From NAFLD to MAFLD: characterising fatty liver disease in Sri Lanka

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is defined as hepatic steatosis detected either on imaging or histology in the absence of secondary causes, especially unsafe alcohol use.[1] It is an umbrella term covering a spectrum of diseases ranging from simple non-alcoholic fatty liver (NAFL) (i.e. fat deposition with no or mild inflammation, but no fibrosis) to non-alcoholic steatohepatitis (NASH) (i.e. fat deposition with inflammation and hepatocellular injury, with or without fibrosis) to established cirrhosis.[1]

Most NAFLD subjects are likely to have one or more features of metabolic syndrome (MetS) such as obesity, type 2 diabetes mellitus (T2DM), hypertension and dyslipidemia.[2] Therefore, at present, there is an ongoing debate whether a new, proposed disease acronym, MAFLD [metabolic (dysfunction)-associated fatty liver disease], instead of NAFLD, is more suited for the description of fatty liver disease.[3] While NAFLD definition requires excluding secondary causes of the fatty liver such as unsafe alcohol use, MAFLD definition requires the fatty liver to be associated with either overweight or obesity or T2DM or the presence of two or more minor metabolic features.[3] Therefore, MAFLD is more descriptive, inclusive and encompasses the associated metabolic dysfunction of hepatic steatosis than NAFLD.

Parallel to the rapid increase in obesity and diabetes worldwide, NAFLD has become the leading cause of chronic liver disease worldwide.[2] The worldwide prevalence of NAFLD is estimated to be 24%.[2] A community prevalence of 32.6% for NAFLD in an urban, adult Sri Lankan population was reported using stringent ultrasound criteria.[4] However, further characterisation of NAFLD in South Asian people, including Sri Lanka, was lacking using data from prospective, community-based cohort studies.

The Ragama Health Study (RHS) is an ongoing, large, community-based cohort study on non-communicable diseases in Sri Lanka.[4] 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. We conducted a series of studies within the RHS cohort to characterise NAFLD in this urban, adult, Sri Lanka population with up to 10-years of follow up.

The findings related to 1) the incidence and risk factors for incident NAFLD, 2) characteristics of lean-NAFLD, 3) the non-resolving nature of NAFLD in the absence of sustained lifestyle modification, 4) MetS as a critical, independent risk factor for mortality associated with NAFLD, 5) the outcome of NAFLD compared to MAFLD and 6) clinical utility of accurate ultrasound grading of NAFLD are presented in this manuscript.

Studies

RHS study (2007, 2014 and 2017)

The study was conducted in the Ragama Medical Officer of Health (MOH) administrative area situated 18 km north of Colombo. Ragama MOH area has urban

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characteristics and a multi-ethnic population. The study population consisted of 35 to 64-year-old adult residents, initially selected by age-stratified random sampling from electoral lists in 2007. The target population screened initially in 2007 was invited back after 7-years for the first follow-up for re-evaluation in 2014. They were also traced after 10-years for the second follow-up for assessing all-cause mortality (ACM) and fatal [cardiovascular mortality (CVM)] and non-fatal cardiovascular event (CVEs) in 2017.

In 2007 at inception and at first follow-up, in 2014, all participants were invited to attend a data collection clinic. During the visit, each participant was assessed using a structured interview, review of medical records, determination of clinical and anthropometric variables, liver ultrasound, and biochemical and serological tests. In 2017, the participants or their households were contacted by telephone or post. In death, the cause was confirmed by home visits and examination of death certificates.

Ethical approval for the study was obtained from the Ethics Review Committees of the Faculty of Medicine, University of Kelaniya. Informed written consent was obtained from all participants at inception and at a 7-year follow-up. Verbal and implied consent was obtained from respondents during the 10-year follow-up.

Observations

1. Incidence and risk factors for non-alcoholic fatty liver disease

The incidence rate and the risk factors for developing new-onset NAFLD were lacking from the South Asian region. This study reports an annual incidence of NAFLD of 6.2% from Sri Lanka.[5] There was a significant independent association of new-onset NAFLD with metabolic trials (MTs) such as central (OR 3.82) and general obesity (OR 3.26), presence of diabetes (OR 2.14) and raised TG (OR 1.96) at baseline. New-onset NAFLD was also independently associated with an increase in weight (5-10%) (OR 5.70) and an increase in the waist (>5%) (OR 2.46) after 7-years. A tendency of the association at PNPLA3 (rs738409) gene polymorphism with incident NAFLD was observed after the 7-year follow-up, similar to the finding for prevalent NAFLD.

The present study is the first prospective follow-up of a large community cohort to report NAFLD incidence and risk factors. This study highlights the growing burden of NAFLD in the community in emerging economies such as Sri Lanka. With the already high prevalence, the confirmed high incidence of NAFLD, and the predicted increase of underlying risk factors, predominantly obesity and diabetes, an increased burden of chronic liver disease due to NAFLD could be expected in Sri Lanka in the future.

2. Lean non-alcoholic fatty liver disease (Lean-NAFLD): characteristics, metabolic outcomes and risk factors

Most patients with NAFLD are overweight (BMI≥23 kg/m^2) or obese (BMI≥25 kg/m^2) (non-lean NAFLD). However, some patients with NAFLD are lean (BMI<23 kg/m^2). There has been an increasing clinical interest in this group of patients. A high index of suspicion is needed not to miss individuals with lean-NAFLD.

In a cohort of adults living in an urban Sri Lankan community, the prevalence of lean-NAFLD was 4% in 2007 and 13.2% in 2014.[6] After 7-years of follow-up, the annual incidence of lean-NAFLD was 4.1%. Lean-NAFLD was commoner among males ($p<0.001$) and had a lower prevalence of hypertension ($p<0.001$) and central obesity ($p<0.001$) than their non-lean NAFLD counterparts at baseline. Lean-NAFLD had a similar risk to non-lean NAFLD for developing incident metabolic co-morbidities at follow up. Logistic regression identified the presence of diabetes (OR 5.40) at baseline, increase in weight (OR 2.53) from baseline to follow-up and a higher educational level (OR 2.84) as independent risk factors for the development of incident lean NAFLD. NAFLD association of PNPLA3 (rs738409) gene polymorphism was more pronounced among lean individuals (one-tailed $p<0.05$) compared to the whole cohort sample.

Although lean-NAFLD constitutes a small proportion of NAFLD, this study's findings suggest that individuals with lean-NAFLD are also associated with adverse incident metabolic traits and warrant careful evaluation and follow-up.

3. Non-resolution of non-alcoholic fatty liver disease (NAFLD) in the absence of sustained lifestyle modification

NAFLD tends to persist in the absence of aggressive lifestyle modification. We did not find complete ultrasound resolution of NAFLD after 7-years in this prospectively followed-up general population cohort known to have a high prevalence and incidence of NAFLD, metabolic syndrome and obesity, who did not undergo a sustained lifestyle modification programme.[7]

Although there were statistically significant improvements in some anthropometric, clinical and biochemical measurements [reductions in weight

(1.6%), WC (2.2%), WHR (5.2%), SBP (2.2%), TG (11.9%), HDL (2%), TC (11.4%)] among those with NAFLD after a 7-year follow up, they were inadequate for the complete resolution of NAFLD.

The reductions in weight and WC achieved during follow-up in the absence of a structured lifestyle modification program were inadequate for the complete resolution of NAFLD. Therefore, more intense, sustained, personalised lifestyle interventions are necessary to achieve more significant improvements in anthropometric measurements and for the full resolution of NAFLD.

4. Metabolic syndrome, but not the non-alcoholic fatty liver disease, increases 10-year mortality

In this community-based study, in an urban population in Sri Lanka, we compared mortality between those with and without NAFLD. On Cox-regression analysis, we found that increasing age (>55-years) (HR 7.32, HR 11.13), male sex (HR 2.17, HR 2.15) and MetS, (HR 1.82, HR 2.57) but not NAFLD, were risk factors for ACM and CVM respectively, after 10-years of follow-up[8]. Among those with NAFLD, MetS (HR 2.25) and age>55-years (HR 2.48) were associated with ACM, while MetS (HR 5.81) and male sex (HR 3.42) were associated with CVM.

This study highlights the importance of identifying NAFLD patients who are metabolically active, as this predicts a poor outcome but provides an opportunity for corrective interventions to reduce future CVM.

5. Outcomes of NAFLD and MAFLD

We recently described the results of a prospective, community-based cohort study in suburban Sri Lanka, evaluating new-onset MTs and CVEs after a 7-year follow up among patients defined as NAFLD and MAFLD vs controls without hepatic steatosis.[9] At baseline, out of study participants with hepatic steatosis, 87.7% met both definitions, 2.9% met the definition of MAFLD but not NAFLD (fatty liver with metabolic abnormality and alcohol use), and 1.3% met the definition of NAFLD but not MAFLD (lean- NAFLD without metabolic dysregulation) out of the total population.

Anthropometry and MTs were similar in the NAFLD and MAFLD groups at baseline. However, at follow-up after 7-years, the risk of new-onset MTs and fatal/non-fatal CVEs was identical in the two groups but significantly higher in both these groups than controls. However, at follow-up after 7-years, those excluded by the NAFLD definition but captured by the MAFLD definition showed higher baseline MTs than those excluded by the MAFLD definition but captured by the NAFLD definition had a substantially higher risk for having new-onset MTs and CVEs compared to controls.

To our knowledge, this is the first longitudinal study to examine the clinical utility of the newly proposed MAFLD definition in a real-world setting. Although it increased the index population by only a small proportion, redefining NAFLD as MAFLD seemed to improve clinical utility.

6. The clinical utility of accurate NAFLD ultra-sound grading

We evaluated the utility of increased hepatic echogenicity alone (intermediate) compared to using additional criteria, which included signal attenuation and/or vascular blunting along with the increase of hepatic echogenicity (moderate-severe), to diagnose fatty liver in NAFLD.[10] We compared the two radio-logically defined groups to choose a classification method for NAFLD, which may better predict baseline adverse MTs, and incident adverse MTs and CVEs after 7-years of follow-up.

Both intermediate and moderate-severe degrees of NAFLD diagnosed by B-mode ultrasound was associated with abnormal MTs at baseline. In contrast, only moderate-severe NAFLD predicted incident adverse metabolic features except for elevated triglycerides and CVE. Although “intermediate” NAFLD did not predict incident adverse MTs, it was associated with prevalent adverse anthropometric indices and MTs, thereby identifying individuals who need medical intervention. Therefore, we recommend using increased hepatic echogenicity, not only the more stringent criteria (which include signal attenuation and vascular blunting), to diagnose fatty liver in individuals with NAFLD.

Conclusions

The RHS cohort’s follow-up has enabled us to characterise NALFD in the Sri Lankan population better. NAFLD is on the increase in Sri Lanka. With confirmed high prevalence and incidence, and an increased burden of NAFLD related chronic liver disease can be expected in Sri Lanka in the future. Therefore, a high index of suspicion is needed not to miss individuals with lean-NAFLD. Although lean-NAFLD constitutes a small proportion of NAFLD, individuals with lean-NAFLD also warrant careful evaluation and follow-up.

NALFD tends to persist in the absence of aggressive lifestyle modification. Small reductions (<5%) in weight and WC are inadequate for the complete resolution of NAFLD. More intense, sustained, personalised lifestyle interventions are necessary to achieve more significant improvements in anthropometric measurements that may lead to the full resolution of NAFLD.

The presence of MetS increases the risk of ACM and CVM among those with NAFLD. This supports the proposed new definition for fatty liver, MAFLD, replacing NAFLD. Unfortunately, MAFLD was able to increase the index population by only a small proportion compared to NAFLD. However, redefining NAFLD as MAFLD seemed to improve clinical utility by including those excluded by NAFLD definition with higher baseline MTs and a substantially higher risk of new-onset MTs and CVEs than controls.

There is the clinical utility of increased hepatic echogenicity alone (intermediate) compared to using additional criteria that include signal attenuation and/or vascular blunting and increase of hepatic echogenicity (moderate-severe) to diagnose fatty liver in NAFLD as it identifies further individuals who need medical intervention.

The knowledge gained through the findings of RHS on NAFLD in this population will invariably help tackle the present and future burden of NAFLD not only in Sri Lanka but the whole of the South Asian Region.

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