Original Article JOURNAL OF CLINICAL AND EXPERIMENTAL HEPATOLOGY

# Incidence and Predictors of Liver-Related Events in Patients With Nonalcoholic Fatty Liver Disease

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***Background:*** **Nonalcoholic fatty liver disease (NAFLD) is the commonest type of liver disease worldwide. We aimed to assess the incidence and predictors of liver-related events (LREs) and mortality in NAFLD patients.** ***Methods:*** **NAFLD patients (n = 957) evaluated between January 2000 and November 2021 were included. Patients were categorised as noncirrhosis (NC), compensated cirrhosis (CC) and decompensated cirrhosis (DC), and the incidence of LRE and mortality were estimated and compared.** ***Results:*** **The proportions of NC, CC and DC were 87.8% (n = 840), 8.8% (n = 84) and 3.4% (n = 33), respectively. The median follow-up duration was 3.9 (3.0–5.7) years, and the total cumulative duration was 4633 person-years. The incidence of LRE per 100 person-years was 0.14, 2.72 and 10.24 in patients with NC, CC and DC, respectively. The incidence of mortality was 0.12, 1.05 and 4.24 per 100 person-years, respectively, in the 3 groups. The causes of mortality in the 3 groups were liver related in 1/5 (20%), 3/4 (75%) and 6/9 (66.7%), respectively. Overall, the mortality rate was higher in those with diabetes than those without diabetes (log-rank *P* value = 0.005). On further analysis, diabetes was associated with poor outcomes only in NC group (log-rank *P* value = 0.036), and not in CC (log-rank *P* value = 0.353) or DC groups (log-rank *P* value = 0.771). On multivariate Cox proportional hazard analysis, age (hazard ratio [HR] 1.070), hypertension (HR 4.361) and DC (HR 15.036) were independent predictors of poor outcomes. Liver stiffness measurement, bilirubin, CC and DC were independent predictors of LRE.** ***Conclusion:*** **In our study of NAFLD from India, the incidence of LRE was found to be similar to that seen in Western studies. In NC NAFLD, diabetes was associated with poor outcomes. (J Clin Exp Hepatol xxxx;xxx:xxx)**

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease globally, with a prevalence of 25%.[1] The incidence and prevalence of NAFLD are increasing because of the rising rates of obesity and diabetes.[2] A recent meta-analysis from India suggests that 38.6% of adults and 35.4% of children have NAFLD.[3] Despite the high prevalence, only a small fraction of patients develop cirrhosis and liver-related complications.[4–7] The population dynamics vary globally in terms of age, the prevalence of obesity, diabetes, hypertension, dyslipidaemia, genetic polymorphism, dietary and exercise patterns, which influence the development and progression of NAFLD.[1]

The data from paired liver biopsy studies suggest that patients with nonalcoholic fatty liver and nonalcoholic steatohepatitis (NASH) progress slowly from one fibrosis stage to the next (14 versus 7 years).[8] However, the rate of progression is not uniform in all patients, with some patients progressing faster.[8] Factors associated with fibrosis progression include hypertension, low aspartate aminotransferase (AST):alanine aminotransferase (ALT) ratio and higher grades of hepatic steatosis.[8] The predominant causes of mortality in NAFLD patients include cardiovascular disease, cancer and liver disease. The fibrosis stage is the most important predictor of mortality in patients with NAFLD.[9] The limitations of the existing literature include inclusion of patients presenting with symptoms and undergoing a liver biopsy predominantly from tertiary care centres, as well as inclusion of patients from specific ethnicities. Given that the outcome in NAFLD may be affected by multiple cofactors, it is important to assess the outcomes in different population cohorts. Therefore, in this retrospective analysis of a prospectively maintained database, we assessed the outcomes and incidence of various liver-related events (LREs) in

*Keywords:* decompensation, metabolic syndrome, MAFLD, portal hypertension, alcohol
*Received:* 11.5.2022; *Accepted:* 27.9.2022; *Available online:* xxx
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*Abbreviations:* AST: aspartate aminotransferase; ALT: alanine aminotransferase; CC: compensated cirrhosis; DC: decompensated cirrhosis; ESLD: end-stage liver disease; GI: gastrointestinal; HCC: hepatocellular carcinoma; HE: hepatic encephalopathy; HR: hazard ratio; LSM: liver stiffness measurement; LRE: liver-related events; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; NC: noncirrhosis
https://doi.org/10.1016/j.jceh.2022.09.007




Please cite this article as: Shalimar et al., Incidence and Predictors of Liver-Related Events in Patients With Nonalcoholic Fatty Liver Disease, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.09.007

patients with NAFLD recruited in a tertiary care centre in India.

## Patients and methods

Patients diagnosed with NAFLD and evaluated in the liver clinic between January 1, 2000, and November 3, 2021, were included. Adults aged ≥18 years with fatty liver on ultrasound were evaluated for inclusion. Patients with another co-existing aetiology of liver diseases, such as hepatitis B virus, hepatitis C virus, autoimmune hepatitis or drugs, were excluded. Patients with incomplete details and those presenting with hepatocellular carcinoma (HCC) or acute-on-chronic liver failure were also excluded. For assessment of the outcomes, we excluded patients with a follow-up of <12 months and those who had undergone bariatric surgery or received a liver transplant. Patients were diagnosed with cirrhosis (Table 1) based on histological evidence of stage 4 fibrosis (F4) or imaging evidence of cirrhosis or portal hypertension such as nodular liver, splenomegaly, dilated portal vein or varices on endoscopy or liver stiffness measurement (LSM) ≥12 kPa. Patients with no radiological or histological evidence of cirrhosis were classified as noncirrhosis (NC). Based on the presence or absence of decompensation features such as jaundice, ascites, gastrointestinal (GI) bleed or hepatic encephalopathy (HE), cirrhosis patients were further categorised into compensated cirrhosis (CC) and decompensated cirrhosis (DC) as shown in Table 1.

## Data collection

The following details were retrieved: age, weight, body mass index, diabetes and hypertension at first presentation. Blood investigations, including haemoglobin, platelet count, total bilirubin, AST, ALT, alkaline phosphatase, total protein, albumin and lipid profile, were retrieved from the database. We noted investigations to exclude other aetiologies of liver disease, such as hepatitis B surface antigen, antihepatitis C virus antibody, antinuclear antibody, antismooth muscle antibody, antiliver kidney microsome type 1 antibody and serum ceruloplasmin. We excluded patients with alcohol consumption of more than 14 units per week for females and 21 units per week for males.[10] The study was approved by the Institute's Ethics committee. Informed consent was waived off. This retrospective analysis was in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

## Assessment of liver stiffness measurement and controlled attenuation parameter

LSM and controlled attenuation parameter measurements were performed with FibroScan touch 502 (Echosens, Paris, France).[11,12] The LSM and controlled attenuation parameter values were available in 787 (82.2%) and 711 (74.3%) patients. For comparing outcomes, LSM values were divided into 3 cohorts: <8 kPa, 8–12 kPa and >12 kPa.

Diabetes was defined as fasting plasma glucose 126 mg/dL or haemoglobin A1c >6.5% or patients on antidiabetic medicines. Hypertension was defined as blood pressure 130/85 mm Hg or requiring treatment, and hypertriglyceridemia was defined as fasting triglycerides 150 mg/dL. Metabolic syndrome was defined by the National Cholesterol Education Program Adult Treatment Panel III criteria with modified waist circumference for Asians/Indians.[13]

## Liver biopsy

Expert pathologists graded the activity and fibrosis on liver biopsy according to recommendations by the NASH clinical research network staging system.[14] NASH was defined as NAFLD activity score (NAS) score ≥5. The liver biopsy details were available for 287 (30.0%) patients.

## Assessment of outcomes

The details of clinical events such as death (all-cause, liver-related and non–liver-related death), ascites, HE, GI bleeding and HCC were noted, along with their time of

**Table 1 Criteria for Classification as Noncirrhosis, Compensated Cirrhosis and Decompensated Cirrhosis.**

| Parameters | Noncirrhosis | Compensated cirrhosis | Decompensated cirrhosis |
|---|---|---|---|
| Clinical | Absence of jaundice, ascites, GI bleed and HE | Absence of jaundice, ascites, GI bleed and HE | Jaundice, ascites, GI bleed or hepatic encephalopathy |
| Endoscopy | No varices | Varices | Varices |
| Liver biopsy | F0-F3 | F4 | F4 |
| FibroScan | <12 kPa | ≥12 kPa | ≥12 kPa |
| Radiology | Normal | Nodular liver, splenomegaly, dilated portal vein | Nodular liver, splenomegaly, dilated portal vein |

GI, gastrointestinal; HE, hepatic encephalopathy.
Cirrhosis was diagnosed based on histology or imaging or liver stiffness measurement.




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occurrence. Events that occurred before the first presentation to the liver clinic were classified as baseline events. Events that happened after the presentation were classified as new-onset events. The time interval (in years) between the first presentation to the liver clinic and the occurrence of new-onset events was defined as the time to event onset. The occurrence of death due to liver-related causes, ascites, HE, GI bleeding, HCC and the progression from no cirrhosis to cirrhosis were considered LRE. The time of occurrence of the first event was noted in the case of multiple events in a patient.

### Statistical analysis

Normally distributed continuous variables were expressed as mean (standard deviation), and the continuous variables with skewed distribution were expressed as median (interquartile range). A one-way analysis of variance with Bonferroni correction as a post-hoc test was used to compare normally distributed continuous variables among more than 2 groups. The data with skewed distribution were compared using the Kruskal–Wallis analysis of variance test followed by the Mann–Whitney test with adjusted *P* values. Chi-square or Fisher exact test for categorical variables was used. A *P* value of <0.05 was considered statistically significant. The rates of new-onset events per 100 person-years were calculated by dividing the number of new events that occurred during the follow-up divided by the total follow-up time in years multiplied by 100. Predictors of survival and LRE were assessed by the Cox proportional hazard model. Survival curves were calculated by the Kaplan–Meier method and compared with the log-rank test. Data were analysed using IBM SPSS Statistics software (version 20.0; Chicago, IL, USA) and MedCalc software (version 15.11.4; MedCalc Software, Ostend, Belgium).

## RESULTS

A total of 1402 patients were screened for inclusion, and finally, 957 patients with NAFLD were included. The reasons for exclusion of 445 patients were age <18 years (n = 26), follow-up <12 months (n = 251), dual aetiology of fatty liver (n = 77), acute-on-chronic liver failure (n = 38) and HCC at presentation (n = 53). There were more male patients (67.8%), and the median age was 40 (33–49) years. At the time of inclusion, 840 (87.8%) patients had NAFLD without cirrhosis (NC), whereas CC and DC were diagnosed in 84 (8.8%) and 33 (3.4%) patients, respectively. At presentation, diabetes was present in 255 (26.6%), and hypertension was present in 174 (18.2%) patients. These patients were followed up for a median of 3.9 (3.0–5.7) years, and the total cumulative duration of follow-up was 4633 years. The baseline demographic and clinical variables are shown in Table 2.

### Incidence of diabetes

Diabetes at presentation was found in 255 (26.6%) patients with a higher prevalence in DC (72.7%) and CC (57.1%) compared with NC group (21.8%), $P < 0.001$. During follow-up, 39 patients developed new-onset hyperglycaemia (diabetes mellitus in 33 and 6 impaired fasting plasma glucose) with an incidence of 1.20 (95% CI, 0.87–1.63) per 100 person-years of follow-up.

Among the NC group, a total of 33 of 657 (5.0%) patients developed diabetes mellitus with an incidence of 1.10 (0.76–1.52) per 100 person-years. A higher proportion of patients with CC (4/36, 11.1%) and DC (2/9, 22.2%) developed new-onset diabetes mellitus, with an incidence of 2.45 (0.77–5.91) and 3.07 (0.51–10.17) per 100 person-years, respectively.

### Incidence of LREs

Of the 840 patients with NC, progression to CC and DC occurred in 4 and 2 patients, respectively. The overall incidence of progression to cirrhosis over a follow-up of 4034 person-years was 0.15 (0.06–0.30) per 100 person-years. In patients with CC (n = 84), over a follow-up duration of 375 person-years, 7 patients developed decompensation (DC) and 2 patients became NC. The incidence of decompensation was 1.86 (0.81–3.69) per 100 person-years.

A total of 21 patients had a history of variceal bleeding at baseline; all in DC group. Overall, 9 patients developed new-onset variceal bleeding over a follow-up of 4455 person-years, with an incidence of 0.20 (0.09–0.37) per 100 person-years. In patients with NC, none had variceal bleeding during follow-up. A higher proportion of patients with CC and DC had a new-onset variceal bleed (CC: 4/84, 4.8%; and DC: 5/12, 41.7%), with an incidence of 1.07 (0.34–2.60) and 11.90 (4.36–26.39) per 100 person-years, respectively (Table 3).

A total of 4 patients had a history of HE at baseline. Overall, 8 patients developed new-onset HE during a follow-up of 4593 person-years with an incidence of 0.17 (0.08–0.30) per 100 person-years. In the NC group, none had HE during follow-up. Development of new-onset HE was seen in a higher proportion of patients with CC (3/84, 3.6%) and DC (5/29, 17.2%), with an incidence of 0.79 (0.20–2.16) and 2.89 (1.05–6.40) per 100 person-years, respectively (Table 3).

A total of 10 patients had ascites at baseline. Sixteen patients developed new-onset ascites during follow-up. Patients with NC (2/840, 0.2%), CC (4/84, 4.8%) and DC (10/23, 43.4%) developed new-onset ascites, with an incidence of 0.04 (0.008–0.16), 1.06 (0.33–2.55) and 6.41 (3.25–11.43) per 100 person-years, respectively (Table 3).

The occurrence of new LRE was significantly higher in patients with CC and DC than in NC. Patients with NC (6/840, 0.7%), CC (10/84, 11.9%) and DC (17/33, 51.5%) developed new LRE, with an incidence of 0.14 (0.06–



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**Table 2 Comparison of Baseline Characteristics in NAFLD Patients With Noncirrhosis, Cirrhosis and Decompensated Cirrhosis.**

| Parameters | Whole cohort (n = 957) | Noncirrhosis (N = 840) | Compensated cirrhosis (N = 84) | Decompensated cirrhosis (N = 33) | *P* value |
|---|---|---|---|---|---|
| Age, years | 40 (33.0–49.0) | 39.0 (32.0–47.75) | 50.0 (40.0–57.0) | 53.0 (45.0–62.0) | <0.001[a,b] |
| Sex (male:female) | 649 (67.8%):308 (32.2%) | 571 (68.0%):269 (32.0%) | 53 (63.1%):31 (36.9%) | 25 (75.8%):8 (24.2%) | 0.402 |
| Weight, kg | 73 (65.0–73.0) | 73.0 (65.0–80.0) | 73.5 (68.0–82.75) | 72.0 (65.0–80.0) | 0.250 |
| Height, m | 165.0 (157.35–170.0) | 165.0 (158.0–170.0) | 165.0 (156.25–171.0) | 164.0 (158.0–168.0) | 0.462 |
| Body mass index, kg/m$^2$ | 26.82 (24.65–29.40) | 26.64 (24.48–29.38) | 27.46 (25.34–30.88) | 27.70 (25.01–29.97) | 0.040[a] |
| Body mass index categories | | | | | 0.353 |
| <18 | 3 (0.3%) | 3 (0.4%) | 0 | 0 | |
| 18–23.9 | 113 (11.8%) | 106 (12.6%) | 5 (6.0%) | 2 (6.1%) | |
| 24–24.9 | 164 (17.1%) | 147 (17.5%) | 11 (13.1%) | 6 (18.2%) | |
| >25 | 677 (70.7%) | 584 (69.5%) | 68 (81.0%) | 25 (75.8%) | |
| Waist, cm (n = 759) | 94.50 (90.0–103.50) | 97.0 (90.0–103.0) | 102.75 (97.12–108.37) | 100.50 (94.12–103.37) | <0.001[a] |
| Hip, cm (n = 758) | 98.0 (93.0–104.0) | 98.0 (93.0–103.5) | 101.0 (95.25–108.37) | 98.0 (93.50–101.75) | 0.009[a] |
| Haemoglobin, g/dL | 13.6 (12.20–14.90) | 13.80 (12.40–15.0) | 12.60 (11.57–13.95) | 11.0 (9.30–12.80) | <0.001[a,b,c] |
| Total leukocyte count/mm$^3$ | 7200.00 (6000.2–8650.0) | 7300.0 (6200.0–8700) | 6800.0 (5100.0–8650.0) | 5020.0 (3650.0–7950) | <0.001[b,c] |
| Platelet count, $\times 10^3$/mm$^3$ | 191.0 (148.0–249.0) | 196.0 (151.0–250.5) | 154.0 (111.75–213.0) | 133.0 (99.50–248.0) | <0.001[a,b] |
| Bilirubin, mg/dL | 0.60 (0.50–0.98) | 0.60 (0.50–0.90) | 0.80 (0.50–1.30) | 1.20 (0.80–2.05) | <0.001[a,b,c] |
| Total protein, g/dL | 7.60 (7.20–7.80) | 7.60 (7.30–7.80) | 7.50 (7.20–7.90) | 7.10 (6.40–7.90) | 0.052 |
| Albumin, g/dL | 4.70 (4.30–5.00) | 4.70 (4.40–5.0) | 4.30 (4.0–4.07) | 3.60 (3.0–4.20) | <0.001*[†‡] |
| Aspartate aminotransferase, IU/L (n = 939) | 40.0 (27.0–60.0) | 38.0 (26.0–58.0) | 48.50 (36.0–74.25) | 46.0 (38.0–59.0) | <0.001[a] |
| Alanine aminotransferase, IU/L (n = 938) | 54.0 (31.0–88.0) | 55.0 (31.0–90.0) | 49.0 (32.0–81.0) | 36.0 (25.5–48.50) | 0.001[b,c] |
| Alkaline phosphatase, IU/L (n = 933) | 202.0 (132.0–269.0) | 204.0 (134.0–268.25) | 197.50 (135.37–286.50) | 160.0 (114.0–258.50) | 0.539 |
| Urea, mg/dL (n = 885) | 22.0 (18.0–27.0) | 22.0 (18.0–27.0) | 23.0 (18.0–28.0) | 27.0 (18.25–33.75) | 0.036[b] |
| Creatinine, mg/dL (n = 902) | 0.80 (7.0–1.0) | 0.80 (0.70–1.0) | 0.80 (0.70–0.90) | 0.90 (0.80–1.15) | 0.057 |
| Cholesterol (n = 881) | 180.0 (153.0–207.0) | 183.0 (157.0–209) | 147.50 (124.75–185.0) | 140.0 (131.0–155.0) | <0.001[a,b] |
| Low-density lipoprotein, mmol/L (n = 865) | 112.0 (91.0–134.0) | 115.0 (95.0–136.25) | 89.0 (69.0–114.50) | 82.50 (67.50–102.0) | <0.001[a,b] |
| HDL (n = 868) | 42.0 (37.0–46.0) | 42.0 (37.0–46.0) | 40.0 (35.0–45.0) | 39.50 (30.50–48.0) | 0.097 |
| Very-low-density lipoprotein, mmol/L (n = 803) | 22.0 (15.0–31.0) | 22.0 (16.0–32.0) | 20.0 (15.0–31.0) | 19.50 (7.75–145.5) | 0.052 |
| Triglyceride, mmol/ L (n = 878) | 145.0 (106.0–201.0) | 147.0 (111.25–205.0) | 128.50 (89.50–167.75) | 95.0 (75.75–145.50) | <0.001[a,b] |
| Hypertriglyceridemia, mmol/L (n = 878) | 405/878 (46.1%) | 375/776 (48.3%) | 25/76 (32.9%) | 5/26 (19.2%) | 0.001 |
| Low HDL (n = 868) | 455/868 (52.4%) | 398/771 (51.6%) | 42/71 (59.2%) | 15/26 (57.7%) | 0.411 |





Please cite this article as: Shalimar et al., Incidence and Predictors of Liver-Related Events in Patients With Nonalcoholic Fatty Liver Disease,Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.09.007

**Table 2** (*Continued*)

| Parameters | Whole cohort (n = 957) | Noncirrhosis (N = 840) | Compensated cirrhosis (N = 84) | Decompensated cirrhosis (N = 33) | *P* value |
|---|---|---|---|---|---|
| Diabetes, yes | 255 (26.6%) | 183 (21.8%) | 48 (57.1%) | 24 (72.7%) | <0.001 |
| Hypertension, yes | 174 (18.2%) | 133 (15.8%) | 29 (34.5%) | 12 (36.4%) | <0.001 |
| Metabolic syndrome (n = 867) | 436 (50.3%) | 374 (48.6%) | 48 (67.6%) | 14 (53.8%) | 0.008 |
| Coronary artery disease at presentation, yes | 12 (1.3%) | 10 (1.2%) | 2 (2.4%) | 0 (0%) | 0.520 |
| Controlled attenuation parameter, dB/m (n = 711) | 316.0 (282.0–343.0) | 317.0 (288.0–344.0) | 301.0 (259.50–341.0) | 236.0 (233.75–314.0) | <0.001[b] |
| Liver stiffness measurement, kPa (n = 787) | 6.10 (4.90–8.50) | 5.70 (4.70–7.30) | 21.30 (14.60–31.40) | 34.55 (16.22–46.87) | <0.001[a,b] |
| NASH (on liver biopsy) | 59/287 (20.6%) | 44/248 (17.7%) | 15/36 (41.7%) | 0/3 (0%) | 0.003 |
| Death, yes | 18 (1.9%) | 5 (0.6%) | 4 (4.8%) | 9 (27.3%) | <0.001 |

HDL, high-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
[a]Significant between noncirrhosis and compensated cirrhosis.
[b]Significant between noncirrhosis and decompensated cirrhosis.
[c]Significant between compensated cirrhosis and decompensated cirrhosis.

**Table 3 New-Onset Complications in Patients With Noncirrhosis, Cirrhosis and Decompensated Cirrhosis.**

| Complications | Noncirrhosis (n = 840) | Follow-up (years) | Rates per 100 person-years | Compensated cirrhosis (n = 84) | Follow-up (years) | Rates per 100 person-years | Decompensated cirrhosis (n = 33) | Follow-up (years) | Rates per 100 person-years | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| Follow-up duration | | 4.8 ± 3.1 years<br>3.9 (3.0–5.6) years | | | 4.5 ± 2.3 years<br>3.9 (3.2–5.1) | | | 6.4 ± 4.5 years<br>4.7 (3.9–8.2) years | | |
| New ascites | 2 (0.2%) | 4040 | 0.04 (0.008–0.16) | 4 (4.8%) | 377 | 1.06 (0.33–2.55) | 10/23 (43.4%) | 156 | 6.41 (3.25–11.43) | <0.001 |
| New hepatic encephalopathy | 0 | | – | 3/84 (3.6%) | 377 | 0.79 (0.20–2.16) | 5/29 (17.2%) | 173 | 2.89 (1.05–6.40) | <0.001 |
| New variceal bleed | 0 | | – | 4/84 (4.8%) | 371 | 1.07 (0.34–2.60) | 5/12 (41.7%) | 42 | 11.90 (4.36–26.39) | <0.001 |
| Hepatocellular carcinoma | 0 | | – | 1/84 (1.2%) | 378 | 0.26 (0.01–1.30) | 1/33 (3.0%) | 218 | 0.45 (0.02–2.26) | <0.001 |
| Any liver event | 6 (0.7%) | 4035 | 0.14 (0.06–0.30) | 10 (11.9%) | 367 | 2.72 (1.38–4.85) | 17 (51.5%) | 166 | 10.24 (6.16–16.06) | <0.001 |
| Death | 5 (0.6%) | 4043 | 0.12 (0.04–0.27) | 4 (4.8%) | 379 | 1.05 (0.33–2.54) | 9 (27.3%) | 212 | 4.24 (2.07–7.79) | <0.001 |



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0.30), 2.72 (1.38–4.85) and 10.24 (6.16–16.06) per 100 person-years, respectively (Table 3 and Figure 1a).

## Incidence of HCC

Only 2 patients developed HCC during follow-up, one each in CC (after a follow-up duration of 60 months) and DC (after 24 months). HCC incidence in the whole cohort over a follow-up of 4639 person-years was 0.04 (0.007–0.14) per 100 person-years. The incidence of HCC in CC and DC was 0.26 (0.01–1.30) and 0.45 (0.02–2.26) per 100 person-years, respectively (Table 3 and Figure 1b).

## Incidence of mortality

Eighteen of 957 (1.9%) patients died on a follow-up of 4633 person-years, with an incidence of 0.38 (0.23–0.60) per 100 person-years. The incidence of death in NC, CC and DC was 0.12 (0.04–0.27), 1.05 (0.33–2.54) and 4.24 (2.07–7.79) per 100 person-years, respectively (Table 3 and Figure 1c).

Among the NC group, the causes of death were liver-related end-stage liver disease (ESLD) in 1 of 5 (20%) patients, coronary artery disease in 2 (40%), coronavirus disease 2019 in 1 (20%) and bone tumour in 1 (20%). The causes of death in patients with CC were liver related in 3 of 4 (75%), which included ESLD in 2 and HCC in 1 patient, while the cause could not be ascertained in 1 patient. In patients with DC, the cause of death was liver related in 6 of 9 (66.7%) patients, including ESLD in 5, HCC in 1 patient, coronavirus disease 2019 in 1 and unascertainable in 2 patients. The mortality was higher in patients with diabetes than in those without (log-rank *P* value = 0.005; Figure 2a). However, the effect of diabetes on the outcome was significant in patients with NC only (log-rank *P* value = 0.036; Figure 2b). There was no significant effect of diabetes on mortality in patients with CC (log-rank *P* value = 0.353; Figure 2c) and DC (log-rank *P* value = 0.771; Figure 2d).

### *Incidence of LRE among patients with liver biopsy available*

Overall, 7 of 287 (2.4%) patients with an available liver biopsy had an LRE on follow-up. In patients with F0-2, F3 and F4 fibrosis, LRE incidence was 0.07 (0.003–0.35), 0.81 (0.04–4.04) and 3.76 (1.37–8.33) per 100 person-years, respectively (Table 4 and Supplementary Figure 1a). There was no mortality in the F0-2 and F3 groups. In the F4 group, the incidence of death was 2.12 (0.54–5.79) per 100 person-years (Table 4 and Supplementary Figure 1b).

### *Incidence of LRE as per the LSM values*

In patients with LSM <8 kPa, 8–12 kPa and >12 kPa, LRE incidence was 0.04 (0.002–0.19), 1.07 (0.39–2.36) and 3.60 (2.20–5.59) per 100 person-years, respectively (Table 4 and Figure 3a). Overall, 12 of 787 (1.5%) patients with available LSM values died on follow-up. In patients with LSM <8 kPa, 8–12 kPa and >12 kPa, the incidence of death was 0.19 (0.07–0.42), 0.42 (0.07–1.40) and 0.93 (0.34–2.07) per 100 person-years, respectively (Table 4 and Figure 3b).

### *Factors associated with LRE*

On univariate Cox proportional analysis, the factors associated with LRE were advanced age, diabetes and hypertension at presentation, haemoglobin, platelet count, bilirubin, albumin, serum creatinine, international normalised ratio, LSM and CC/DC (Table 5). On adjustment for all significant factors, only CC (adjusted hazard ratio [HR] 18.631 [5.309–65.382]) and DC (adjusted HR 597.076 [115.412–3089.939]) were independently associated with LRE. In another multivariate model, LSM (adjusted HR 1.057 [1.036–1.078]) and bilirubin (adjusted HR 1.459 [1.021–2.086]) were independently associated with LRE after adjustment.

### *Factors associated with mortality*

On univariate Cox proportional hazard analysis, the factors associated with mortality were advanced age, diabetes and hypertension at presentation, haemoglobin, bilirubin, albumin, AST, serum creatinine, international normalised ratio, LSM and CC/DC (Table 6). On multivariate analysis, only age (adjusted HR 1.070 [1.008–1.135]), hypertension (adjusted HR 4.361 [1.258–15.122]) and DC (adjusted HR 15.036 [3.802–59.457]) were independently associated with mortality.

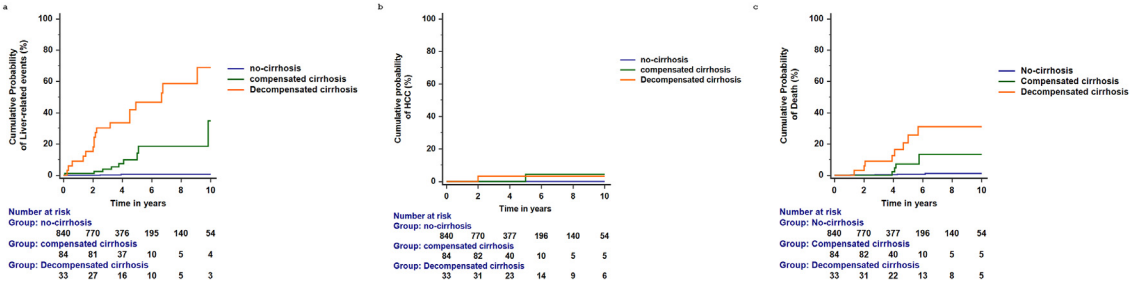


**Figure 1** Cumulative probability. (a) New liver-related events (log-rank $P < 0.001$), (b) HCC (log-rank $P < 0.001$), (c), mortality (log-rank $P < 0.001$) in patients with noncirrhosis, compensated cirrhosis and decompensated cirrhosis.




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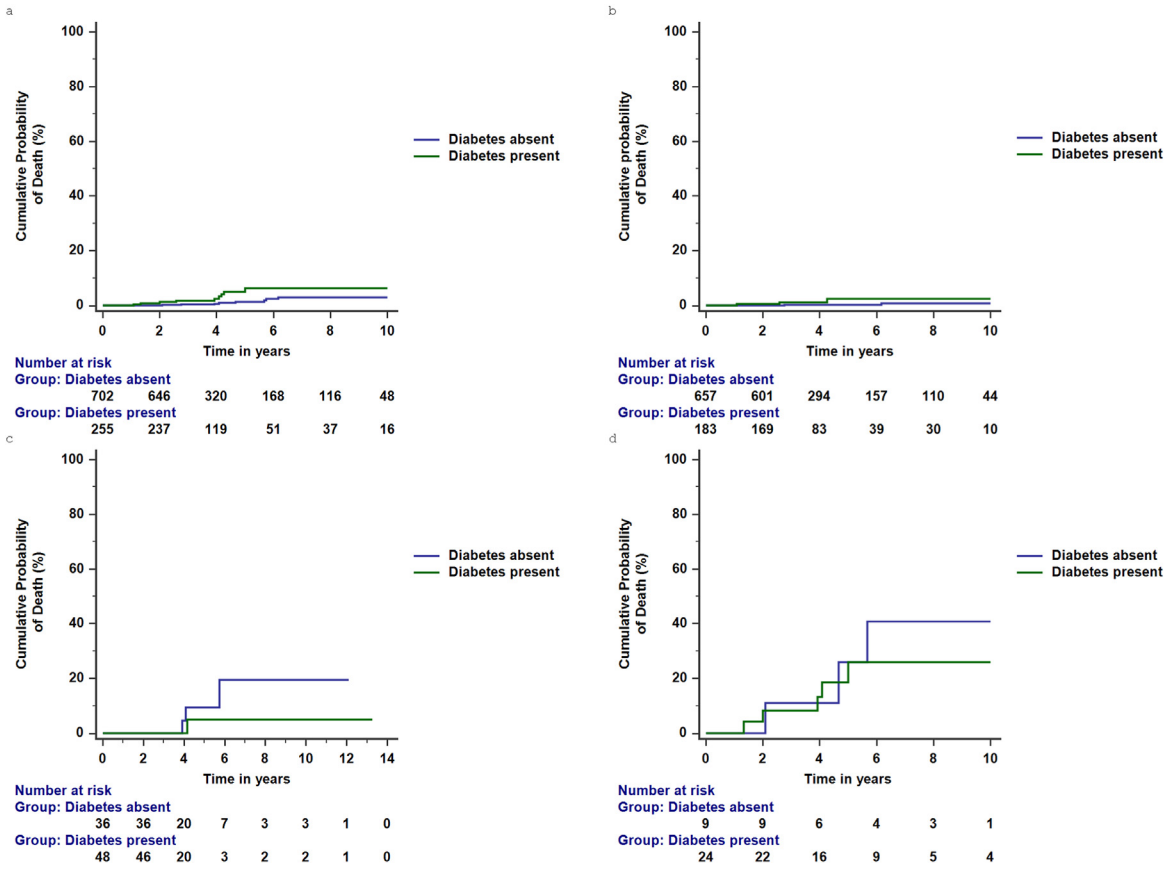


**Figure 2** Cumulative probability. (a) Whole cohort mortality (log-rank $P = 0.005$), (b) noncirrhosis (log-rank $P = 0.036$), (c) compensated cirrhosis (log-rank $P = 0.353$) and (d) decompensated cirrhosis (log-rank $P = 0.771$) in patients with and without diabetes.

## DISCUSSION

NAFLD has a wide range of clinical phenotypes, and many factors such as genetic, epigenetic, environmental and clinical have a role in disease progression. As a result, the natural course and clinical outcomes may differ across the population. The present study assessed the natural history of patients with NAFLD evaluated in a tertiary care centre in India. The development of new-onset LRE and mortality were higher in patients with cirrhosis than in those without cirrhosis. The commonest cause of death in patients with cirrhosis was liver related, whereas in patients without cirrhosis, non–liver-related causes were more common. The independent predictors of mortality in the whole cohort were advanced age, hypertension and DC.

Patients with NASH have reduced survival compared with those without NASH.[15] Furthermore, a recent systematic review and meta-analysis reported that the stage of fibrosis on liver biopsy correlates with liver-related morbidity and overall mortality.[16] Most of the published data on the natural history of NAFLD comes from the West, whereas data from the Asian populations are scarce. A multicentre consortium from India recently reported significant liver disease in 20% of NAFLD patients; however, no LRE incidence rates were provided.[17] Our results suggest that the incidence of LRE in Indian NAFLD patients is similar to those reported in the West.[7] In contrast, the incidence of death was lower in our cohort. These differences in mortality could be explained by the fact that our study population was a decade younger and had a lower body mass index compared with the study by Sanyal *et al.*[7] Multiple factors influence the outcomes in patients with NAFLD, including diabetes, presence of underlying cirrhosis and NASH.[8,18]

HCC prevalence is increasing globally.[19,20] Recent data suggest the proportion of patients with NASH-related HCC has increased almost 8 times between 2002 and 2016 (from 2.1% to 16.2%; $P < 0.001$).[21] A recent review estimated that the annual incidence of HCC is higher among patients with NASH cirrhosis (0.5%–2.6%), whereas those without cirrhosis have a lower incidence (0.01%–0.13%).[22] The overall incidence of HCC in patients with NAFLD is lower than the viral aetiologies such as hepatitis C virus.[22,23] In our cohort, none of the NC group developed HCC consistent with the fact that the incidence of HCC in NAFLD without cirrhosis is low. The incidence of HCC in CC and DC was 0.26 and 0.45 per 100 person-



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**Table 4 New-Onset Complications in Patients With F0-2, F3 and F4 Fibrosis and LSM <8, 8–12 and > 12 kPa.**

| Complications | F0-2 (n = 232) | Follow-up (years) | Rates per 100 person-years | F3 (n = 23) | Follow-up (years) | Rates per 100 person-years | F4 (n = 32) | Follow-up (years) | Rates per 100 person-years | *P* value |
|---|---|---|---|---|---|---|---|---|---|---|
| Any liver-related event | 1 (0.4%) | 1387 | 0.07 (0.003–0.35) | 1 (4.3%) | 122 | 0.81 (0.04–4.04) | 5 (15.6%) | 133 | 3.76 (1.37–8.33) | <0.001 |
| Death | – | – | – | – | – | – | 3 (9.4%) | 141 | 2.12 | <0.001 |
| | **LSM <8 (n = 573)** | | | **LSM8-12 (n = 102)** | | | **LSM >12 (n = 112)** | | | |
| Any liver-related event | 1 (0.2%) | 2616 | 0.04 | 5 (4.9) | 469 | 1.07 | 18 (16.1%) | 499 | 3.60 | <001 |
| Death | 5 (0.9%) | 2617 | 0.19 (0.07–0.42) | 2 (2.0%) | 472 | 0.42 (0.07 –1.40) | 5 (4.5%) | 536 | 0.93 (0.34 –2.07) | <0.031 |

LSM, Liver stiffness measurement.

years, respectively, which is similar to that reported in the literature.[7,23] The risk factors for HCC include age, alcohol consumption, diabetes, obesity and intestinal microflora dysregulation.[24,25] Because our study cohort was younger than previous studies on NAFLD outcomes and the cumulative risk of liver-related morbidity and mortality increases with time, it is reasonable to predict that the complication rate would increase on longer follow-up. These results have significant implications from the public health perspective. With the overall higher burden of NAFLD, the most common indication for liver transplantation in the future is likely to be NAFLD.[26] A recent meta-analysis estimated that 38.6% of adults and 35.4% of children in India have NAFLD.[3] This would suggest a significant number of NAFLD-related complications that are likely to become more evident over time, putting a huge burden on the health care system.

Apart from the LRE, non-LREs are a significant cause of morbidity and mortality in NAFLD patients. A recent study reported that cardiovascular, cerebrovascular, hypertension and nonhepatic cancers occurred at 0.81, 0.99, 14.49 and 1.0, respectively, per 100 person-years in patients with cirrhosis.[7] These rates were similar in patients with various stages of fibrosis (F0-2, F3 and F4). We did not collect the data of nonliver events in our cohort of patients. The overall LRE incidence rate among those with liver biopsy (F0-F3) was 0.13 (0.02–0.43), which was similar to the whole cohort NC group LRE incidence of 0.14 (0.06–0.30). Whereas the LRE incidence rate among those with liver biopsy (F4) was 3.76 (1.37–8.33) and was higher than the whole cohort cirrhosis group LRE incidence of 2.72 (1.38–4.85). Possible reasons for these differences could be the small sample size of the group who underwent liver biopsy, apart from differences in associated comorbidities.

Our results suggest that NAFLD patients without cirrhosis have a low incidence of LRE of 0.15 per 100 person-years. Only 0.7% of patients with NC progressed to cirrhosis, and 20% of deaths in this group were liver related. NC have a slow rate of progression and hence need not be monitored very closely and can be considered at low risk of LRE. However, this group of patients are at risk for nonliver events. Thus, those with risk factors should be evaluated and monitored accordingly. Among patients with NAFLD, factors associated with progression include older age and diabetes at presentation.[27] A previous meta-analysis reported the presence of hypertension to be associated with the development of progressive fibrosis (odds ratio, 1.94; 95% confidence interval, 1.00–3.74).[8] Our results suggest that factors such as advanced age, hypertension and decompensation are associated with poor outcomes and are in accordance with prior publications. We did not find diabetes to be an independent factor associated with outcome on multivariate analysis. The effect of diabetes was significant in patients with the NC group only and not in




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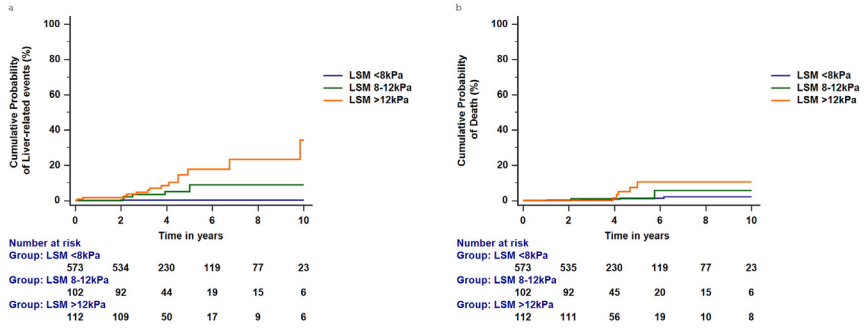


**Figure 3** Cumulative probability. (a) New liver-related events (log-rank $P < 0.001$), (b) mortality (log-rank $P < 0.001$) in patients with LSM <8 kPa, 8–12 kPa and 12 kPa.

those with CC and DC, suggesting that the severity of liver disease is a more important predictor of outcome. Importantly, our results suggest that a subgroup of NAFLD patients with risk factors for poor outcomes should be closely monitored.

There are certain limitations of this study. This retrospective cohort study was conducted in a tertiary care centre and mainly included symptomatic patients; hence, the results may not be applicable to asymptomatic NAFLD individuals. It is possible that our results may have overestimated the rates of LRE as the study included patients from a tertiary care centre. The large confidence intervals need to be interpreted cautiously, and more studies are needed to validate these findings. Because only a small proportion of patients had a liver biopsy, the influence of nonalcoholic fatty liver and NASH on progression could not be studied independently. Our study does not provide data on the occurrence of non-LREs. The results of our

**Table 5 Cox Proportional Hazard Analysis of Predictors of LRE (Whole Group).**

| Characteristics | Hazard ratio | *P* value |
|---|---|---|
| Age | 1.076 (1.045–1.107) | <0.001 |
| Sex (female) | 1.036 (0.491–2.186) | 0.926 |
| Diabetes at presentation | 4.628 (2.300–9.314) | <0.001 |
| Hypertension at presentation | 3.824 (1.873–7.806) | <0.001 |
| Metabolic syndrome | 0.813 (0.363–1.821) | 0.813 |
| Haemoglobin, g/dL | 0.629 (0.535–0.739) | <0.001 |
| Total leukocyte count/mm$^3$ | 0.846 (0.721–0.994) | 0.042 |
| Platelet count $\times 10^3$/mm$^3$ | 1.003 (1.000–1.006) | 0.034 |
| Bilirubin, mg/dL | 1.201 (1.095–1.316) | <0.001 |
| Albumin, g/dl | 0.195 (0.134–0.284) | <0.001 |
| Aspartate aminotransferase, IU/L | 1.004 (0.998–1.009) | 0.164 |
| Alanine aminotransferase, IU/L | 0.991 (0.982–1.001) | 0.066 |
| Creatinine, mg/dL | 3.665 (1.200–11.195) | 0.023 |
| International normalised ratio | 5.324 (2.382–11.898) | <0.001 |
| Liver stiffness measurement | 1.065 (1.049–1.080) | <0.001 |
| NC | 1 | |
| CC | 25.431 (7.968–81.171) | <0.001 |
| DC | 970.031 (272.111–3458.007) | <0.001 |

LRE, liver-related events; NC, Noncirrhosis; CC, Compensated cirrhosis; DC, Decompensated cirrhosis.
Multivariate model 1: Only CC and DC were statistically significantly associated with LRE—CC: hazard ratio (HR) 18.631 (5.309–65.382) and DC: 597.076 (115.412–3089.939) after adjustment for age, diabetes at presentation, hypertension at presentation, haemoglobin, total leucocyte count, platelet count, albumin, alanine aminotransferase and serum creatinine.
Multivariate model 2: Liver stiffness measurement—HR, 1.057 (1.036–1.078) and bilirubin HR, 1.459 (1.021–2.086) were statistically significant after adjustment for age, diabetes at presentation, hypertension at presentation, haemoglobin, total leucocyte count, platelet count, albumin, alanine aminotransferase and serum creatinine.



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**Table 6 Cox Proportional Hazard Analysis of All Cause of Mortality.**

| Characteristics | Hazard ratio | *P* value | Adjusted hazard ratio[a] | *P* value |
|---|---|---|---|---|
| Age | 1.111 (1.065–1.158) | <0.001 | 1.070 (1.008–1.135) | 0.026 |
| Sex (female) | 0.938 (0.333–2.638) | 0.903 | | |
| Diabetes at presentation | 3.511 (1.385–8.903) | 0.008 | 0.552 (0.174–1.747) | 0.312 |
| Hypertension at presentation | 9.987 (3.795–26.279) | <0.001 | 4.361 (1.258–15.122) | 0.020 |
| Metabolic syndrome | 1.077 (0.327–3.548) | 0.904 | | |
| Haemoglobin, g/dL | 0.689 (0.557–0.852) | 0.001 | 0.953 (0.725–1.251) | 0.727 |
| Total leukocyte count/$mm^3$ | 1.000 (1.000–1.000) | 0.965 | | |
| Platelet count $\times 10^3/mm^3$ | 1.001 (0.997–1.005) | 0.744 | | |
| Bilirubin, mg/dL | 1.270 (1.138–1.417) | <0.001 | | |
| Albumin, g/dL | 0.140 (0.082–0.238) | <0.001 | | |
| Aspartate aminotransferase, IU/L | 0.983 (0967–0.998) | 0.028 | 1.003 (0.997–1.009) | 0.392 |
| Alanine aminotransferase, IU/L | 1.004 (0.998–1.010) | 0.195 | | |
| Creatinine, mg/dL | 10.425 (3.997–27.192) | <0.001 | 2.267 (0.981–10.880) | 0.054 |
| International normalised ratio | 5.069 (1.675–15.345) | 0.004 | | |
| Liver stiffness measurement | 1.045 (1.022–1.069) | <0.001 | | |
| NC | 1 | | 1 | |
| CC | 8.098 (2.170–30.216) | 0.002 | 2.407 (0.490–11.834) | 0.280 |
| DC | 32.201 (10.729–96.642) | <0.001 | 15.036 (3.802–59.457) | <0.001 |

NC, Noncirrhosis; CC, Compensated cirrhosis; DC, Decompensated cirrhosis.
Multivariate model 2: On replacing cirrhosis with liver stiffness measurement and including bilirubin and albumin, only albumin was significantly associated with mortality, hazard ratio 0.289 (0.091–0.913), after adjustment for age, age, diabetes at presentation, hypertension at presentation, haemoglobin, aspartate aminotransferase and serum creatinine.
[a]Liver stiffness measurement, bilirubin, international normalised ratio and albumin were not included.

study may not be applicable to all cohorts of NAFLD, such as those with morbid obesity and lean NAFLD. In our cohort, patients were divided into groups based on findings of imaging, FibroScan and liver biopsy, wherever available as NC, CC and DC. Our cohort represents a real-world clinical scenario of patients and is representative of patients seen in routine clinics.

In conclusion, our findings imply that occurrence of LREs in Indian NAFLD patients is similar to that reported in the West. As expected, LREs and mortality are higher in patients with cirrhosis than in no cirrhosis.

## CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Shalimar contributed to study concept and design, interpretation of data and critical revision of article for important intellectual content and guarantor of the article. Sabreena Shafi Sheikh, Manas Vaishnav, Piyush Pathak, Aditya Vikram Pachisia, Himanshu Narang, Shubham Prasad, Shubham Mehta, Anugrah Dhooria, Shekhar Swaroop, Rithvik Golla and Ankit Agarwal contributed to acquisition of data and drafting of article. Sagnik Biswas contributed to acquisition of data; analysis and interpretation of data; and drafting of article. Ramesh Kumar and Subrat Kumar Acharya contributed to acquisition of data and drafting and critical review of the article.

## CONFLICTS OF INTEREST

All authors have none to declare.

## ACKNOWLEDGEMENTS

The authors would like to thank Ms Manisha for maintenance of data.

## SOURCE OF FUNDING

This study was supported by Science and Engineering Research Board (SPR/2020/000315).

## TRIAL REGISTRATION NUMBER

NA.

## ETHICAL CLEARANCE NUMBER

IEC/343/5/2017.




Please cite this article as: Shalimar et al., Incidence and Predictors of Liver-Related Events in Patients With Nonalcoholic Fatty Liver Disease, Journal of Clinical and Experimental Hepatology, https://doi.org/10.1016/j.jceh.2022.09.007

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## SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2022.09.007.



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