The Indian Network of Drug-Induced Liver Injury: Etiology, Clinical Features, Outcome and Prognostic Markers in 1288 Patients

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Background: **Etiology of and outcomes following idiosyncratic drug-induced liver injury (DILI) vary geographically. We conducted a prospective study of DILI in India, from 2013 to 2018 and summarize the causes, clinical features, outcomes and predictors of mortality.** ***Methods:*** **We enrolled patients with DILI using international DILI expert working group criteria and Roussel Uclaf causality assessment method. Follow-up was up to 3 months from onset of DILI or until death. Multivariate logistics regression was carried out to determine predictors of non-survival.** ***Results:*** **Among 1288 patients with idiosyncratic DILI, 51.4% were male, 68% developed jaundice, 68% required hospitalization and 8.2% had co-existing HIV infection. Concomitant features of skin reaction, ascites, and encephalopathy (HE) were seen in 19.5%, 16.4%, and 10% respectively. 32.4% had severe disease. Mean MELD score at presentation was 18.8 ± 8.8. Overall mortality was 12.3%; 65% in those with HE, 17.6% in patients who fulfilled Hy's law, and 16.6% in those that developed jaundice. Combination anti-TB drugs (ATD) 46.4%, complementary and alternative medicines (CAM) 13.9%, anti-epileptic drugs (AED) 8.1%, non-ATD antimicrobials 6.5%, anti-metabolites 3.8%, anti-retroviral drugs (ART)3.5%, NSAID2.6%, hormones 2.5%, and statins 1.4% were the top 9 causes. Univariate analysis identified, ascites, HE, serum albumin, bilirubin, creatinine,**

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Abbreviations: AED: Anti-epileptic drugs; ALF: Acute liver failure; ALT: Alanine aminotransferase; ART: Anti-retroviral drugs; AST: Aspartate aminotransferase; ATD: Anti- tuberculosis drugs; CAM: Complementary and alternative medicine; C.I: Confidence interval; DILI: Drug-induced liver injury; DILIN: Drug induced liver injury network; HE: Hepatic encephalopathy; HIV: Human immunodeficiency virus; INR: International normalised ratio; MELD: Model for end stage liver disease; NSAID: Nonsteroidal anti-inflammatory drugs; OR: Odds ratio; ROC: Receiver operating characteristic; RUCAM: Roussel uclaf causality assessment method; TB: Tuberculosis.; TCM: Traditional chinese medicines.; USA: United states of america; ULN: Upper limit of normal

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INR, MELD score ($p < 0.001$), transaminases ($p < 0.04$), and anti-TB drugs ($p = 0.02$) as predictors of non-survival. Only serum creatinine ($p = 0.017$), INR ($p < 0.001$), HE ($p < 0.001$), and ascites ($p = 0.008$), were significantly associated with mortality on multivariate analysis. ROC yielded a C-statistic of 0.811 for MELD and 0.892 for combination of serum creatinine, INR, ascites and HE. More than 50 different agents were associated with DILI. Mortality varied by drug class: 15% with ATD, 13.6% with CAM, 15.5% with AED, 5.8% with antibiotics. *Conclusion:* In India, ATD, CAM, AED, anti-metabolites and ART account for the majority of cases of DILI. The 3-month mortality was approximately 12%. Hy's law, presence of jaundice or MELD were predictors of mortality. (J Clin Exp Hepatol 2021;11:288–298)

The liver's position at the intersection between the gastrointestinal tract (gut) and systemic circulation exposes it continuously to a myriad of food products, bacterial by-products, drugs and other xenobiotics from birth with minimal or no adverse reaction to the body. However, rarely this default function gets disrupted, either from the direct injurious effect of drugs or toxins or as a result of idiosyncratic reaction to these agents. These reactions can vary from self-limited often asymptomatic liver biochemical test abnormalities to severe liver injury manifesting as jaundice, rarely progressing to acute liver failure.

Drug induced liver injury (DILI) is relatively rare. The reported incidence varies from 14 per 100,000 inhabitants in France[1] to 19 per100,000 inhabitants in Iceland.[2] In South Korea it was 12 per 100,000 inhabitants,[3] while it is higher in China.[4] Drug classes causing DILI vary according to geographic regions. In the West, paracetamol (acetaminophen)[5] and antimicrobials[6] are the leading cause of acute liver failure (ALF) and idiosyncratic DILI respectively. In the East, traditional Chinese medicines (TCM) and anti-tuberculosis DILI are equally prevalent with some geographic variability.[4] There is mounting evidence of an increasing burden of DILI related to complementary and alternative medicine (CAM) worldwide, especially in East Asia where TCM is integrated into the health systems.[3,4]

Information about DILI in India is limited mostly to single centre reports.[7,8] Generally, anti-TB drugs are the most common cause of DILI, although there are regional variations with increasing reports of CAM causing DILI.[9] Multicenter and nationwide DILI registries such as those in the United States of America (USA) or Spain are lacking.[6,10] With a heterogeneous population of 1.3 billion people, India has several unique challenges, from varying disease burden to prescription practices including the widespread use of alternative (Ayurveda/Unani/Siddha/Homeopathic) systems of medicine, the contribution to DILI from which are unclear and under recognized.

Therefore, under the aegis of the Indian National Association for the Study of Liver (INASL), we undertook this nationwide study to evaluate the causes and outcome of DILI and identify predictors of mortality in a large cohort of patients enrolled prospectively from a number of centers across India. We examined and compared the characteristics of common drugs causing DILI, including the subset causing severe DILI resulting in ALF. We also evaluated the utility of established prognostic indices such as model for end stage liver disease (MELD) score[11] and identified predictors of outcome.

METHODS

The Indian Network for Drug-Induced Liver Injury (INDILI) prospectively collected data pertaining to consecutive cases with DILI, from different centers throughout India over a 5-year period (2013–2018). Patient details were captured on a case record form (Supplement file 1) and sent to a nodal center (St. John's Medical College Hospital, Bangalore). The diagnosis of DILI and its severity were made based on criteria adopted by international DILI Expert Working Group.[12] Briefly, patients were considered to have DILI if they met the following criteria: (a) documented drug ingestion resulting in recent onset abnormalities in liver biochemistry tests (rise in bilirubin of at least 2 mg/dl or symptoms of liver injury with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 times the upper limit of normal or alkaline phosphatase > 2 times the upper limit of normal or (b) AST or ALT >5 times the upper limit of normal without symptoms and exclusion of other competing causes of liver injury, including viral and autoimmune among others, by appropriate serological testing and imaging studies. Severe disease was defined using international DILI expert working group criteria[12] i.e. bilirubin >2 gm/dl and INR> 1.5 with ascites or encephalopathy or death. Patterns of liver injury were classified as hepatocellular, cholestatic and mixed based on the R value of ≥ 5, ≤ 2, >2 and < 5 respectively, where R= (AST or ALT/ULN)/(ALP/ULN).[12] Jaundice was defined as clinically apparent jaundice.

Causality assessment was carried out using the Roussel Uclaf Causality Assessment Method (RUCAM) model.[13] Patients with suspected DILI with at least a possible relationship by RUCAM were enrolled. Anti-tuberculosis therapy, including combination regimen with isoniazid, rifampicin with or without pyrazinamide and ethambutol were considered as a single entity.[12] The diagnosis of ALF was made when standard criteria were met.[14] Patients

were followed for 3 months from onset of DILI or until death. We investigated the effect of Hy's law[15,16] and clinically apparent jaundice on outcome. We analyzed patients with idiosyncratic DILI, after excluding patients with predictable hepatotoxicity resulting from intentional overdose. Model for end stage liver disease (MELD) score was calculated by standard means.[11] The study was approved by institutional review boards of participating centers.

Statistical methods

Descriptive statistics in the form of mean and standard deviations for interval variables and frequency with percentages for categorical variables were calculated. Student t tests (Normal data) or Mann Whitney U tests (non-normal data) were applied to see significant mean or median levels between recovered and non-recovered outcome variables. Chi-square test was used to determine the association between outcomes and demographic/clinical characteristics. Multivariate logistics regression was performed to identify risk factors for non-recovery. ROC curves with C-statistics were calculated to determine predictive accuracy of outcome from MELD score and the predictive probabilities. *P* value 0.05 (two tailed) was considered for statistically significant levels. SPSS 22.0 statistical package was used for the analysis.

RESULTS

The INDILI enrolled 1373 subjects, of whom 70 subjects were excluded because of incomplete or missing information. We also excluded an additional 15 patients with intrinsic DILI (10 from paracetamol hepatotoxicity and 5 from ferrous sulfate toxicity, both from intentional overdose). Thirty centers and 5 physicians in solo practice participated in the study (Figure 1). We analyzed detailed information on 1288 patients with idiosyncratic DILI. This included 79 children aged <18 years (8%).

The baseline demographic and laboratory characteristics are presented in Table 1. Of the 1288 subjects 51.4% subjects were males, and 8.2% had co-existing HIV infection. Jaundice was noted at presentation in 67.2%, and overall 68.3% were hospitalized. Based on R values calculated using data available on 1217 patients, 362 (29.7%), 521 (42.8%) and 334 (27.4%) were classified as having hepatocellular, cholestatic and mixed hepatitis respectively. Features of hypersensitivity skin reaction were seen in 19.4% and Ascites and encephalopathy on admission or during

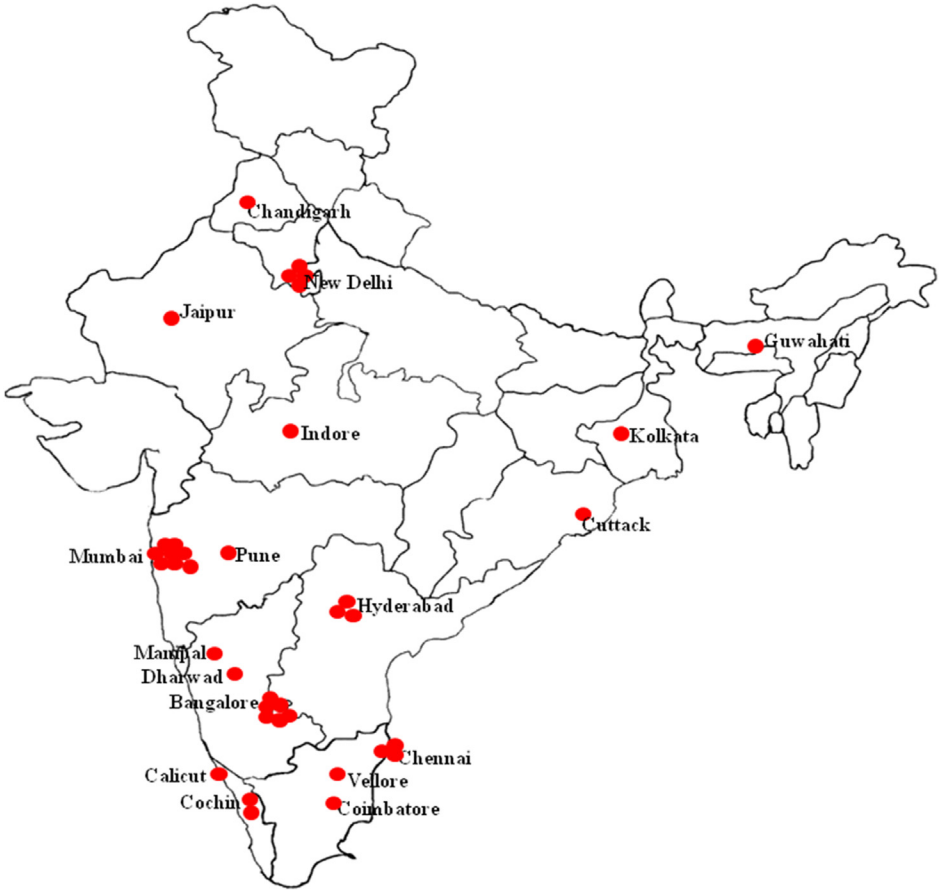

Figure 1 Indian map depicting location of contributing institutions.

Table 1 Demographic, and Laboratory Characteristics of 1288 Patients With Idiosyncratic DILI.

	Mean ± Std. Deviation	Range
Age (years)	43 ± 16.5	1–86
Sex (males: females)	661 (51.4%): 627 (48.6%)	–
Duration (days) IQR	27 (11–60)	1–929
Weight (kg)	55 ± 14	34–106
BMI	22.0 ± 4.5	10.6–43.2
Serum protein (g/dl)	6.5 ± 2.4	2.0–82.0
Serum albumin (g/dl)	3.1 ± 0.7	0.6–5.2
Total bilirubin (mg/dl)	8.3 ± 10.0	0.13–44.0
Direct bilirubin (mg/dl)	5.6 ± 6.6	0.04–32.0
AST IU/L IQR	220 (119–438)	28.7–7538
ALT IU/L IQR	241 (110–519)	29–9115
ALP IU/L IQR	180 (123–287)	25–2986
GGT IU/L IQR	130 (62.294)	14–5964
Serum creatinine (mg/dl)	1.0 ± 0.8	0.13–10.2
INR	1.7 ± 1.5	0.50–19.3
Hemoglobin (g/dl)	11.2 ± 2.1	2.7–18.2
WBC (/mm^3) IQR	8600 (6238–11500)	1100–23020
Platelets 10^5/dl)	2.3 ± 1.1	.15–9.0
MELD	18.7 ± 8.8	6–56

Abbreviations: ATD: anti-tuberculosis drugs, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, BMI: Body Mass Index, GGT: gamma glutamyl transferase, INR: International normalized ratio, IQR: inter quartile range, MELD: Model for end stage liver disease, WBC: white blood cells.

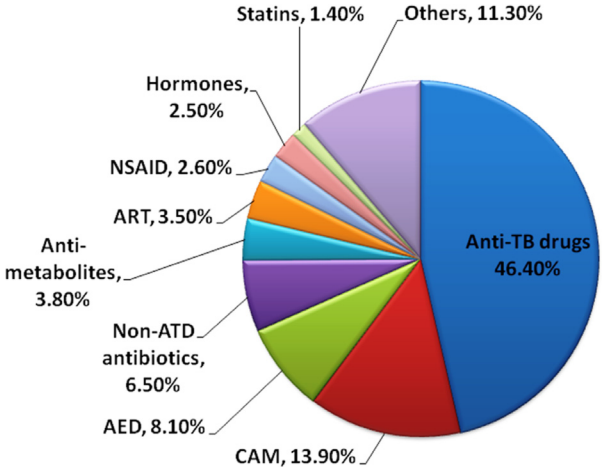

Figure 3 Agents/Classes causing DILI.

hospitalization were seen in 16.3% and 10% respectively. A history of regular alcohol consumption was obtained in 10.7% patients and 6.2% had concomitant type 2 diabetes mellitus.

Applying RUCAM, 53% were deemed to be definite (highly probable), 31% probable, 16% possible. Almost one third of patients (n = 422; 32.4%) had severe disease (total bilirubin >2 gm/dl and INR> 1.5 or ascites or encephalopathy or death). The mean MELD score was 18.8 ± 8.8.

Drugs associated with DILI

More than 50 different agents/classes were associated with DILI. Combination anti-TB drugs (ATD) was the most common class (46.4%) followed by complementary and alternative medicines (13.9%), anti-epileptic drugs (AED) 8.1%, non-ATD antibiotics 6.5%, anti-metabolites 3.8%, anti-retroviral drugs (ART) 3.5%, NSAID 2.6%, hormones 2.5%, statins 1.4% and others (Figure 3).

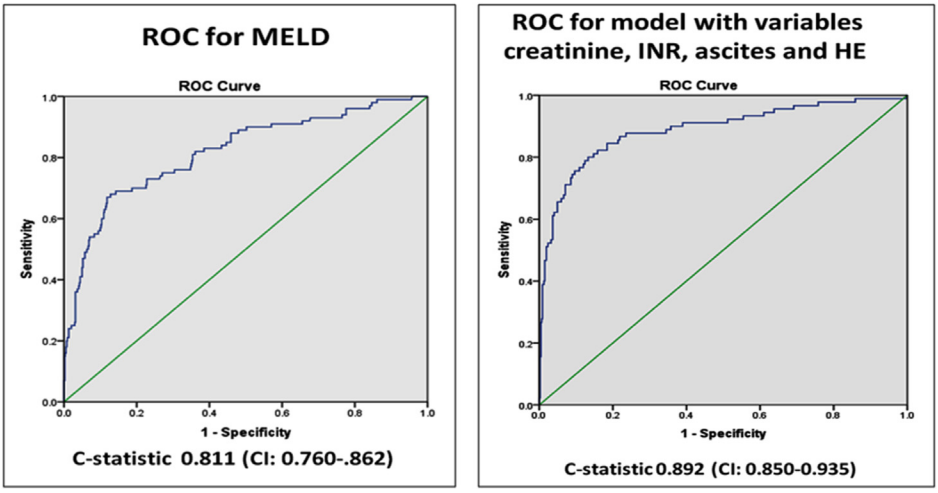

Figure 2 Receiver operator curve for MELD and combination of factors (creatinine, INR, ascites and hepatic encephalopathy).

Table 2 Comparison of Characteristics of Survivors and Non-survivors With Idiosyncratic DILI.

Variable	Survivors (N = 1084)	Non-survivors (N = 153)	*P* value
Age (Years)	42 ± 16.	48 ± 17	0.001
Duration of treatment (days) IQR	26 (10–60)	24 (12–101)	0.80
Weight (kg)	55 ± 14	56 ± 14	0.50
BMI	22.0 ± 4	22 ± 5	0.60
ATD	85.4%	14.6%	0.027
Serum total protein (g/dl)	6.6 ± 2.5	6.0 ± 1.1	0.005
Serum albumin (g/dl)	3.1 ± 0.7	2.7 ± 0.8	0.001
Total bilirubin (mg/dl)	7.3 ± 8.6	14.2 ± 15.4	0.001
Direct bilirubin (mg/dl)	5.1 ± 6.4	8.6 ± 6	0.001
AST (IU/L) IQR	211 (117–700)	286 (152–758)	0.004
ALT (IU/L) IQR	236 (109–480)	315 (128–731)	0.04
ALP(IU/L) IQR	176 (123–276)	190 (130–315)	0.40
GGT (IU/L) IQR	132 (64–296)	101 (56.207)	0.40
Serum creatinine (mg/dl)	0.9 ± 0.8	1.4 ± 1	0.001
INR	1.5 ± 1.2	2.9 ± 2.5	0.001
HB (g/dl)	11.3 ± 2.1	10.8 ± 2	0.015
WBC (10/dl) IQR	8500 (6200–11100)	9320 (7000–13480)	0.50
Neutrophils (%)	68 ± 15	73 ± 13	0.005
Platelets (10^5/dl)	2.4 ± 1.1	2.1 ± 1.3	0.008
MELD	16.8 ± 7.5	28.3 ± 10.4	0.001
Females	47.6%	55.6%	0.064
Admission	65.7%	88.3%	0.001
Jaundice	63.9%	88.8%	0.001
Skin rashes	20.3%	15.3%	0.15
Encephalopathy	4.1%	52.7%	0.001
Ascites	12.5%	42.7%	0.001
Alcohol	10%	17%	0.16
Diabetes	6%	8.5%	0.28
Severe disease	23%	93.5%	0.001

Abbreviations: ATD: anti-tuberculosis drugs, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, BMI: Body Mass Index, GGT: gamma glutamyl transferase, INR: International normalized ratio, IQR: inter quartile range, MELD: Model for end stage liver disease, WBC: white blood cells.

Table 3 shows the differences in characteristics between the top 5 drugs**.** Overall demographic characteristics were similar across all 5 major groups/agents except that indices for severity of liver injury and mortality was low in those patients with DILI caused by antibiotics and NSAIDs. Mortality varied by drug class: 15% with ATD, 13.6% with CAM, 15.5% with AED, 5.8% with antibiotics, and 0% with NSAIDs.

Mortality

Information about final outcome was available in 1263 patients, 156 of whom died (12.3%). Mortality was 64.8% (79 of 124) in those with ALF. Clinically apparent jaundice entailed a mortality of 16.6% (135 of 814) compared to 123 (17.6%) of 705 patients who fulfilled Hy's law criteria. Table 2 shows the characteristics between survivors and non-survivors.

Table 3 Comparison of Selected Characteristics Among Top 5 Drug Classes Causing DILI.

	ATD	CAM	AED	Antimicrobials	NSAID
Female	49.5%	38.7%	47.2%	49.1%	47.1%
Jaundice	70.2%	87.7%	55.2%	55.8%	50%
Skin Rash	9.2%	16.7%	61%	32.7%	9.1%
HE	13.6%	8.4%	9.5%	0%	2.9%
Ascites	25.2%	21.8%	13.3%	7.7%	14.7%
Recovery	85.4%	86.4%	84.5%	94.2%	100%
Severity	35.8%	37%	33%	18.2%	17.6%
Hy's Law	59.8%	58%	49.1%	41.8%	44.1%
Age (years)	43.7 ± 16.6	41.7 ± 14.8	37.0 ± 16.9	44.4 ± 18.6	52.3 ± 19.4
Duration of treatment (days) IQR	25 (12–60)	21 (6–62)	31 (15–42)	7 (5–14)	15 (6–34)
BMI	21.4 ± 4.4	23.4 ± 4.2	21.5 ± 4.8	22.1 ± 3.8	24.3 ± 4.5
Weight (kg)	53.6 ± 13.1	61.7 ± 11.3	54.1 ± 14.0	50.8 ± 17.6	58.6 ± 13.8
Total protein (g/dl)	6.3 ± 1.0	7.3 ± 5.9	6.2 ± 0.8	6.7 ± 0.9	6.8 ± 0.8
Serum albumin (g/dl)	2.9 ± 0.7	3.3 ± 0.7	3.1 ± 0.6	3.3 ± 0.9	3.3 ± 0.6
Total Bilirubin (mg/dl)	6.8 ± 6.8	15.6 ± 12	6.8 ± 8.3	6.0 ± 8.0	5.1 ± 6.1
Direct Bilirubin (mg/dl)	4.7 ± 5.4	10.3 ± 8.8	4.7 ± 6.0	4.3 ± 6.4	3.3 ± 4.1
AST (IU/L) IQR	236 (131–510)	235 (133-4450	258 (159–761)	154 (89–322)	236 (123–396)
ALT (IU/L) IQR	237 (104–525)	224 (85–561)	347 (158–761)	202 (76–419)	276 (139–660)
ALP (IU/L) IQR	165 (118–250)	171 (128–255)	228 (152–346)	281 (142–423)	197 (136–313)
GGT (IU/L) IQR	111 (53–213)	80 (42–162)	438 (213–1014)	203 (103–352)	199 (76–375)
Creatinine (mg/dl)	1.0 ± 0.7	1.2 ± 1.3	0.9 ± 0.6	0.9 ± 0.9	1.2 ± 1.1
INR	1.9 ± 1.7	1.6 ± 0.6	1.4 ± 0.6	1.2 ± 0.4	1.2 ± 0.2
Hb (g/dl)	10.9 ± 2.0	11 ± 2.2	11.6 ± 2.0	11.7 ± 1.6	12.1 ± 2.2
WBC (10/dl) IQR	8270 (6200–11000)	9200 (7250–11800)	9450 (6370–13650)	8950 (6190–12760)	7800 (7100–14100)
Eosinophils (%)	3.37 ± 4.710	3.9 ± 3.8	9.57 ± 12.9	3.6 ± 3.8	3.8 ± 3.6
Platelets (10^5/dl)	2.3 ± 1.2	2.1 ± 0.9	2.4 ± 0.9	2.7 ± 1.0	2.7 ± 1.7
MELD	19.1 ± 9.5	21.8 ± 7.2	16.4 ± 9.6	16.2 ± 8.2	14.9 ± 9.1

Abbreviation.ATD: Anti-TB drugs; CAM: Complimentary alternative medicine; AED: Anti-epileptic drugs; NSAID: Non-steroidal anti inflammatory drug. AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, BMI: Body Mass Index, GGT: gamma glutamyl transferase, INR: International normalized ratio, IQR: inter quartile range, MELD: Model for end stage liver disease, WBC: white blood cells.

Univariate analysis identified the following variables to be independently associated with mortality: age ($p < 0.001$), ascites ($p < 0.001$), HE ($p < 0.001$), serum albumin ($p < 0.001$), bilirubin ($p < 0.001$), transaminases ($p < 0.04$), creatinine ($p < 0.001$), INR ($p < 0.001$), MELD score ($p < 0.001$), and anti-TB drugs ($p = 0.02$).

On multivariate analysis only serum creatinine ($p = 0.017$) (95% CI: 1.06–1.91), INR ($p < 0.001$) (95% CI: 1.18–1.97), HE ($p < 0.001$) (95% CI: 5.3–22.8), and ascites ($p = 0.002$) (95% CI = 1.5–5.9), were significantly associated with mortality. ROC yielded a C-statistic of 0.811 (CI: 0.760-.862) for MELD and 0.892 (CI: 0.850–0.935) for combination of serum creatinine, INR, ascites and HE (Figure 2). Admission MELD score of 19 at presentation was noted to have sensitivity and specificity for mortality of 81% and 65% respectively.

Table 4 Clinical and Laboratory Characteristics of Patients With and Without ALF.

	Encephalopathy (ALF) (n = 124; 10%)	No Encephalopathy (No ALF) (n = 1150; 90%)	*P* value
Females n (%)	71 (57.3%)	539 (48.3%)	0.06
Jaundice n (%)	116 (93.5%)	720 (64.7%)	0.001
Skin rashes n (%)	20 (16.5%)	217 (19.9%)	0.38
Ascites n (%)	54 (43.5%)	149 (13.4%)	0.001
Non-Survivors n (%)	64.8%	6.6%	0.001
Age (years)	49 ± 16.2	42 ± 16.4	0.001
Duration of treatment (days) IQR	32 (12–105)	27 (11–60)	0.46
Weight (kg)	57.5 ± 14.9	55.2 ± 13.5	0.22
Serum total protein (g/dl)	6 ± 1	6.6 ± 2.6	0.010
Serum albumin (g/dl)	2.6 ± 0.7	3.1 ± 0.7	0.001
Total bilirubin (mg/dl)	15.5 ± 16.7	7.7 ± 8.8	0.001
Direct bilirubin (mg/dl)	9 ± 5.9	5.3 ± 6.6	0.001
AST (IU/L) IQR	342 (170–981)	210 (104–505)	0.001
ALT (IU/L) IQR	312 (162–713)	235 (104–505)	0.014
ALP (IU/L) IQR	187 (132–315)	176 (122–279)	0.37
GGT (IU/L) IQR	101 (53–214)	132 (64–296)	0.52
Serum creatinine (mg/dl)	1.3 ± 1.1	0.9 ± 0.8	0.003
INR	3 ± 2.2	1.5 ± 1	0.001
Hemoglobin (g/dl)	10.7 ± 2.2	11.2 ± 2.1	0.027
WBC (10/dl) IQR	9400 (7000–14850)	8565 (6200–11200)	0.051
Neutrophils (%)	71.3 ± 17	68 ± 14	0.068
Platelets (10^5/dl)	2.1 ± 1.1	2.9 ± 1.1	0.040
MELD	28.5 ± 10	17 ± 7.5	0.001

Abbreviations: ATD: anti-tuberculosis drugs, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, BMI: Body Mass Index, GGT: gamma glutamyl transferase, INR: International normalized ratio, IQR: inter quartile range, MELD: Model for end stage liver disease, WBC: white blood cells.

Drug-induced acute liver failure

We then analyzed the subset of 124 patients who exhibited features of idiosyncratic drug-induced ALF. Characteristics of patients with and without ALF are illustrated in Table 4. There was a trend towards a greater proportion of women in the ALF group (p = 0.06). Treatment duration was not significant. Of the 124 with idiosyncratic drug-induced ALF, 43 (35.2%) survived and 79 (64.8%) died. MELD score was 28.5 in non-survivors compared to 17 in survivors (? *p* value). Principal drug classes causing ALF were as follows: anti-TB drugs (N = 78; 63%), CAM (N = 15; 12.1%), AED (N = 10; 8.1%; CNS agents (n = 4; 3.2%), dapsone (n = 3; 2.4%) ADM (N = 1; 0.8%), Antifungal (n = 1; 0.8%), ART (N = 4; 3.2%), chemotherapeutic (N-1; 0.8%), hormone (N = 1; 0.8%) methotrexate (N = 1; 0.8%) NSAID (N = 1; 0.8%), Statin (n = 2; 1.6%) unknown (n = 1; 0.8%).

In the drug-induced ALF cohort the mean MELD score in survivors was 20.2 ± 7 9, as compared to 30.7 ± 9.9 in non-survivors (p < 001). Although ascites, bilirubin, INR, creatinine and MELD were significant on univariate analysis, only MELD was noted to be a significant predictor of mortality on multivariate regression (p < 0.001). ROC curve yielded an area under curve of 0.829 (95% CI: 0.743–0.915) (data not shown).

CAM and DILI

Table 5 shows the characteristics of CAM vs prescription drugs. More men than women were linked to CAM

Table 5 Characteristics of Patients With Complementary and Alternative Medication (CAM) -Induced DILI vs DILI From Prescription Medications.

	CAM	Prescription drugs	*P* value
Gender (Females) (%)	38.7	50.3	0.004
Admitted (%)	69.4	67.8	0.73
Jaundice (%)	87.7	64.3	0.001
Skin rashes (%)	16.7	20	0.324
Encephalopathy (%)	8.4	10.3	0.433
Ascites (%)	21.8	15.5	0.034
Died (%)	13.6	12	0.569
Age (years)	41.7 ± 14.8	42.9 ± 16.8	0.31
Duration of treatment (days) IQR	21 (6–62)	27 (12–60)	0.95
Weight (kg)	61.7 ± 11.3	54.6 ± 13.7	0.001
BMI	23.4 ± 4.2	21.9 ± 4.5	0.028
Serum total protein (g/dl)	7.3 ± 5.9	6.4 ± 1.1	0.069
Serum albumin (g/dl)	3.3 ± 0.7	3.1 ± 0.7	0.004
Total bilirubin mg/dl)	15.6 ± 12	7.1 ± 9.1	0.001
Direct bilirubin (mg/dl)	10.3 ± 8.8	4.8 ± 5.7	0.001
AST IU/L IQR	235 (133–445)	215 (118–435)	0.347
ALT IU/L QIR	224 (85–562)	242 (115–513)	0.439
ALP IU/L IQR	171 (128–255)	181 (122–292)	0.945
GGT IU/L IQR	80 (42–162)	139 (167–320)	0.001
Serum creatinine (mg/dl)	1.2 ± 1.3	1 ± 0.7	0.050
INR	1.6 ± 0.6	1.7 ± 1.6	0.032
Hemoglobin (g/dl)	11 ± 2.2	11.2 ± 2.1	0.470
WBC (10/L) IQR	9200 (7250–11800)	5800 (6190–11400)	0.018
Platelets (10^5/L)	2.1 ± 0.9	2.4 ± 1.2	0.001
MELD	21.8 ± 7.2	18.2 ± 9	0.001

Abbreviations: ATD: anti-tuberculosis drugs, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, BMI: Body Mass Index, CAM: Complimentary alternative medicine GGT: gamma glutamyl transferase, INR: International normalized ratio, IQR: inter quartile range, MELD: Model for end stage liver disease, WBC: white blood cells.

associated DILI. DILI secondary to CAM was associated with more severe disease as illustrated by greater frequency of jaundice, ascites and higher MELD scores. CAM, very often consists of undeclared constituents in the form of powders, pastes, leaves, barks and tablets. Very often, a single tablet consists of a number of ingredients and in 1 instance up to 49 ingredient. Furthermore, our case record form does not have provision to capture individual drug or component details. Only in very few instances was the prescription for CAM traced and in one patient with marked jaundice the following combination was identified: kanchhar Guggul, punar nawashtak vati, pratap lankeshwar vati, abhipattikar churna, sup shekhar vati, and triphala churna. However, outcome (mortality) was similar between the CAM (13.6%) and prescription medicine (12%) cohorts.

DISCUSSION

In this prospective nationwide DILI study from India, anti-TB drugs followed by complementary and alternative medicines and anti-epileptic drugs were the top 3 classes causing DILI. Together with anti-microbials, CAM, AED, anti-metabolites and ART they accounted for 85% of cases. Ten percent of all cases of DILI presented as or progressed

to ALF. The overall 3-month mortality was 12% while mortality from NSAID was none and from non-anti-TB antimicrobials was 6%. Presence of clinically apparent jaundice itself was associated with a mortality of 16%%. Hy′s law or clinical jaundice and MELD were predictors of mortality. Although more men than women developed DILI, females seemed to have a higher risk of dying from DILI. Worse survival in women than men has been described in paracetamol,[17] amoxicillin-clavulanate[18] and anti-tuberculosis hepatotoxicity.[19] The reasons for increased severity of DILI in women are far from clear, and could relate to greater use of hepatotoxic medications in women,[20] and sex based differences in drug metabolism[21] and to innate immune response. Furthermore, weight based dosing could result in higher concentration and drug exposure in women. The low mortality of 6% associated with non-anti-TB antimicrobials is similar to the 6% mortality described by Bjornsson and Olsson in a Swedish series.[22]

Unlike the Western experience, direct (predictable) DILI from paracetamol (acetaminophen) toxicity represented <1% of cases of DILI. Despite its wide and easy availability, paracetamol related DILI is distinctly rare in India. Anti-TB drugs were the major cause of idiosyncratic DILI accounting for 46.4% of cases. This is similar to prior single center series and reflects the disease burden of TB in India. With India home to 22.7% of the world′s TB burden[23] and with ~5 of all patients with TB developing DILI of any severity,[24] it is not surprising that anti-TB DILI is the commonest cause of both DILI and drug-induced ALF in the country. In the reported Spanish and American series, anti-microbials, particularly amoxicillin-clavulanate,[6] are the commonest drugs causing idiosyncratic DILI followed by isoniazid in the DILIN series, when used as primary prophylaxis of TB. This is in contrast to India where combination anti-TB drugs for therapy of TB disease are a major cause. Anti-TB DILI is associated with higher than expected mortality due to the greater number of patients presenting with advanced disease such as jaundice, hyperbilirubinemia, ascites, encephalopathy, and MELD score (data not shown).

CAM was the second most common cause of DILI. This picture mirrors the worldwide experience[6] and given the ubiquitous use of CAM for all kinds of diseases and promotion of wellness, is not surprising. Unlike the experience in the rest of the world, more men (61%) than women (39%) developed CAM induced DILI (p = 0.004). Although liver injury was more severe than in non-CAM patients (as reflected by bilirubin and MELD score), mortality was similar.

Contrary to reports from the West, our study did not identify age or female gender as risk factors for DILI. Our patients were much younger, with a mean age of 42 years, as compared to 49, 53 and 58 years from USA,[6] Spain,[10] and Sweden,[22] respectively. This is because of the unique demographic characteristics of India with a median age of the population estimated at 28.4 years (statista.com) and also because of the predominance of TB afflicted population in the age group of 35–45 (WHO 2017). Furthermore, the agents responsible for DILI reflect the disease and prescription patterns unique to the Indian population. For example the use of first generation antiepileptic drugs such as phenytoin, carbamazepine and phenobarbitone because of the low cost and decades of experience lends itself to a higher rate of adverse effects compared to low or negligible risk of hepatotoxicity with newer agents such as levetiracetam and clobazam.[25]

Details of clinical outcome were available in 1263 patients; of whom 156 (12.4%) died. The presence of clinically apparent jaundice also implied a higher risk of mortality (16.6%), which was similar to the observed mortality in patients fulfilling the Hy′s law (17.4%).

The drugs causing ALF mirrored the overall DILI cohort, with anti-TB DILI, CAM and AED being the top 3 drugs. However, anti-TB DILI constituted almost three fourths of cases of DILI-ALF, indicating a propensity to progress to severe disease in anti-TB drug-related liver injury. These results are similar to the experience of previous single center reports.[26–28] It is intuitive to link severity of injury with mortality. Indices of liver function severity such as albumin, bilirubin, INR, and severity index such as MELD score were, not surprisingly, significantly increased in non-survivors. Furthermore, patients that fulfilled severity criteria of international working group[12] were also at risk of dying from DILI. These parameters may be used to educate patients and caregivers about DILI and the need for early diagnosis and prompt discontinuation of the offending agent, expedited transfer to centers that perform liver transplantation or potential consideration of treatment options with reported efficacy such as plasmapheresis, in cases of severe DILI.

Admittedly, our study has limitations. Two thirds of our INDILI subjects were enrolled from teaching hospitals and tertiary referral centers. The resulting heterogeneity of patient care across centers needs to be taken into consideration. In addition, details of treatment received were not available in all cases, as this was not captured fully in the case record form. It is likely that patients with severe disease who were extensively worked up were preferentially recruited. Our study is not population based but we believe the causes of DILI are reflective of national trends although there may be regional variations. Since India is home to over a quarter of the world′s TB and since the drugs used to treat TB are potentially hepatotoxic, it is not surprising that anti-TB DILI constitutes a major proportion of the patients. Another limitation is the difficulty in determining the type, nature and constituents of CAM, which very often consists of undeclared constituents in the form of powders, pastes, leaves, barks and tablets. Furthermore, our case record form did not have the provision to capture individual drug or component/ingredient in

detail. Only in very rare instances was the prescription for CAM traced. The challenges encountered in identifying and analyzing CAM has been highlighted in a recent publication where CAM was the leading cause of drug-induced ACLF in Asia.[29] Regardless, the association of liver injury from a common formulation has recently been highlighted from a western series.[30] A further limitation is non-feasibility of determining chronic DILI given the lack of long term follow up. Our strengths include the prospective nature of the study with contributions from all regions of the country (see Figure 1).

AUTHORS CONTRIBUTION

HD: Designed, initiated, and supervised the study, enrolled patients, analyzed, updated, and interpreted the data, and drafted, edited, and approved the final draft of the paper. **TJ, VVR, MP**: supervised the study, enrolled, updated and interpreted the data and approved the final draft of the paper. **SPS**: Designed, initiated and supervised the study, enrolled patients, revised the manuscript for intellectual content and approved the final draft of the paper. **RS**: performed statistical analysis, interpreted the data, and revised the manuscript for intellectual content, and approved the final draft of the paper. **NSK, JV, VT, BG, GB, PR, RD, AN, S**: enrolled patients, revised the manuscript for intellectual content and approved the final draft of the paper. **CR, SPS, PS, AG, CEE, AA, VL, GG, RP, ST, AK, PNR, SSK, AKD, JV, AKJ, MW, PR, DJ, PG, SN, GKD, ACK, AJ, PR**: enrolled patients, and approved the final draft of the paper.

CONFLICTS OF INTEREST

The authors have none to declare.

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FINANCIAL DISCLOSURE

None.

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SUPPLEMENTARY DATA

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