diagnosis and treatment options of CCLD (DILI) in the Indian population** | | | | | |
| **Q28** | How do you diagnose DILI with cholestasis? (Tick all that apply) | | | | |
| | Detailed history taking with clinical features | Lab investigations (LFT deranged [including ALT/ ALP ratio <2], PT and INR values) | USG of abdomen | Liver biopsy | |
| **Q29** | What pharmacological approach is used in managing patients with DILI with cholestasis? (Tick all that apply) | | | | |
| | N acetyl cysteine | Hepatoprotective like UDCA | Corticosteroids | SAMe | Any other please specify |
| **Section 5b: Role of UDCA in the management of CCLD (DILI)** | | | | | |
| **Q30** | On average, what is the duration of therapy with UDCA in DILI with cholestasis in your clinical practice? | | | | |
| | 2-4 weeks | 4-8 weeks | 8-12 weeks | >12 weeks | |
| **Q31** | Do you use UDCA with a dose of 10-15 mg/kg body weight in DILI with cholestasis in your clinical practice? | | | | |
| | Yes | | No (Please specify the dose do you use) | | |
| **Q32** | Based on clinical practice, do you agree that UDCA helps in the improvement of LFT in ALD with the cholestasis? | | | | |
| | 10%-20% | 21%-30% | 31%-50% | >50% | Does not improve |
| **Q33** | How would you rate the tolerability of UDCA in DILI with cholestasis? | | | | |
| | Good | Average | Poor | | |
| **Q34** | How would you rate the efficacy of the UDCA in DILI with cholestasis? | | | | |
| | Good | Average | Poor | | |
| **Q35** | In which indications do you use UDCA in your clinical practice? (Tick all that apply) | | | | |
| | PBC/PSC | ICP | DILI | Transaminitis of any origin | Others (please specify) |

ALD-alcoholic liver disease, ALP-alkaline phosphatase, ALT-alanine transaminase, DILI-drug-induced liver injury, ICP-intrahepatic cholestasis of pregnancy, INR-international normalized ratio; LFT-liver function test, PBC-primary biliary cholangitis, PSC-primary sclerosing cholangitis, PT-prothrombin time, SAMe-S-adenosyl methionine, UDCA-ursodeoxycholic acid, USG- ultrasonography.

**Table 2: Physicians' perspectives on comorbidities and complications in patients with CCLD (ALD).**

| Parameters | Frequency, n=215 (%) |
|---|---|
| **Duration of presence of CCLD (ALD) symptoms before consultation** | |
| >1 month | 46 (21.4) |
| 1-3 month | 75 (34.9) |
| 3-6 months | 52 (24.2) |
| >6 months | 42 (19.5) |
| **Percentage of patients with CCLD (ALD) who have discontinued alcohol consumption** | |
| <20% | 110 (51.2) |
| 21%-30% | 63 (29.3) |
| 31%-50% | 40 (18.6) |
| >50% | 2 (0.9) |
| **Comorbidities observed with CCLD (ALD)** | |
| None | 2 (0.9) |
| Cardiac conditions | 4 (1.9) |
| Diabetes | 31 (14.4) |
| Hypertension | 5 (2.3) |
| Hypertriglyceridemia and hyperuricemia | 50 (23.3) |
| Multiple | 123 (57.2) |
| **Common complications observed with CCLD (ALD)** | |
| Ascites | 23 (10.7) |
| GI bleeding | 11 (5.1) |
| Hepatic encephalopathy | 16 (7.4) |
| Hepatorenal syndrome | 2 (1.0) |
| Multiple | 163 (75.8) |

ALD-alcoholic liver disease, CCLD-chronic cholestatic liver disease, GI-gastrointestinal.

**Table 3: Physicians' perspectives on the diagnosis and treatment of CCLD (ALD).**

| Parameters | Frequency, n=215 (%) |
|---|---|
| **Diagnostic criteria for CCLD (ALD)** | |
| Detailed history taking with clinical features | 7 (3.3) |
| Lab investigations* | 26 (12.1) |
| USG of abdomen | 2 (0.9) |
| Multiple | 180 (83.7) |
| **Preference for fibroscan** | 174 (80.9) |
| **Preference for fibrotouch** | 106 (49.3) |
| **Pharmacological approach in CCLD (ALD) management** | |
| Hepatoprotectives like UDCA | 51 (23.7) |
| SAMe | 7 (3.3) |
| Pentoxifylline | 3 (1.4) |
| Corticosteroids | 2 (0.9) |
| Any other | 1 (0.5) |
| Multiple | 151 (70.2) |
| **Percentage of patients prescribed corticosteroids** | |
| 10%-20% | 147 (68.4) |
| 21%-30% | 47 (21.9) |
| 31%-50% | 19 (8.8) |
| >50% | 2 (0.9) |
| **Percentage of patients with severe hepatitis prescribed nutritional supplements** | |
| 10%-20% | 21 (9.8) |
| 21%-30% | 43 (20.0) |
| 31%-50% | 54 (25.1) |
| >50% | 97 (45.1) |
| **Percentage of patients prescribed herbal hepatoprotectives (sylimarin, *Capparis spinosa* [Himsara], *Cichorium intybus*)** | |
| 10%-20% | 55 (25.6) |
| 21%-30% | 28 (13.0) |
| 31%-50% | 20 (9.3) |
| >50% | 5 (2.3) |
| Do not use | 107 (49.8) |
| **Percentage of patients showing improvement in the liver function test with the herbal hepatoprotective supplements** | |
| 10%-20% | 172 (80.0) |
| 21%-30% | 27 (12.5) |
| 31%-50% | 14 (6.5) |
| >50% | 2 (1.0) |

*LFT deranged (including ALT/ALP ratio < 2), PT and INR values, ALD, alcoholic liver disease, CCLD-chronic cholestatic liver disease, INR-international normalized ratio, LFT-liver function test, ALP-alkaline phosphatase, ALT-alanine transaminase, INR-international normalized ratio, LFT-liver function test.

**Table 4: Physicians' perspectives on prevalence, complications, diagnosis as well as the treatment of the CCLD (DILI).**

| Variables | Frequency, n=215 (%) |
|---|---|
| **Percentage of patients with DILI due to herbal drugs** | |
| <5% | 34 (15.8) |
| 5%-10% | 75 (34.9) |
| 11%-20% | 62 (28.8) |
| >20% | 44 (20.5) |
| **Percentage of patients with CCLD (DILI) due to herbal drugs** | |
| <5% | 23 (10.7) |
| 5%-10% | 63 (29.3) |
| 11%-20% | 62 (28.8) |
| >20% | 67 (31.2) |

Continued.

| Variables | Frequency, n=215 (%) |
|---|---|
| **Common complications associated with CCLD (DILI)** | |
| Acute liver failure | 24 (11.2) |
| Acute on chronic liver failure | 39 (18.1) |
| Drug-induced autoimmune hepatitis | 16 (7.4) |
| Others | 10 (4.7) |
| Multiple | 126 (58.6) |
| **Diagnostic criteria for CCLD (DILI)** | |
| Detailed history taking with clinical features | 12 (5.6) |
| Lab investigations* | 21 (9.8) |
| Liver biopsy | 1 (0.5) |
| USG of abdomen | 5 (2.3) |
| Multiple | 176 (81.86) |
| **Target pharmacological approach in the management of DILI with Cholestasis** | |
| N acetyl cysteine | 6 (2.8) |
| Hepatoprotective like UDCA | 48 (22.3) |
| Corticosteroids | 4 (1.9) |
| SAMe | 1 (0.5) |
| Other | 2 (0.9) |
| Multiple | 154 (71.6) |

*LFT deranged (including ALT/ALP ratio < 2), PT and INR values, ALP-alkaline phosphatase, ALT-alanine transaminase, CCLD-chronic cholestatic liver disease, DILI-drug-induced liver injury, INR-international normalized ratio, LFT-liver function test, SAMe-S-adenosyl methionine, UDCA-ursodeoxycholic acid, USG-ultrasonography.

**Table 5: Physicians' experience with UDCA in patients with CCLD (ALD) and CCLD (DILI).**

| Parameters | Frequency, n=215 (%) | |
|---|---|---|
| **Average duration of therapy with UDCA (Week)** | **ALD** | **DILI** |
| 2- 4 | 19 (8.8) | 26 (12.1) |
| 4-12 | 104 (48.4) | 70 (32.6) |
| 12-24 | 55 (25.6) | 82 (38.1) |
| >24 | 37 (17.2) | 37 (17.2) |
| **10-15 mg/kg body weight as recommended dose of UDCA** | 200 (93.0) | 205 (95.4) |
| **Percentage of patients showing improvement in LFT with UDCA** | | |
| 10%-20% | 19 (8.8) | 19 (8.8) |
| 21%-30% | 34 (15.8) | 58 (27.0) |
| 31%-50% | 72 (33.5) | 61 (28.4) |
| >50% | 87 (40.5) | 75 (34.9) |
| Does not improve | 3 (1.4) | 2 (0.9) |

## DISCUSSION

This survey was the first to assess the epidemiology, current treatment strategies and gaps in the management of patients with CCLD across diverse Indian clinician groups. Liver cirrhosis has been shown to be a major cause of health burden worldwide.[16] Data from the world health organization suggests that liver cirrhosis has been one of the top ten causes of death in India for years,[17] although data on the prevalence of CCLD, which if left untreated can progress to cirrhosis, remains scarce.[6] In the current survey, we found that the prevalence of CCLD ranges between 10% and 50% patients in the Indian clinical setting.

Alcohol has been shown to be the most common (34.3% of 4413) etiological factor for liver cirrhosis in India.[18] Alcoholic steatohepatitis is a frequent and serious liver disease caused due to the high alcohol consumption, and cholestasis has been shown to be one of the strong predictors of poor short-term consequences of the disease.[19] Present study results are in line with the existing literature, suggesting ALD with cholestasis to be a common finding in Indian clinical practice. Conversely, DILI is quite rare in India. In our study, DILI with cholestasis was generally seen in <20% of patients with liver disorders.

Most of the survey participants used multiple methods for the diagnosis of CCLD (ALD) in their practice. It has been reported that the diagnosis of ALD can be difficult and may require the results of detailed patient history, clinical features and laboratory investigations including imaging and biopsy in certain cases.[20] A similar approach is recommended by the European Association for the Study of the Liver (EASL) clinical practice guidelines on the management of alcohol-related liver disease.[21] Moreover, transient elastography (Fibroscan) has been

shown to yield good results in the diagnosis of various chronic liver diseases.[22] Further, it is the most commonly used and verified technique recommended by EASL as well as by the Asian Pacific Association for the Study of the APASL.[23,24] Consistent with these recommendations, the current survey findings indicate that Fibroscan was the most preferred technique in Indian clinical settings.

EASL 2009 clinical practice guidelines on the management of cholestatic liver diseases recommend using multiple drugs for the treatment of PBC, one of the common causes of liver cholestasis.[25] Likewise, multiple pharmacological approaches were favored for the management of CCLD (ALD) by our survey physicians. It is noteworthy that, EASL clinical practice guidelines on nutrition in chronic liver disease recommend performing rapid screening to evaluate the nutritional status of a cirrhotic patient and prescribe the supplement accordingly.[26] Pertaining to nutritional recommendations, most physicians in our survey prescribed nutritional supplements to CCLD (ALD) patients in their clinical practice. Prevalence of DILI due to use of herbal drugs was low in our survey; however, existing guidelines recommend considering herbal supplements to be strongly associated with liver injury.[27] Multiple diagnostic methods were preferred for CCLD (DILI) by our survey participants, which is supported by EASL stating the lack of specific diagnostic markers for suspected DILI require interpretation of several laboratory tests, sometimes including imaging and biopsy results to rule out the final diagnosis.[27] Multiple pharmacological approaches were preferred by most of the current survey participants for the management of CCLD (DILI); however, UDCA was often used to treat the condition although its efficacy in CCLD (DILI) is still unproven.[27]

UDCA was commonly prescribed by the survey physicians for the management of CCLD (ALD), reflecting the evidence obtained from prior literature findings.[28] UDCA was previously shown to be efficiently protect of liver function, and combination of S-adenosyl-L-methionine and UDCA treatment in patients with PBC yielded a better outcome with more promising results.[29,30] In the present study, UDCA was frequently prescribed for 4-12 weeks of duration for patients with CCLD (ALD) and for 12-24 weeks for patients with CCLD (DILI). These findings are contrary to the existing literature that suggests UDCA was given daily to patients with PBC for a period of two years.[31] Further, the British Society of Gastroenterology guidelines recommend treatment with UDCA for a period of 1 year for those with a high level of disease (PBC) progression. It strongly recommended that oral UDCA at a dose of 13-15 mg/kg/ day should be used as the first-line, long term treatment for all patients with PBC, if well-tolerated.[32] Similarly, EASL recommends UDCA treatment at a dose of 13-15 mg/kg of body weight for a longer duration.[25] In our study, a substantial proportion of physicians prescribed UDCA at a dose of 10-15 mg/kg body weight, which is consistent with the above recommendations.

In the present study, the opinion expressed by participants indicates that UDCA causes LFT improvement in majority of the patients with CLD (ALD) and CLD (DILI). The opinions of clinicians are in agreement with previously published studies.[28,31] A meta-analysis of randomized placebo-controlled clinical trials showed a considerable decrease in various liver enzymes following UDCA treatment, including ALP, aspartate aminotransferase, ALT, gamma-glutamyl transferase, and bilirubin, thereby causing improvement in hepatic function.[33] Further, UDCA treatment depicted excellent long-term survival in patients with PBC after a period of 1 year with a drop in ALP level by >40% of baseline values.[34] In fact, clinicians surveyed in this study reported that UDCA treatment exhibited good tolerability and efficacy in both cholestatic conditions, CCLD (ALD) and CCLD (DILI).

The present study has certain limitations and warrant consideration, including the restricted internal validity (generalizability) of the questionnaire. Moreover, modes of data collection by questionnaire may have led to recall bias by the survey participants. Despite having those limitations, to the best of our knowledge, there is yet a lack of studies assessing the burden of CCLD in Indian population. Therefore, we believe the findings of this study provides a novel contribution to the scientific literature. Lastly, the survey respondents included representation of clinician groups treating patients with liver disorders across different parts of the nation.

## CONCLUSION

CCLD is a frequently encountered condition in clinical practice in India, and if not treated in time can progress to liver cirrhosis yielding life-threatening consequences. In light of scarce data on CCLD prevalence and management approaches in India, the present survey findings provide useful insights on its prevalence and support the use of UDCA therapy for the management of its symptoms. In particular, the usefulness of UDCA therapy in reducing disease progression was also determined.

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