Alcohol use and alcoholic fatty liver disease: a prospective, community-based study among adults in an urban community in Sri Lanka

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(Index words: alcohol, unsafe drinking, fatty liver, alcoholic fatty liver disease, epidemiology, risk factors)

Abstract

Background: Data on alcoholic fatty liver (AFL) is limited. Therefore, we investigated alcohol use and AFL in a cohort of adults in an urban community in Sri Lanka.

Methods: The study population (selected by age-stratified random sampling) was screened in 2007 (35-64 years) and re-evaluated in 2014. They were assessed by structured interviews, anthropometric measurements, liver-ultrasound, and biochemical and serological tests. AFL was diagnosed on ultrasound criteria, 'unsafe' alcohol consumption (Asian standards: males>14 units, females >7 units per week) and absence of hepatitis B/C markers. Controls were unsafe alcohol consumers who had no fatty liver on ultrasound.

Results: 2985/3012 (99%) had complete data for analysis. 272/2985 (9.1%) were unsafe-drinkers in 2007 [males-270; mean-age-51.9, SD-8.0 years]. 86/272 (31.6%) had AFL [males-85; mean-age-50.2, SD-8.6 years]. Male gender [p<0.001], increased waist circumference (WC) [OR 4.9, p<0.01], BMI>23kg/m^2 [OR 3.5, p<0.01] and raised alanine aminotransferase (ALT) [OR 2.8, p<0.01] were independently associated with AFL. 173/272 (63.6%) unsafe alcohol consumers from 2007 were re-evaluated in 2014. 134/173 had either had AFL or had changed to 'safe' or no alcohol consumption. 21/39 (53.8%) [males-21 (100%), mean-age-57.9, SD-7.9 years] who remained 'unsafe' alcohol users who had no fatty liver in 2007 developed AFL after 7-years (annual incidence 7.7%). On bivariate analysis, only male gender was associated with new-onset AFL. Of the 42 who had AFL at baseline but changed their drinking status from unsafe to safe or no alcohol, 6 had resolution of fatty liver in 2014.

Conclusion: In this community-based study among adults from an urban community, unsafe alcohol use was found in 9.1%. Among unsafe alcohol users, the prevalence of AFL was 31.6% and the annual incidence of AFL was 7.7%. New-onset AFL was independently associated with male gender.

Background

Alcohol-related liver disease (ARLD) is one of the most common types of chronic liver disease (CLD), accounting for almost 50% of cases of cirrhosis worldwide [1, 2]. ARLD can progress from simple steatosis [alcoholic fatty liver (AFL)] to alcoholic steatohepatitis (ASH), which is characterised by hepatic inflammation [2, 3]. Chronic ASH can eventually lead to progressive fibrosis and the development of cirrhosis and hepatocellular cancer [2, 3]. Most individuals with chronic, unsafe, excessive alcohol intake develop the simplest phenotype AFL; however, only a subset of individuals will develop the more advanced phenotypes ASH and cirrhosis. Genetic, epigenetic and non-genetic factors might explain the considerable inter-individual variation in ARLD phenotype [3].

Sri Lanka has a unique pattern of CLD. Hepatitis B virus (HBV) and hepatitis C virus (HCV) prevalence is very low, even among presumed 'high risk' populations [4]. Chronic viral hepatitis-related CLD is also rare (<2% for HBV and <1% for HCV related cirrhosis) [5]. Instead, alcohol-related and cryptogenic or fatty liver-related forms of cirrhosis predominate [5]. Using stringent ultrasound criteria, we previously reported a community prevalence of 32.6% and an annual incidence of 6.6% for non-alcoholic fatty liver disease (NAFLD) in an urban, adult Sri Lankan

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population [6, 7]. However, there are few data on the community prevalence, incidence and risk factors for ARLD from prospective community-based cohort studies from the Asian region.

The Ragama Health Study (RHS) is a large community-based, prospective cohort study on non-communicable diseases [6]. It is a collaborative study between the National Centre for Global Health and Medicine, Tokyo, Japan and the Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka. This study aimed to determine unsafe alcohol use and the incidence and risk factors for AFL in the RHS cohort after seven years of follow-up.

Methods

The study population was initially selected by age-stratified random sampling from electoral lists of the Medical Officer of Health area, Ragama, Sri Lanka. The population was urban, with a multi-ethnic distribution. They were initially screened in 2007 (aged 35-64 years) and invited for re-evaluation after seven years in 2014 (aged 42-71 years). On both occasions, they were assessed by structured interviews, anthropometric measurements, liver ultrasound, and biochemical and serological tests [6]. Details of the inception and the follow-up cohort screening are described elsewhere [6, 7].

Details regarding the type and amount of alcohol consumed and duration of drinking were obtained by direct questioning of participants by trained research assistants using a structured questionnaire. Standardized measures of alcohol were used to quantify the units of alcohol consumed per week [8]. Accordingly, 14 units were defined as 14 single measures of spirit (25ml of 40% alcohol by volume) or 6 glasses of wine (175ml of 13% alcohol by volume) or 6 pints of ordinary strength beer (568ml of 4% alcohol by volume). Illicit alcohol was assumed to have strength of 40% alcohol by volume. Diagnosis of fatty liver was based on established ultrasound criteria (two out of the following three criteria: increased echogenicity of the liver compared to kidney and spleen, obliteration of the vascular architecture of the liver and deep attenuation of the ultrasonic signal) [9]. Ultrasound scans were performed by experienced sonographers and fatty liver was diagnosed based on established criteria to minimize inter-observer variation. AFL was diagnosed in the presence of ultrasound criteria for fatty liver, unsafe alcohol consumption (Asian standards: males >14 units, females >7 units per week) [10] and absence of hepatitis B/C markers. Controls were individuals with unsafe alcohol consumption but who had no ultrasound criteria of fatty liver (9). Resolution of fatty liver was defined as those who had no ultrasound criteria of fatty liver. Characteristics of AFL were compared with controls at baseline using bivariate analysis and thereafter using stepwise logistic regression.

Those with an initial diagnosis of AFL in 2007 were encouraged to adopt a healthy lifestyle modification and alcohol abstinence and referred for medical care for associated metabolic risk factors such as diabetes, hypertension and dyslipidemia, as appropriate. In addition, they were periodically (once every six months) invited to attend a community clinic for reinforcement of healthy lifestyle advice. New onset AFL were those who did not have AFL at baseline in 2007 but developed AFL at reassessment after 7-years in 2014, while continuing unsafe alcohol use. The incidence of AFL was calculated among these individuals. The risk factors at baseline for the development of new-onset AFL compared to controls were assessed among those who continued to consume unsafe alcohol only by bivariate analysis given the small number of new-onset AFL.

Data were entered in Epi Info 7 (Centres for Disease Control and Prevention, Atlanta, GA, USA), and logical and random checks were done. During data entry, contradictions and abnormal values were rechecked individually with patient records and further clarifications were made with senior members of the clinical and research teams. Data were entered in duplicate; the databases were compared, and discrepancies were re-corrected by reviewing physical records to improve accuracy.

Statistical analysis was done using Stata 14.1 (StataCorp, College Station, Texas, USA). Continuous and categorical data were described using mean and standard deviations and percentages, respectively. Bivariate analysis was done using the Chi-squared test. Multivariate analysis was done using binary logistic regression. $P< 0.05$ was considered as significant. The strength of association between baseline characteristics (exposure) and AFL (outcome) was expressed in the odds ratio (OR).

Ethical approval for the study was obtained from the Ethical Review Committees of the Faculty of Medicine, University of Kelaniya. Informed consent was obtained from all participants in the RHS.

Results

There were 3012 participants in the initial study, of whom 2985 (99.1%) had complete data for analysis (Ethnic breakdown: Sinhalese 96.2%, Tamil 1.3%, Muslim 1.3%, Burgher 1.3%). This included 1349 men (45.2%), mean age (SD) of 54.2 (7.8) years. 2148/2985 (72%), including 910 (42.4%) men who participated in the follow-up assessment. Except for fewer males attending follow up, the rest of the characteristics were similar among initial and follow up cohorts (Table 1) [7].

At baseline in 2007, 272/2985 (9.1%) were unsafe-drinkers [males-270 (99.3%); mean-age (SD) 51.9 (8.0) years]. 86/2985 (2.9%) of initial cohort [86/272 (31.6%) of unsafe-drinkers] had AFL [males-85 (98.8%); mean-age (SD) 50.2 (8.6) years]. 186/272 (68.4%) had unsafe alcohol intake but did not have AFL at baseline. On bivariate analysis, male gender [$p<0.001$], younger age [$p<0.05$],

abnormal waist circumference (WC) [p=0.001], BMI>23kg/m^2 [p<0.001], presence of diabetes [p<0.01] raised triglycerides (TG) [p<0.01] and raised alanine aminotransferase (ALT) (>2 x upper limit of normal) [p<0.01] were associated with AFL. Low education level (LEL-not completed secondary-education) [p<0.01] and low monthly household-income (<median-Rs. 25,000) [p<0.001] were associated with unsafe alcohol intake without ALF (Table 2). On multivariate analysis, only increased waist circumference [OR 4.9, p<0.01], BMI>23kg/m^2 [OR 3.5, p<0.01] and raised ALT [OR 2.8, p<0.01] independently associate with AFL at baseline in 2007 (Table 3).

173/272 (63.6%) who consumed unsafe amounts of alcohol in 2007 presented for follow up in 2014. Of these 173, 55 already had AFL in 2007 and 79 had changed their drinking status to 'safe' or no alcohol consumption (Figure 1). Thirty-nine unsafe drinkers who did not have fatty liver at baseline in 2007 continued hazardous drinking, and 21/39 (53.8%) [all males, mean age (SD) 57.9 (7.9) years] of them had developed fatty liver after seven years (annual incidence 7.7%) (Figure 1). Only male gender was significantly associated with new-onset AFL (Table 4). Of the 42 who had AFL at baseline, who changed their drinking status from unsafe to safe or no alcohol, 6 had a resolution of fatty liver in 2014 (annual resolution 2.0%). There were too few who had resolution of AFL for analysis of factors associated with the resolution.

Table 1. Baseline characteristics of the initial and follow-up cohorts

Baseline characteristic in 2007	*Initial cohort 2007 n=2985*	*Attended follow-up 2014 n=2148*	*Did not attend follow-up 2014 n=837*
Males (%)	1349 (45.2)	910 (42.4)*	439 (52.4)*
Mean age (SD)	52.4 (7.8)	52.4 (7.7)	52.5 (8.1)
Mean BMI (SD)	24.1 (4.2)	24.3 (4.1)	23.7 (4.4)
Mean waist-hip ratio (SD)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
DM (raised FBS) [%]	709 (23.8)	477 (22.2)	232 (27.7)
HBP (SBP>140, DBP>90) [%]	1820 (60.4)	1298 (60.4)	522 (62.3)
Mean TG (SD)	131.6 (68.2)	130.8 (68.0)	133.5 (68.6)
Mean HDL (SD)	49.6 (4.5)	49.6 (4.5)	49.6 (4.4)
Mean LDL (SD)	136.2 (37.8)	136.5 (37.7)	135.3 (38.0)

*Z=4.97; p<0.001 (Z test comparing two proportions)

Table 2. Comparison of those who had AFL and those at risk of AFL at baseline in 2007

Risk factors (at baseline - 2007)	*AFL in 2007 n=86*	*No AFL in 2007 n=186*	*p value*
Males	85 (98.8%)	185 (99.4%)	-
Mean age (SD)	50.2 (8.6)	52.7 (7.6)	0.02
Waist circumference (above sex specific cut-off)	60 (69.8%)	34 (18.3%)	<0.001
BMI > 23kg/m^2	74 (86%)	59 (31.7%)	<0.001
DM	26 (30.2%)	29 (15.6%)	0.005
Raised TG (>150mg/dl)	43 (50%)	61 (32.8%)	0.005
Low HDL (male <40; female <50mg/dl)	5 (5.8%)	9 (4.8%)	0.735
Raised ALT (> 2 × upper limit of normal)	48 (55.8%)	56 (30.1%)	<0.001
Low educational level (not completed secondary education)	28 (32.6%)	99 (53.2%)	0.001
Low monthly income (< Rs 25,000)	22 (25.6%)	81 (43.5%)	0.005

Table 3. Results of the multivariate analysis of factors associated with AFL at baseline in 2007

Risk factors (at baseline - 2007)	*Odds Ratio*	*95% confidence intervals*	*p value*
Waist circumference (above sex specific cut-off)	4.907	2.680 - 8.984	<0.001
BMI > 23kg/m^2	3.485	1.832 - 6.631	<0.001
Raised ALT (> 2 × upper limit of normal)	2.758	1.628 - 4.674	<0.001

Table 4. Comparison of those with new onset AFL and those at risk of AFL at follow up in 2014

Risk factors (at baseline - 2007)	*AFL in 2014 n=21*	*No AFL in 2014 but remained at risk n=18*	*p value*
Males	21 (100%)	18 (100%)	-
Mean age (SD)	53.2 (6.6)	53.7 (7.9)	0.854
Waist circumference (above sex specific cut-off)	1 (5.6%)	4 (19.0%)	0.349
BMI > 23kg/m^2	9 (42.9%)	3 (16.7%)	0.096
DM	3 (14.3%)	1 (5.6%)	0.609
Raised TG (>150mg/dl)	10 (47.6%)	5 (27.8%)	0.323
Low HDL (male <40; female<50mg/dl)	3 (14.3%)	1 (5.6%)	0.609
Raised ALT (> 2 × upper limit of normal)	10 (47.6%)	6 (33.3%)	0.372
Low educational level (not completed secondary education)	13 (61.9%)	9 (50.0%)	0.528
Low monthly income (< Rs 25,000)	8 (38.1%)	6 (33.3%)	1.000

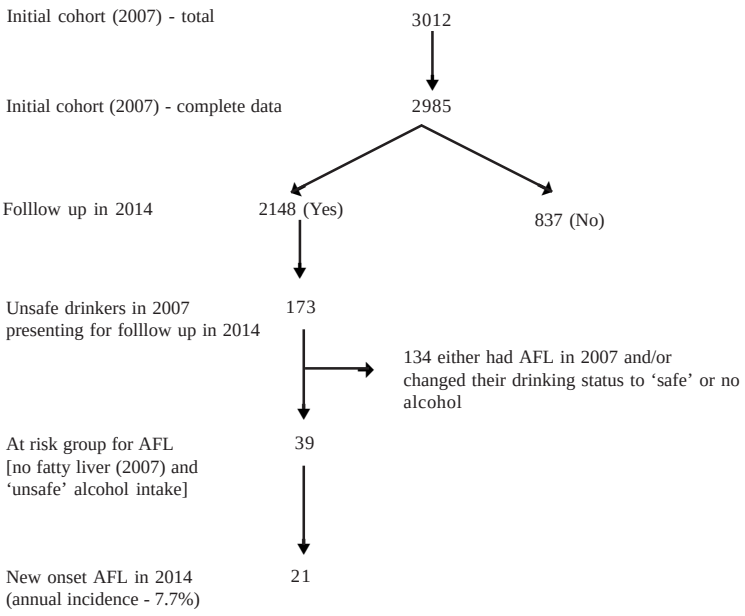

Figure 1.**Study population.**

Discussion

In this community-based study, unsafe alcohol intake was seen in 9.1%, and the problem was almost exclusively in males at baseline and follow up. Among unsafe drinkers, the annual incidence of AFL was 7.7%. Only male gender was significantly associated with the development of new-onset AFL. Of those with AFL at baseline and changed their drinking status from unsafe to safe or no alcohol, few had resolution of the fatty liver after seven years.

Unsafe alcohol consumption was almost exclusively seen among males in our cohort. Men are more likely to engage in alcohol use and are at a much greater risk of developing alcohol use disorder (AUD) than women worldwide [11]. In Asian countries, women are known to abstain from using alcohol due to social and cultural reasons [12]. The unsafe alcohol consumption rate observed in the present study is slightly higher than previous reports from urban community surveys in Sri Lanka (9.1 vs 5.2% and 6.2%) [13,14]. The estimates of the WHO Global status report on alcohol and health (which used data from the WHO global survey on Alcohol and Health (2012) in addition to other surveys conducted in the respective countries) estimated the 12-month prevalence of AUD among men in Sri Lanka to be 5.6% [15].

The community prevalence of AFL in the present study was 2.9%. The reported median prevalence of AFL in China is higher at 4.5% [16]. We could find no other reports of community prevalence data on AFL. The prevalence of AFL contrasts with the wealth of data available regarding the global and regional burden of non-alcoholic fatty liver disease [17].

We invited individuals who had AFL at baseline to periodically (every six months) visit a community-based clinic for reinforcement of healthy lifestyle practices to abstain from unsafe alcohol use. However, those with AFL at baseline attended these clinics very infrequently.

The male gender was significantly associated with new-onset ALF. We also found that the central obesity, over-weight state and raised ALT (> 2 × upper limit normal) were independently associated with AFL at baseline. However, the baseline over-weight state and central obesity were not associated with new-onset AFL. Some observational studies have suggested that being overweight is an independent risk factor for the development of ARLD [18, 19]. However, the Dionysos Study, a large cohort study on the prevalence of alcohol habits and chronic liver disease in the general population from Italy, did not report an association between body weight or body mass index and risk of ARLD [20].

We observed that metabolic abnormalities such as centrally obesity, over-weight, or DM and raised TG at baseline were associated with AFL. However, of the metabolic abnormalities, only central obesity and over-weight status were independently associated with AFL at baseline. The independent association of central and general obesity with AFL raises the possibility of the disease being NAFLD and AFL overlap. This is in agreement with the new proposed definition of fatty liver disease. A consortium has proposed the term metabolic (dysfunction) associated fatty liver disease (MAFLD) as a more appropriate nomenclature for this disease, and a simplified and easily applicable scheme for redefining fatty liver disease [21].

There have been no previous prospective community-based studies from emerging economies that report on new-onset AFL. The strengths of the present study include the robust design and that over 70% of the relatively large baseline population presented for re-evaluation. One limitation is that information on alcohol consumption was obtained only by direct questioning the participants. This may have led to under-reporting with consequent underestimation of the prevalence and incidence of AFL in both the inception and follow up cohorts. Although multivariate analysis was performed to determine the factors associated with AFL at baseline, only bivariate analysis was performed to determine the factors associated with new-onset AFL at follow-up given the small numbers observed. The initial cohort also comprised predominantly of Sinhalese (96.2%) and only a small proportion of other ethnicities (Tamils 1.3%, Muslims 1.3%, Burghers 1.3%) [14]. Therefore, we could not analyse any ethnic variability in the occurrence of AFL. Only the ALT was measured among the participants, and aspartate aminotransferase (AST) was not measured due to a lack of funds. Having both AST and ALT would have helped assess alcohol-induced liver injury among the ALF group. We could not investigate liver-related outcomes of those detected to have AFL at baseline due to a lack of resources.

In conclusion, in this prospective, community-based study among adults, we observed unsafe drinking almost exclusively in males. Unsafe alcohol use was seen in 9.1% of the study population. The prevalence of AFL among unsafe alcohol users was 31.6%, and after 7 years of follow-up, the annual incidence of AFL among unsafe drinkers was 7.7%. AFL at baseline was associated with male gender, over-weight state and central obesity. New onset-AFL was only associated with male gender.

List of abbreviations

AFL - alcoholic fatty liver

ALT - alanine aminotransferase

AST - aspartate aminotransferase

AUD - alcohol use disorder

ARLD - alcohol related liver disease

ASH - alcoholic steatohepatitis

CLD - chronic liver disease

HBV - hepatitis B virus

HCV - hepatitis C virus

LEL - low education level

NAFLD - for non-alcoholic fatty liver disease

RHS - Ragama Health Study

TG - triglycerides

Declarations

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Author contributions

MAN, and HJdeS conceptualised and developed the methodology of the study. HJdeS supervised the study and acquired the funds along with NK. AK, SdeS, MAN, ARW and HJdeS were involved in the establishment of the Ragama Health Study cohort and its follow up. AK was the project administrator. SdeS and ASD was involved in the investigation and data collection. AP, AK and TUB was involved in the formal analysis of the data assisted by MAN and HJdeS. MAN and AP prepared the original manuscript. HJdeS, ASD, AK, RW and NK were substantially involved in review and editing of the manuscript. All authors checked the final manuscript before submission.

Conflicts of interest

The authors declare no conflicts of interest.

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Availability of data and materials

The de-identified datasets used and analysed during the current study are only available from the corresponding author on prior request, after notification to and approval of the ERC, Faculty of Medicine, University of Kelaniya, Sri Lanka.

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