Original Article

Number needed to screen to prevent progression of liver fibrosis to cirrhosis at primary health centers: An experience from Delhi

Bharathnag Nagappa[1], Archana Ramalingam[1], Aayushi Rastogi[1], Shantanu Dubey[2], Sherin Sarah Thomas[3], Ekta Gupta[4], Shiv Kumar Sarin[5]

[1]Department of Epidemiology, [2]Assistant Head Operations (Medical), [3]Department of Biochemistry (Metabolic Medicine and Immunopathology), [4]Department of Virology, [5]Department of Hepatology and Director, Institute of Liver and Biliary Sciences, Delhi, India

Abstract

Background: Early diagnosis has been a bottleneck in the care of chronic liver disease patients and can be addressed by Community-based screening for liver fibrosis using non-invasive diagnostic techniques. **Objectives:** The study aimed to determine the prevalence of liver fibrosis and the number needed to screen (NNS) to prevent the progression of fibrosis, among adults visiting urban Primary Health Centres (PHC). **Methods:** A facility-based cross-sectional study was conducted from May 2018 to April 2019 in 72 randomly chosen PHCs using a mobile screening van. A pre-tested questionnaire was used to collect relevant history from adult patients and patient attenders. A venous blood sample was collected for biochemical markers and Transient Elastography was also done to measure Liver stiffness (LSM). LSM ≥6.0 kPa was taken as the cut-off for detecting liver fibrosis. Lifestyle modifications and alcohol cessations were considered as interventions for non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease (ALD) respectively, to calculate NNS. **Results:** 7624 participants were recruited in the study with a mean age of 46 ± 12 years. Around 35.5% of participants had liver fibrosis and 3% had cirrhosis. Nearly 4% had ALD and 30% had NAFLD. NNS for preventing progression of fibrosis for ALD and NAFLD was 12 and 29 respectively. NNS was least among obese, diabetes and hypertensive participants. **Conclusion:** One-third of adults visiting urban PHCs had significant liver fibrosis. Low NNS to prevent the progression of fibrosis to cirrhosis among alcohol users and other high-risk groups, substantiates the need for screening among these groups.

Keywords: Alcoholic liver disease, non-alcoholic fatty liver disease, number needed to screen, primary health care

Background

Cirrhosis is the most common presentation of Chronic Liver Disease (CLD) and is a serious public health problem affecting populations worldwide. Over the last two decades, there has been a 46% increase in deaths due to cirrhosis.[1] The Global Burden of Disease report (2015) showed that cirrhosis alone accounted for 2.2% of total global mortality.[1] If deaths due to hepatocellular carcinoma (HCC) were to be included, as most cases of HCC have underlying cirrhosis, then, nearly 3.7% of all deaths are due to chronic liver diseases, thereby becoming the 5th leading cause of death.[2] Autopsy studies conducted in many parts of the world shows that the prevalence of cirrhosis varies from 4.5% to 9.5%.[3–5] The global burden of disease study estimates that more than fifty million people in the world would be affected by chronic liver disease.[6]

Address for correspondence: Dr. Archana Ramalingam, Department of Epidemiology, Institute of Liver and Biliary Sciences, Delhi, India.
E-mail: Archanajipmer04@gmail.com

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Cirrhosis occurs due to several causes like alcohol use, behavioral and diet factors, diabetes, metabolic syndrome, viral infection, drugs, and chemical exposure.[7,8] Of these, alcohol-related liver disease and Non-Alcoholic Fatty Liver Disease lead to significant morbidity. Alcohol is emerging as one of the most common causes of liver diseases in India and many other developing countries.[6] According to World Health Organization (WHO), consumption of alcohol accounts for 3.8% of the mortality and 4.6% of DALYs worldwide.[9] Liver disease represents 9.5% of alcohol-related DALY's globally, while individual rates vary in different regions.[6] Non-Alcoholic Fatty Liver Disease (NAFLD) is closely associated with diabetes, metabolic syndrome, behavioral, and diet factors.[10,11] Globally, the prevalence of NAFLD ranges from 6% to 35%, with a median of 20% and in India, it ranges from 9% to 42%.[12,13]

If detected early, fibrosis due to most of the causes could be reversed through targeted interventions like abstinence from alcohol, lifestyle modification, weight reduction, strict blood sugar control, and by treating viral hepatitis. Cost-effective interventions that can be easily implemented by primary care physicians can prevent the progression of fibrosis in chronic liver disease patients. Literature shows that abstinence from alcohol prevents the progression of liver disease in 20% of patients with alcoholic liver disease (ALD).[14] Studies also show that by reducing weight and behavioral change, the progression from fibrosis to cirrhosis can be prevented in 10% of NAFLD patients.[15] Addressing fatty liver and fibrosis due to these causes at an early stage can prevent a significant proportion of liver diseases which will result in decreased burden on health system and the community.[6] ALD and NAFLD are also related with many other non-communicable diseases like components of metabolic syndrome, cardiovascular diseases, and chronic kidney diseases.[8,10,16–18] Thus, identifying ALD and NAFLD at earlier stages through early diagnosis is crucial to reduce health burden due to non-communicable diseases.

A major barrier to early detection of liver fibrosis is that in most cases, it is asymptomatic till a very advanced stage when treatment options become very limited.[19,20] Until recently, liver biopsy was the only available test to detect liver fibrosis.[16] But owing to its invasive nature, complications like bleeding and high cost it could not be used for population-level screening. With the advent of non-invasive tests like transient elastography, screening for liver diseases at the community level has become possible. Transient elastography (TE) is a simple procedure, could be done in less than 5 minutes and does not have subjective variation.[16] TE is non-invasive, less time consuming and suitable for community-level screening.[21]

The number needed to screen (NNS) is an estimate that offers great value in comparing strategies used for disease screening. The number needed to be screened is defined as the number of people who need to be screened to prevent one death or one adverse event for a given duration.[22] Previous studies have shown that the NNS values to prevent one death, by screening for abnormal lipid profile followed by statin therapy for five years was 418 and by screening for hypertension followed by diuretic therapy for five years with reduction in 5.7 mmHg of diastolic blood pressure was 1307.[22] Hence by studying the number needed to screen for preventing progression of liver fibrosis we can compare screening strategies for detecting liver fibrosis with those for other chronic non-communicable diseases and would offer significant insights for policymakers.

With this background, we aimed to study the prevalence of liver fibrosis and the number needed to screen to prevent the progression of fibrosis, among adults visiting urban Primary Health Centres (PHC).

Methodology

Study design and setting

A facility-based cross-sectional study was conducted from May 2018 to April 2019 in 72 randomly chosen "Mohalla clinics" using a mobile screening van. Mohalla clinics are primary care centers supported by the Government of Delhi. These clinics provide outpatient carefree of cost to the residents of their catchment area from 9 am to 2 pm. On average, each Mohalla clinic is visited by around a hundred patients every day.

Study population

All adult patients seeking care from selected Mohalla clinics and their attendees were invited to participate in the study. Patients with any liver-specific symptoms or known liver diseases were excluded from the study as we aimed to estimate the liver fibrosis in the asymptomatic population.

Sample Size and sampling method

The lowest recorded prevalence of cirrhosis (4.5%)[5] in the literature, with a 95% confidence interval and 20% relative precision, yielded a sample size of 2034 to estimate the prevalence of cirrhosis. However, since this study was part of an outreach activity of a tertiary care center for detecting liver diseases, the study size was well above the estimated sample size. Simple random sampling method was used to select the Mohalla clinics from the list provided by the Government of Delhi and all eligible participants who attended the services of the Mohalla clinics were invited to volunteer themselves to participate in this initiative.

Study procedure

Seventy-two Mohalla clinics were chosen randomly from the list of clinics obtained from the Government of Delhi. Permission was obtained from the Department of Health and Family Welfare, Delhi to conduct the study. A fixed schedule for visit by the mobile screening unit was prepared and communicated to all medical officers of Mohalla clinics through the Department of Health and Family Welfare. The day before visiting the scheduled clinic, a member of the project team visited the site and carried out pre-operational activities. On the day of the visit, the Mobile medical unit was stationed near the clinic. Patients visiting the clinic if eligible were invited to participate in the

screening activity by the Medical officer. When the participants reached the mobile medical unit, they were once again assessed for enrolment using the eligibility criteria. The eligible participants were recruited after obtaining informed consent. Data about age, gender, history of liver disease and existing co-morbidities were collected using a pre-tested semi-structured questionnaire. After the interview, a trained nurse performed transient elastography to assess liver stiffness measurement (LSM) and then the venous blood sample was collected by the lab technician. The blood sample was transported in a biological sample carrier to the lab on the same day of collection. Rapid card tests for HBsAg and Anti-HCV antibody was done. Alanine aminotransferase (ALT) and Total Cholesterol were also assessed. The results of these tests were communicated to the study participants through the medical officers of Mohalla clinics.

Operational definitions used in the study:

Liver fibrosis and Cirrhosis:

For analysis, LSM ≥6.0 kPa and ≥13.0 kPa were considered as cut-offs for suggesting liver fibrosis and cirrhosis, respectively.[16,21]

Alcoholic Liver Disease (ALD):

Participants with liver fibrosis or Cirrhosis and a positive history of alcohol use with negative screening test results for Hepatitis B and Hepatitis C were considered as those with Alcoholic Liver Disease (ALD).

Non-Alcoholic Fatty Liver Disease (NAFLD):

Participants with significant fibrosis or Cirrhosis without any of the following:

1) history of alcohol use
2) positive screening test result for Hepatitis B and Hepatitis C

were considered to have Non-alcoholic fatty liver disease

Calculation of Number Needed to Screen (NNS)

NNS was calculated by dividing the number needed to treat (NNT) calculated from the literature by the proportion of participants with liver fibrosis in the current study (NNS = NNT/proportion of participant with liver fibrosis).[22,23]

The Number Needed to Treat to prevent the progression of fibrosis (NNT) was calculated based on studies available in the literature (enumerated below). We have considered alcohol abstinence and lifestyle modification interventions due to ease of administration of these interventions in the primary care setting.

Interventions considered to calculate NNS

Lifestyle Modification for NAFLD-related fibrosis:

The number needed to reverse the fibrosis (NNT) due to NAFLD by lifestyle modification (considering absolute risk reduction as 10%) based on a previous study was calculated to be 10.[15,24]

The intervention used in this previous study consisted of a low-fat hypocaloric diet that was 750 kcal/d lesser than the daily energy need of the participants, (estimated as resting energy expenditure using the Mifflin St. Jeor equation). In addition to diet modification, all participants were encouraged to walk 200 minutes per week. Behavioral individual sessions to promote adherence to the assigned diets were held every 8 weeks and the outcome was assessed at the end of one year.

Alcohol cessation for alcohol-related fibrosis:

The number needed to reverse the fibrosis (NNT) due to alcohol by abstaining from the alcohol (considering absolute risk reduction as 20%) was calculated to be 5.[14] In this study, participants were in a state of complete abstinence from alcohol and outcome was measured at the end of 3 years.

Statistical methods

Data were entered in Microsoft Excel software and analyzed using STATA v14. Continuous variables were summarized as mean with standard deviation (SD). Categorical variables were summarized as proportion. Prevalence of liver fibrosis and cirrhosis were expressed as a percentage with a 95% confidence interval.

The number needed to screen (NNS) was calculated for fibrosis due to alcohol and non-alcoholic fatty liver disease. Participants with the previous history of liver diseases and previous test results that were reactive for Hepatitis B and C viral markers were excluded in the analysis for NNS estimation.

Table 1: Socio-demographic and clinical characteristics of study population (*n*=7624)

Characteristics	Frequency (*n*)	Proportion (%)
Age (in years)		
<30	1167	15.3
30-40	1323	17.3
41-50	1204	15.8
51-60	3348	43.9
> 60	582	7.6
Gender		
Male	4239	55.6
Female	3385	44.4
BMI category		
<18.5	216	2.8
18.5-22.9	1274	16.7
23-24.9	878	11.5
25-30	2696	35.5
>30	2542	33.42
Positive History of Alcohol use	818	10.7
History of Diabetes	851	11.1
History of Hypertension	806	10.5
History of Dyslipidemia	10	0.13
History of Liver Disease	83	1.09
HBsAg Reactive	87	1.14
Anti-HCV reactive	31	0.41
Raised ALT levels	1793	23.6
Raised Total Cholesterol	1813	23.9
Fibrosis	2744	35.5
Cirrhosis	271	3.5

Ethical issues:
The study was conducted with the permission from the institute, using data obtained from the outreach activity of the institute. Therefore, ethical clearance was not obtained from the institute ethical committee before collecting the data.

Results

A total of 7624 participants was recruited into the study with the mean age of 46 years (SD ± 12 years). Of the total participants recruited 44% belonged to the age group of 51 to 60 years and 56% were men. Around 69% of participants had a body mass index (BMI) of more than 25 and 11% gave history of alcohol use. Of the total subjects, 11% had hypertension, 1% had a history of liver disease. Rapid screening test for HBsAg and anti HCV was positive in 1% and 0.4% respectively. ALT and cholesterol levels were raised in 24% of the participants [Table 1].

The prevalence of liver fibrosis was 35.5% that of cirrhosis was 3%. Around 4% and 30% of the participants had fibrosis due to ALD and NAFLD, respectively.

Among the participants with a positive history of alcohol use, 41% had fibrosis due to Alcohol-related Liver Disease (ALD). The prevalence of fibrosis was higher among those in the age group of more than 60 years (50%), women (50%), those with BMI more than 30 (50%) and participants with diabetes (45%) [Table 2].

The prevalence of fibrosis due to NAFLD was around 35%. Fibrosis was higher among participants with history of dyslipidemia (50%), diabetes (47%), hypertension (45%), those with BMI more than 30 (48%), and age more than 60 years (41%) [Table 3].

Table 2: Proportion of fibrosis due to Alcohol Liver Disease (ALD) among the study population

Characteristics	Total Alcohol Users (*n*=799)	Number with fibrosis (%)
Age (in years)		
<30	74	25 (33.78)
30-39	113	41 (36.28)
40-49	83	35 (42.17)
50-59	513	222 (43.27)
>=60	16	8 (50)
Gender		
Male	791	327 (41.34)
Female	8	4 (50)
BMI category		
<18.5	13	6 (46.15)
18.5-22.9	104	35 (33.65)
23-24.9	76	21 (27.63)
25-29.99	263	96 (36.5)
>=30	340	170 (50)
Diabetes	38	17 (44.74)
Hypertension	52	27 (51.92)
Raised ALT	315	153 (48.57)
Raised Cholesterol	208	100 (48.08)
Total alcohol users	799	331 (41.34)

NNS to prevent the progression of liver fibrosis is given in Table 4. NNS to prevent progression of fibrosis due to ALD was estimated to be 12 and it was least among participants with diabetes (11), those with BMI < 18.5 (11) and age more than 60 years (10) [Table 4]

NNS to prevent the progression of fibrosis due to NAFLD was estimated to be 29 and it was least among participants with diabetes (21), hypertension (22), BMI more than 30 (21), aged more than 60 (24) and males (25) [Table 4].

Discussion

The study aimed to estimate the prevalence of significant liver fibrosis and calculate the NNS to prevent the progression of fibrosis due to ALD and NAFLD. The prevalence of liver fibrosis was found to be 35% and that of cirrhosis was 3%. There is minimal data on significant liver fibrosis among subjects visiting the primary health care setting, which makes it difficult to compare our findings. However, the study findings are well in the range of estimated prevalence of NAFLD (9% to 35%) in India.[13] Many autopsy studies had reported that cirrhosis in general population varies from 4% to 9% which is closer to our findings of 3%.[3–5]

The prevalence of fibrosis due to NAFLD was higher among participants with dyslipidemia, diabetes, raised ALT, obesity, hypertension, age more than 60 years and males. These findings are similar to that in literature, which shows a close association of components of metabolic syndrome and NAFLD.[7,8,10,11,16] ALT is a marker of liver damage, and it is expected that those with raised ALT levels would have a higher prevalence of liver fibrosis. The prevalence of liver fibrosis due to ALD was also higher in similar groups.

The present study showed that to prevent the progression of fibrosis in one individual with alcoholic liver disease (using abstinence from alcohol for 3 years as intervention), one needs to screen 12 alcohol users for fibrosis using transient elastography. The study also showed that to prevent the progression of liver fibrosis in one individual with NAFLD (using lifestyle changes as an intervention for one year), one needs to screen 25 subjects with NAFLD using transient elastography. This finding can be compared with a previous meta-analysis which showed that to prevent one pre-diabetic from developing diabetes (using lifestyle interventions changes as an intervention for 6 months), one needs to screen 330 pre-diabetic subjects using blood glucose measurements.[25]

Therefore, there is a need to provide services to screen for liver fibrosis in primary care settings similar to screening for diabetes. This measure would facilitate the prevention of fibrosis in subjects with chronic liver diseases.

Table 3: Proportion of fibrosis due Non-Alcohol Fatty Liver Disease (NAFLD) among study population (*n*=6621)

Characteristics	Total study population without Alcohol use and non-reactive to Viral Hepatitis (*n*=6621)	Fibrosis due to NAFLD *n* (%)
Age (in years)		
<30	880	234 (26.59)
30-39	1107	329 (29.72)
40-49	1125	425 (37.78)
50-59	2773	1016 (36.64)
> =60	736	309 (41.99)
Gender		
Male	3322	1355 (40.69)
Female	3299	958 (29.04)
BMI category		
<18.5	193	40 (20.73)
18.5-22.9	1133	240 (21.18)
23-24.9	777	192 (24.71)
25-29.99	2358	799 (33.88)
>=30	2146	1033 (48.13)
Diabetes	798	376 (47.11)
Hypertension	747	334 (44.71)
History of Dyslipidemia	10	5 (50)
Raised ALT	1415	685 (48.41)
Raised Cholesterol	1577	628 (39.83)
Total	6621	2313 (34.94)

Table 4: Number needed to screen (NNS) to prevent the progression of fibrosis due Alcoholic and Non- alcoholic Fatty Liver Disease (NAFLD) among patients visiting to primary health care centres in Delhi

Characteristics	NNS for Fibrosis due to NAFLD*	NNS for Fibrosis due to alcohol liver disease#
Age (in years)		
<30	38	15
30-40	34	14
41-50	26	12
51-60	27	12
>60	24	10
Gender		
Male	25	12
Female	34	10
BMI category		
<18.5	48	11
18.5-22.9	47	15
23-24.9	40	18
25-30	30	14
>30	21	10
Diabetes	21	11
Hypertension	22	10
History of Dyslipidemia	20	-
Raised ALT	21	10
Raised Cholesterol	25	10
Total	29	12

*NNS for NAFLD was calculated among the participants without history of alcohol use and nonreactive to viral marker. #NNS for ALD was calculated among the participants who had history of alcohol use and nonreactive to viral markers

The study showed that the number needed to screen would be lower if we screen high-risk individuals both for ALD and NAFLD. The NNS was found to be merely 20 among participants with dyslipidemia, 21 in diabetics, 21 in participants with BMI >30 and 22 in hypertensive, for prevention of fibrosis due to NAFLD. Among alcohol users, NNS was lower in subjects with diabetes (11), those with BMI <18.5 (11), age more than 60 years (10), hypertensives (10), women (10), and BMI >30 (10). these findings are similar to NICE guidelines "Cirrhosis over 16s: diagnosis and management",[26] which recommends adopting a high-risk approach to screen for liver diseases, especially for ALD and NAFLD. By implementing a high-risk approach, we can reduce the burden of chronic liver diseases like cirrhosis, hepatocellular cancer, and also reduce the need for liver transplantation. This, in turn, reduces health and economic burden due to CLD related to NAFLD and ALD.

Strengths of the present study are: (1) Fibroscan was used for screening, which has an area under the curve value of 0.95 (0.87–0.99) for the diagnosis of liver fibrosis. The fibroscan results are objective and thus reduces the inter-observer variability. The LSM values which were considered for diagnosis were median values of 10 observations and it was considered valid only if the range was less than 10% median. This will reduce bias due to procedural variation while measuring LSM. The training requirements to operate fibroscan by a health worker is also minimum. All these factors would act in favor of scaling up this modality for the diagnosis and management of liver fibrosis at all levels of healthcare. (2) The sample size of the study is larger than the estimated sample size and helps in obtaining a more precise estimate of results. (3) The present study had recruited participants from 72 randomly selected Mohalla clinics from various parts of the National Capital Territory of Delhi. This ensured the representativeness of the participants

and generalizability to patients seeking care from Primary health care setting in urban India.

The limitations of the study are: (1) participation in the study was voluntary and the schedule of visit of the mobile medical unit was well advertised in advance. This might have may lead to the pooling of high-risk group subjects in our study and may explain the higher proportion of obese participants in our study. (2) The absolute risk reduction considered to calculate the NNS was the same for all subgroups of participants. It may vary between different groups (high and low-risk groups). But due to the paucity of data in the available literature, we had to restrict to a single value of absolute risk reduction for all the subgroups. The present study is one of the few studies which try to explore NNS in each high-risk group. (3) Due to resource constraints, we were not able to test for other causes of liver fibrosis like autoimmune diseases and genetic disorders.

The present study recommends using non-invasive diagnostic tools like transient elastography for diagnosis and management of liver fibrosis and its causes in the primary care setting. It also recommends having a high-risk approach in resource-poor settings, so that interventions can be more cost-effective. All primary care physicians should be trained in prevention, diagnosis, and preliminary management of liver diseases. There is a need for further research on simpler screening tools and the effectiveness of preventive interventions in high-risk groups.

Conclusion

One in three patients seeking care in the primary health care settings had significant liver fibrosis. Low NNS to prevent the progression of fibrosis to cirrhosis among alcohol users, obese, diabetics, hypertensives, and geriatric age group, substantiate the need for screening for fibrosis among these high-risk groups.

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Conflicts of interest

There are no conflicts of interest.

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