

# Magnitude of Non-alcoholic Fatty Liver Disease in South East Asia Region

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## ABSTRACT

**Background:** Non-alcoholic Fatty Liver Disease (NAFLD) is a recognised public health problem in the developed world. The prevalence of NAFLD is escalating in developing countries along with increased prevalence of metabolic syndrome. Limited medical literature on NAFLD is contributed by American and European countries which may not be generalizable to Asians. Hence, it is important to study the Asian experience, particularly South-East Asian region (SEAR) with respect to NAFLD for better understanding. **Methods:** All published articles in the MEDLINE database on NAFLD in South-East Asia were included. The important findings were summarized and critically analysed. **Results:** Prevalence of NAFLD in the SEAR region ranges from 8.0% to 77.0%. NAFLD in South east Asia was associated with metabolic syndrome particularly obesity and insulin resistance. 'Lean NAFLD' is a novel concept that describes NAFLD among non-obese individuals. **Conclusion:** NAFLD is an emerging problem in South-east Asia. This review summarizes the prevalence of NAFLD in SEAR region and discusses the implications of these findings. Further population-based studies on prevalence and incidence are required on obese and lean NAFLD to quantify the magnitude of the disease in SEAR for better management of the condition.

**Keywords:** NAFLD; NASH; Asia; South-East Asia; India; Sri Lanka, Bangladesh; Indonesia

## Introduction

Non-alcoholic fatty liver disease (NAFLD) is a broad-umbrella term to describe a spectrum of conditions ranging from hepatic steatosis to steatohepatitis either identified by imaging or histological analysis [1]. The definition of NAFLD also includes the elimination of other secondary causes of hepatic steatosis including viral hepatitis (e.g., Hepatitis C), various inborn errors of metabolism (e.g., lecithin-cholesterol acyltransferase deficiency, cholesterol ester storage disease, Wolman's disease), auto-immune disorders (e.g., Wilson's disease), parenteral nutrition, chronic use of steatogenic medications (e.g., mipomersen, lomitapide, amiodarone, methotrexate, tamoxifen, corticosteroids) and significant alcohol consumption (daily intake of alcohol up to  $\geq 30$  g for men and  $\geq 20$  g for women) [1–3].

NAFLD majorly includes two pathologically distinct states with different prognoses- non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH). NAFL is a condition characterised by the presence of  $\geq 5.0\%$  hepatic steatosis in absence of any

evidence of hepatocellular injury whereas NASH is characterised as inflammation with hepatocyte injury with or without fibrosis in addition to  $\geq 5.0\%$  hepatic steatosis [1–3]. NASH is described to consist of various disease conditions ranging from mild-stage fibrosis to end-stage conditions like cirrhosis and hepatocellular carcinoma (HCC) [3].

The natural history of NAFLD is under active investigation. Few groups of researchers suggest that the progression from steatosis to NASH is not following a linear curve rather it is more dynamic and exponential as the stage of fibrosis increases. The fibrosis progression rate in NAFL is estimated to be 14 years per stage of fibrosis whereas in NASH it is estimated to be 7 years per stage of fibrosis. The fibrosis progression rates varies from person to person indicating NAFLD being a complex disorder affected by interactions of environmental and genetic factors [4–6]. The heritable component of this hepatic disease, has a heritability ranging from 22.0% to 38.0% [7–9]. Despite NAFLD having genetic predisposition, environmental factors like dietary habits, physical activity, ethnicity, locality and metabolic risk factors of

the various regions can't be overlooked [19].

Both the genetic and environmental factors vary across the globe, so as the prevalence of the disease. The epidemiology of NAFLD varies between regions and within regions. The western countries have considered NAFLD as one of the growing epidemics in their regions and are formulating effective policies and population-level measures to address them whereas Asian countries are yet to recognise NAFLD epidemic in their regions, despite having similar prevalence [11].

It is important to recognise, though there is emerging importance of NAFLD in Asia but most of the medical literature on hepatic disease is contributed by the data on patients of American and European descents. These Western literatures may very well explain few traditional risk factors in Asian counterparts but different clinical profiles and outcomes of the disease are expected based on their regional variability. Hence, it is important to study the prevalence of modifiable and non-modifiable risk factors specifically metabolic risk factors, including obesity, diabetes, and metabolic syndrome among NAFLD patients in Asia. Furthermore, recent studies have also suggested that NAFLD can also affect apparently non-obese Asians commonly referred as the 'Asian Paradox' [12-13].

In this review, we look specifically at South-East Asians affected with NAFLD. South-East Asia region (SEAR) comprises of approximately 25.0% of world's total population and is a growing epicentre for NAFLD. The SEAR encompasses of 11 countries - India, Nepal, Bhutan, Bangladesh, Sri Lanka, Maldives, Thailand, Myanmar, Indonesia, Timor Leste and Democratic People's Republic of Korea (DPRK). The available data from these countries remains limited. Hence, the importance of gaining a better and complete understanding of NAFLD in this region is essentially important in view of its growing population and migration to Western nations. In this review, we describe the prevalence of NAFLD in SEAR and further describe the NAFLD phenotype with respect to 'lean NAFLD in the region..

## Method

Article search in the online Medline database (Medical Literature Analysis and Retrieval System) was performed using MeSH (Medical Subject Headings) terms: 'Non-alcoholic Fatty Liver Disease'. The search was limited to English language. The above results were further narrowed down by adding the names of each country in the SEAR region (India, Nepal, Bhutan, Bangladesh, Sri Lanka, Maldives, Thailand, Myanmar, Indonesia, Timor Leste and Democratic People's Republic of Korea (DPRK)). Since India had a large number of studies, we further narrowed down the studies by adding the MeSH term 'Epidemiology'. We accessed full text articles of the included studies. We didn't perform a formal systematic analysis due to large variations in study

designs. The available data were summarized and presented in the tables categorized by country.

## Global magnitude of the problem

NAFLD is highly prevalent in all regions of the world with global prevalence estimated through recent meta-analysis is 25.2% (95%CI=22.1-28.6). There is noticeable variation observed in the prevalence of NAFLD across the regions. The highest prevalence of NAFLD is reported from the Middle East regions (31.7% (95% CI=13.4- 58.2)) and South American regions (30.4% (95% CI=22.7-39.4)) followed by Asia (27.3% (95%CI=23.2-31.88)), North America (24.1%(95%CI=19.7-29.1)) and Europe (23.7% (95%CI=16.1-33.4)). The lowest prevalence is reported from African countries as 13.4% (95%CI=5.6- 28.6) [11-14]. However, these estimates may be underestimation as the Ultrasound was the most common method for diagnosing NAFLD and it has been found that accuracy of ultrasound is inferior to liver biopsies. The liver biopsy being the 'gold standard' for diagnosing the NAFLD is neither feasible nor ethical to use in apparently healthy and asymptomatic people. Absence of simple and non-invasive diagnostic tests are a big hurdle in getting the true epidemiology of the disease.

The global prevalence of NASH is estimated to be 1.5–6.4% in the general population whereas prevalence of NASH among biopsy confirmed NAFLD cases was 59.1% (95%CI= 47.5-69.7). Less inconsistency was seen in the pooled regional NASH prevalence estimates among NAFLD patients with an indication for biopsy. NASH prevalence among NAFLD cases among Asians were 63.4% (95%CI=47.6-76.7), Europeans were 69.2% (95%CI=55.9-79.9) and Americans were 60.6% (95%CI=49.5-70.7) [11, 14].

In contrast to the prevalence data, there is a significantly fewer number of publications describing the incidence of NAFLD in the general population. It has been estimated that the incidence of NAFLD also varies across the world as prevalence estimates, ranging from 28.01 per 1000 person-years (95%CI=19.3-40.5) to 52.34 per 1000 person-years (95%CI=28.3-96.7) [14-16].

## Magnitude of the problem in SEAR

The pooled prevalence of NAFLD in Asia was documented as 29.6% (95%CI=28.1–31.1), regardless of diagnostic method used. The prevalence of NAFLD in Asian countries is greatly wavering, ranging from 22.2 % in Japan to 51.0% in Indonesia [17]. A pooled analysis from Mainland China reported a prevalence of 20.0% (95%CI=17.9-22.3) [18]. Several small population-based studies suggested variation in the prevalence estimates of NAFLD South-East Asian nations. The highest prevalence has been reported from Thailand as 76.8% whereas lowest prevalence was reported from Indonesia as 7.9% [19, 20] (Table 1).

**Table 1** Prevalence of NAFLD in South-East Asia

| Year              | Author                  | Study           | Setting         | Sample size | Male:Female | Population                     | Prevalence | Mode of diagnosis |
|-------------------|-------------------------|-----------------|-----------------|-------------|-------------|--------------------------------|------------|-------------------|
| <b>Bangladesh</b> |                         |                 |                 |             |             |                                |            |                   |
| 2019              | Khan et al              | Cross-sectional | Hospital-based  | 334         | 148/334     | Apparently Healthy             | 44.3       | Ultrasound        |
| 2019              | Khan et al              | Cross-sectional | Hospital-based  | 100         | 58/42       | T2DM                           | 67         | Ultrasound        |
| 2018              | Kabir et al             | Cross-sectional | Hospital-based  | 258         | -           | T2DM                           | 64.7       | Ultrasound        |
| 2018              | Alam et al              | Cross-sectional | Community-based | 2782        | 1694/1088   | Apparently Healthy             | 33.86      | Ultrasound        |
| 2017              | Saha et al              | Cross-sectional | Hospital-based  | 1019        | 316/703     | Apparently Healthy             | 18.5       | Ultrasound        |
| 2017              | Hossain et al           | Cross-sectional | Hospital-based  | 140         | 77/63       | Pre-diabetic                   | 53.4       | Ultrasound        |
| 2017              | Alam et al              | Cross-sectional | Community-based | 2621        |             | Apparently Healthy             | 34.34      | Ultrasound        |
| 2015              | Hossain et al           | Cross-sectional | Hospital-based  | 110         | 63/47       | Pre-diabetic                   | 43.6       | Ultrasound        |
| 2015              | Rahman et al            | Cross-sectional | Community-based | 789         | 277/512     | Apparently Healthy             | 18.4       | Ultrasound        |
| <b>DPRK</b>       |                         |                 |                 |             |             |                                |            |                   |
| 2009              | Lee et al               | Cross-sectional | Hospital-based  | 13621       | 7221/6400   | Apparently Healthy             | 26.2       | Ultrasound        |
| <b>Nepal</b>      |                         |                 |                 |             |             |                                |            |                   |
| 2019              | Paudel et al            | Cross-sectional | Community-based | 573         | -           | -                              | 70.1       | Ultrasound        |
| 2018              | Mandal et al            | Cross-sectional | Hospital-based  | 210         | 119/91      | T2DM                           | 55.7       | Ultrasound        |
| 2015              | Wang et al              | Cross-sectional | Community-based | 9360        | 0/9360      | Women                          | 12.8       | BAAT/Ultrasound   |
| 2011              | Mittal et al            | Retrospective   | Hospital-based  | 515         | -           | -                              | 17.08      | Raised ALT        |
| <b>Thailand</b>   |                         |                 |                 |             |             |                                |            |                   |
| 2019              | Tantanavipas et al      | Cross-sectional | Hospital-based  | 63          | 0/63        | PCOD                           | 49.2       | Ultrasound        |
| 2017              | Saokaew S et al         | Cross-sectional | Hospital-based  | 509         | 232/277     | Metabolic yndrome              | 76.8       | Ultrasound        |
| <b>Sri Lanka</b>  |                         |                 |                 |             |             |                                |            |                   |
| 2019              | Niriella et al          | Cohort study    | Community-based | 2985        | -           | Apparently Healthy             | 32.6       | Ultrasound        |
| 2019              | Herath et al            | Cross-sectional | Hospital-based  | 573         | 0/573       | Pregnant women                 | 18.2       | Ultrasound        |
| 2019              | Herath et al            | Cross-sectional | Hospital-based  | 233         | 110/123     | T2DM                           | 62.6       | Ultrasound        |
| 2018              | Bulathsinhala et al     | Retrospective   | Hospital-based  | 550         | 473/77      | Hepatocellular carcinoma       | 56         | Liver Biopsy      |
| 2017              | Rajindrajith et al      | Cross-sectional | Community-based | 499         | 236/263     | Adolescent                     | 8.4        | Ultrasound        |
| 2017              | Niriella et al          | Cohort study    | Community-based | 2985        |             | Apparently Healthy             | 32.6       | Ultrasound        |
| 2016              | Perara et al            | Cross-sectional | Hospital-based  | 120         | 75/45       | Acute coronary syndrome        | 46.7       | Ultrasound        |
| 2015              | Kasturiratne et al      | Cohort study    | Community-based | 3002        | 1343/1659   | Apparently Healthy             | 32.6       | Ultrasound        |
| 2014              | Silva et al             | Cross-sectional | Hospital-based  | 34          | 25 / 9      | Liver Donors                   | 44.8       | Ultrasound        |
| 2011              | Pinidiyapathirage et al | Cross-sectional | Community-based | 403         | 189/212     | Rural population               | 18         | Ultrasound        |
| <b>Indonesia</b>  |                         |                 |                 |             |             |                                |            |                   |
| 2019              | Hazim et al             | Cross-sectional | Community-based | 118         | -           | First Degree relatives of T2DM | 22.03      | Ultrasound        |
| 2013              | Cahyono et al           | Cross-sectional | Community-based | 2105        | 185/43      | Apparently Healthy             | 7.9        | Ultrasound        |

The systematic review suggested the significant increase in the prevalence of NAFLD during a period of two decades. The prevalence of NAFLD increased from 25.8% (95%CI= 22.4–28.3) between 1999 and 2005 to 33.9% (95%CI=31.74–36.12) between 2012 and 2017 [17]. In contrast to prevalence, there are scanty data on the incidence of new-onset NAFLD in Asia. The pooled annual NAFLD incidence rate were found to be 50.9 cases per 1000 person-years (95%CI=44.8–57.4) [17].

### *Bangladesh*

A study on apparently healthy population with mean age  $40.1 \pm 12.2$  years reported that the prevalence of NAFLD is 44.3%. The prevalence was found to be highest in the age group 40–60 years (59.3%). Though the prevalence of metabolic syndrome was 27.2% in general population but higher prevalence was reported in NAFLD group (61.5%) [21]. In comparison to this, study from rural Bangladesh displayed overall prevalence of NAFLD to be around 18.4% [22]. This

variation in the prevalence of the disease can either be underestimation of the disease in the rural setting or an overestimation in tertiary clinic due to referral bias. A community-based study, one of the largest studies on NAFLD from Bangladesh, reported the prevalence to be 34.0% and the common age of presentation of NAFLD was found to be 30-50 years. Furthermore, NAFLD was also noted to be more common in people having known metabolic risk factors, with a highest prevalence of NAFLD in diabetics as 71.0% and among hypertensives was 62.8% [23]. A study on Bangladeshi immigrants in London showed an increased susceptibility to developing NAFLD as compared to Caucasians [24]. Other studies from the region mentioned the prevalence of the disease ranges from 18.4 % to 44.3% [22-26]. Further future population-based studies are needed to understand the risk of NAFLD to the country.

#### Bhutan

To the best of our knowledge, there are no studies from Bhutan describing the epidemiology of NAFLD. A country with 8 lakh population reported low levels of physical activity in 52.3% of the general population and 65.3% among diabetics. Moreover, self-reported prevalence of hypertension was 17.4% in general population and 44.7% among diabetics [27]. Approximately, 65.0% of the female population was

found to be overweight and obese and about 69.0% of the women had a waist circumference >80 cm indicating abdominal obesity [28]. Though, there is limited data from the country but increased prevalence of obesity, diabetes, hypertension and reduced physical activity can contribute to high prevalence of NAFLD when investigated.

#### DPRK

A single but large hospital-based study is available from the nation. The prevalence of hepatic steatosis diagnosed by ultrasonography in absence of alcohol consumption was 26.2% in Korea among who visited a health check-up centre. The prevalence of metabolic syndrome in the same population was found to be approximately 18.0% with 35.0% of population having BMI above 25kg/m<sup>2</sup>. The study also reported the risk of NAFLD to be 1.8 times higher in males (35.0%) as compared with females (16.3%) [29].

#### India

India contributes approximately 72% of the population in the SEAR region and hence has the ability to manipulate the prevalence of the SEAR region accordingly. Several but small studies including hospital, community as well as rural and urban regions are available from India (Table 2).

| Year | Author          | Type of Study                                         | Region                 | Location | Setting             | Sample size | Study population                                                    | Prevalence                           | Mode of diagnosis                                              |
|------|-----------------|-------------------------------------------------------|------------------------|----------|---------------------|-------------|---------------------------------------------------------------------|--------------------------------------|----------------------------------------------------------------|
| 2019 | Duseja A        | Cross-sectional                                       | Chandigarh             | Urban    | Hospital/Clinic OPD | 986         | Male Healthy Blood Donors                                           | 55.1                                 | Liver ultrasonography                                          |
| 2019 | Rajput R        | Cross-sectional                                       | Rohtak, Haryana        | Urban    | Hospital/Clinic OPD | 200         | Pre-diabetic                                                        | Prediabetics (59%) Vs controls (26%) | Liver ultrasonography and biochemical parameters               |
| 2019 | Varma S         | Cross-sectional                                       | South India            |          | Hospital/Clinic OPD | 60          | PCOS                                                                | 38.3                                 | Liver ultrasonography                                          |
| 2019 | Bhatt SP        | Cross-sectional                                       | New Delhi              | Urban    | Hospital/Clinic OPD | 240         | Overweight /Obese                                                   | 70                                   | Liver ultrasonography                                          |
| 2018 | Jain V          | Cross-sectional                                       | New Delhi              | Urban    | School based        | 218         | Adolescent (10-16 years)                                            | 62.5                                 | Liver ultrasonography                                          |
| 2018 | Vanjiappan S    | Cross-sectional                                       | Pondicherry            | Urban    | Hospital/Clinic OPD | 300         | T2DM                                                                | 61                                   | Liver ultrasonography                                          |
| 2017 | Choudhary NS    | Retrospectively analysed from a prospective database. | New Delhi              | Urban    | Hospital/Clinic OPD | 573         | Prospective donors (307 females)                                    | 49.2                                 | Liver ultrasonography and Liver attenuation index values       |
| 2016 | Pawar SV        | Cross-sectional                                       | Mumbai                 | Urban    | School based        | 616         | Adolescent (11-15 years)                                            | 62                                   | Liver ultrasonography, elevated serum transaminases, fibroscan |
| 2016 | Majumdar A      | Cross-sectional                                       | Ballabgarh, Haryana    | Rural    | Community           | 216         | Apparently Healthy and asymptomatic subjects                        | 30.7                                 | Liver ultrasonography                                          |
| 2015 | Anurag L        | Cross-sectional                                       | Maharashtra            | Rural    | Hospital/Clinic OPD | 410         | Apparently Healthy and asymptomatic subjects                        | 28.1                                 | Liver ultrasonography                                          |
| 2015 | Praveenraj P    | Cross-sectional                                       | Coimbatore, Tamil Nadu | Urban    | Hospital/Clinic OPD | 134         | Overweight /Obese                                                   | 65.7                                 | Liver Biopsy                                                   |
| 2014 | Vendhan R       | Cross-sectional                                       | Chennai, Tamil Nadu    | Urban    | Hospital/Clinic OPD | 736         | T1DM patients                                                       | 27.7                                 | Liver ultrasonography                                          |
| 2014 | Ajmal MR        | Cross-sectional                                       | Aligarh, Uttar Pradesh | Urban    | Hospital/Clinic OPD | 104         | Patients of coronary artery disease and hypertensive heart disease. | 69.2                                 | Liver ultrasonography                                          |
| 2013 | Kalra S         | Cross-sectional                                       | 101 cities in India    | Urban    | Hospital/Clinic OPD | 924         | T2DM                                                                | 56.5                                 | Elevated aminotransferase levels                               |
| 2012 | Madanagobalan S | Case-Control                                          | Chennai, Tamil Nadu    | Urban    | Hospital/Clinic OPD | 663         | Psoriatic patient and non-psoriatic population                      | 17.4                                 | Liver ultrasonography                                          |
| 2011 | Agarwal A       | Cross-sectional                                       | New Delhi              | Urban    | Hospital/Clinic OPD | 124         | T2DM                                                                | 57.2                                 | Liver ultrasonography                                          |

|      |               |                           |                       |       |                     |      |                                              |      |                                          |
|------|---------------|---------------------------|-----------------------|-------|---------------------|------|----------------------------------------------|------|------------------------------------------|
| 2010 | Das K         | Nested case-control study | West Bengal           | Rural | Community           | 1911 | Apparently Healthy and asymptomatic subjects | 8.7  | Liver ultrasonography and blood sampling |
| 2009 | Mohan V       | Cross-sectional           | Chennai, Tamil Nadu   | Urban | Community           | 541  | Apparently Healthy and asymptomatic subjects | 32   | Liver ultrasonography                    |
| 2007 | Amarapurkar D | Cross-sectional           | Mumbai, Maharashtra   | Urban | Community           | 1168 | Apparently Healthy and asymptomatic subjects | 14.6 | Liver ultrasonography                    |
| 2004 | Singh SP      | Cross-sectional           | Coastal eastern India | Urban | Hospital/Clinic OPD | 159  | Apparently Healthy and asymptomatic subjects | 24.5 | Liver ultrasonography                    |

Though there are several small-scale studies at community level in India from across the country. The community prevalence of NAFLD in India varies from 8.0% to 32.0%. The most common age of presentation is described to be 30 to 50 years in India [30]. Studies from rural India indicate the prevalence in apparently healthy people to range from 8.7% to 30.7%, whereas in urban areas it is ranging from 14.6% to 32.0% [30-33]. A study on apparently asymptomatic adults ranged between 24.0% -28.0% in few studies whereas a study on male blood donors depicted the prevalence to be 55.1% [34-36]. Moreover, the high prevalence in the later can be attributable to metabolic syndrome and its components [36]. Hence, it is difficult to estimate the true prevalence in the country based on the existing data.

Indian studies have shown that prevalence of NAFLD coincides with the prevalence of metabolic syndrome because most of the metabolic covariates of NAFLD are highly prevalent in Indians. The prevalence of metabolic syndrome in India based on prior study is 11.0% - 41.0% [37, 38]. Studies from hospitals or tertiary care units have reported the prevalence as low as 17.4% to as high as 70.0% in the country [39, 40]. These studies were conducted in high-risk groups like pre-diabetics, diabetics, females with PCOS, obese, hypertensives and psoriatic population. The highest prevalence was observed in obese population as 70.0% followed by patients of cardiovascular disease (69.2%) [40, 41]. A study conducted in New Delhi, documented NAFLD cases had significantly higher obesity parameters (BMI, waist circumference and hip circumference), fasting hyperglycemia, fasting hyperinsulinemia, hypercholesterolemia, and hypertriglyceridemia [42]. Another study demonstrated the strong association of NAFLD with high-sensitive C-reactive protein (hs-CRP), hypertension, and Metabolic syndrome in addition to other factors mentioned above [43]. There is paucity of longitudinal studies on the natural history of NAFLD and NASH in Indian patients, hence incidence of NAFLD can't be estimated.

In contrast to this, prevalence of NAFLD among Paediatric population is well explained. The prevalence in apparently healthy children including adolescents is 7.6% [44]. However, few regional studies across the country in obese population (approximately 60.0%) have shown approximately twice the prevalence of NAFLD when compared to the global obese paediatric population (approximately 34.0%) [45-49]. This is almost 8-folds more than the prevalence in apparently

healthy children. Moreover, there is absence of NAFLD among underweight children but a presence of NAFLD among large proportion of normal-weight children [49]. As these data indicate, it is important to recognize that NAFLD may also occur in normal-weight children, though less frequently than in overweight and obese group. The prevalence of NAFLD among urban pre-adolescents (children aged 5-10 years) is 22.4%. The prevalence of NAFLD increases as the child progresses from childhood to adulthood via adolescence [49].

### Indonesia

According to the Global Health Estimates-2015, NAFLD and other causes accounted for 17.4% of all deaths due to chronic liver diseases including NAFLD, and for 20.9% of those due to liver cancer [50]. Data on the prevalence of NAFLD have been rare in Indonesia (7.9%). The study demonstrated males are predominantly (81.1%) affected by NAFLD as compared to opposite sex. The average age of NAFLD patients were  $43.38 \pm 9.26$  years as compared to non-NAFLD patients ( $39.73 \pm 9.94$ ) ( $p$ -value=0.005) [20]. However, risk factors for NAFLD, specifically individual components of metabolic syndrome are prevalent and increasing in the country [51, 52].

Age-standardised estimates for non-communicable risk factors in Indonesian adults have shown a drastic increase from 1975 to 2014, particularly obesity and T2DM irrespective of the gender [51, 52]. Moreover, age-standardised estimates for obesity in paediatric and adolescent population have considerably increased from 0.1% to 7.1% in four decades. These children and adolescents are more susceptible to NAFLD in the future [53].

### Maldives

No studies from the country was found on NAFLD. The data on prevalence of NAFLD needs to be investigated in the county.

### Myanmar

No studies in general population was found from the region. One of the study characterizing liver disease suggested a 20.0% share of fatty liver in all liver etiologies [54].

### Nepal

Limited studies are available from the country. A study by Mittal et al reported the prevalence of NAFLD to be 17.0%. The study used non-invasive markers like AST and ALT to estimate the prevalence

retrospectively [55]. Data collected from 9360 adult females reported the prevalence of NAFLD as 12.8%. Furthermore, the women appearing menopause or reached menopause showed unfavourable risk factor indicating protective nature of estrogen towards NAFLD [56]. However, another community-based study with 573 subjects documented an exceptional high prevalence of 70.0%. The higher prevalence rate can be attributed to higher prevalence of metabolic syndrome in the population [57].

#### Sri Lanka

Several studies have been reported from Sri Lankan island. Prevalence of NAFLD among urban community dwellers is reported to be approximately 33.0%, which is higher than mean prevalence of Asia [58, 59]. In the same community, the incidence of NAFLD was found to be 6.2% and the incidence rate were influenced by general and central obesity, raised triglycerides and diabetes [60]. Some small hospital-based studies on pregnant females and liver donors stated a prevalence of 18.0% and 45.0% respectively [61, 62]. Studies in high-risk groups like diabetics and patients of acute coronary syndrome showed much higher prevalence of NAFLD indicating its association with metabolic derangements [63, 64]. Moreover, NAFLD induced cirrhosis is the most common and aggressive cause of hepatocellular carcinomas (56.0%) in a large Sri Lankan cohort [65]. The higher prevalence rates can be attributable to increased industrialization and reduced physical activity. However, a study on rural community which are more physically active depicted a prevalence of 18.0%, pointing a tendency of association with PNPLA3 gene polymorphisms [66]. Significant association of PNPLA3 (rs738409) polymorphism with susceptibility to NAFLD (OR=1.25; 95%CI=1.08-1.44) has been established in Sri Lankans [59].

Furthermore, the NAFLD is not only restricted to adults but also affect adolescents of the island. Prevalence of NAFLD was high in Lankan teenagers

(8.4%) as compare to global prevalence of NAFLD in adolescents. Metabolic derangements particularly obesity and insulin resistance and early cessation of breast feeding are few factors attributable to high prevalence of NAFLD among adolescents [67].

#### Thailand

There is lack of data on epidemiology of NAFLD in general population. However, few studies are available in special groups. A study on PCOS diagnosed women described the overall prevalence of NAFLD as 49.2% [68]. Another study showed a higher prevalence of NAFLD as 76.8% [19]. It is mainly attributable to population studied were diagnosed with metabolic syndrome. A study in another high-risk group estimated the prevalence of NAFLD as 60.7% in diabetics [69]. Significant liver fibrosis was found in 11.0% of psoriatics. Moreover, waist circumference, diabetes, and AST level were the independent predictors for development of NAFLD [70]. A community-based study among asymptomatic Thai population with predominately females in the study suggested a prevalence of 18.0%. Among NAFLD diagnosed cases, 18.4% demonstrated significant liver fibrosis and 2.6% has cirrhosis. In this study, male gender and history of dyslipidemia were identified as predictors of significant liver fibrosis in NAFLD [71]. Based on a baseline survey conducted in the north-eastern region of Thailand the prevalence of NAFLD in females was 22.9% (95%CI=22.5-23.5), whereas it was only 18.3% (95%CI=17.4-19.2) in males [72]. However, further studies in general population are required to estimate the accurate prevalence of NAFLD in the country.

#### Timor Leste

No studies for the nation could be extracted. Low prevalence of obesity suggests a lower prevalence of NAFLD in the nation but lean NASH may be more popular. To address the true prevalence, studies are to be undertaken in this country [73].

**Table 3** Prevalence of Lean NAFLD in South-East Asia

| Year | Author         | Country    | Study                     | Setting         | Sample size | Male : Female | Population                                   | Prevalence | Mode of diagnosis                        |
|------|----------------|------------|---------------------------|-----------------|-------------|---------------|----------------------------------------------|------------|------------------------------------------|
| 2010 | Das K et al    | India      | Nested case-control study | Community based | 1911        |               | Apparently Healthy and Asymptomatic subjects | 8.7        | Liver ultrasonography and blood sampling |
| 2019 | Niriella et al | Sri Lanka  | Cohort study              | Community based | 2985        |               | Asymptomatic                                 | 4          | Ultrasound                               |
| 2014 | Alam et al     | Bangladesh | Cross-sectional           | Hospital-based  | 119         | 62/57         | Obese/Non-obese                              | 25.6       | Liver Biopsy                             |

#### Prevalence of “Lean NAFLD”

Despite the strong relationship with obesity, NAFLD is known to affect non-obese individuals and the condition is commonly termed as ‘Lean NAFLD’ [74]. The prevalence of lean NAFLD varies from 7.0% in western countries to as high as 19.0% in Asian countries [74, 75]. Despite appearing to have lower BMI and obesity, significant prevalence of NAFLD is seen in the South Asians, this observation is known as

the ‘Asian Paradox’. This phenomenon is further hypothesized to be associated with ethnic disparities in distribution of visceral fat. The study further mentioned the blacks generally have more lean mass and less fat mass when compared to whites [76, 77]. Furthermore, fat distribution in both subcutaneous and total adipose tissues are found to be correlated with pathological severity of NAFLD in South Asians [78, 79]. Hence, screening obese people for NAFLD may not provide

the accurate estimates. Studies have shown that Asian people with lower BMI are also at increased risk of cardiovascular and metabolic diseases and are susceptible to develop insulin resistance as compared to individuals from Western countries [80].

It is important to note that there is no increased mortality in lean (or overweight) people with NAFLD as compared to age and sex-matched controls. However, prior studies in western countries have identified three prognostic indicators associated with mortality in lean NAFLD- older age, fibrosis stage, and hypertension [74]. However, these findings may not be generalizable to Asian descent because of different risk profile.

Limited evidences are available for describing the prevalence of Lean NAFLD in South-east Asia. However, based on available data, community prevalence of lean NAFLD ranges from 4.0% to 21.3% [81, 82] (Table 3). A study by Kumar et al in India reported that diabetes was less common among the lean NAFLD cases as compare to obese NAFLD cases (3.7% vs 26.0% respectively). Insulin resistance (HOMA-IR) is following the similar pattern among lean and obese NAFLD cases (7.4% vs 60.0% respectively). The mean age of presentation of NAFLD was almost similar between the obese and lean NAFLD cases. A noticeable point about the study includes disparity in degree of necro-inflammatory activity and stage of fibrosis, despite having similar incidence of dyslipidemia, steatohepatitis, and advanced fibrosis among lean and obese NAFLD cases [82]. A study from Bangladesh documented lean NAFLD cases are metabolically similar to obese, except they are non-obese by BMI grade [83]. A Sri Lankan study described the prevalence as 4.0% in a cohort study. The study demonstrated the risk of developing diabetes within 3 years of diagnosis of NAFLD increases 3 to 4 times, even among lean individuals [81].

### Way Forward

NAFLD represents only the tip of iceberg, what we see, whereas it reflects the ongoing devastating process inside the body, i.e., occurrence of Metabolic syndrome or increased risk for its occurrence in body with time if not properly managed at an early stage, which is essentially a preventable condition.

This review highlights the fact that the South-East Asians are at increased risk of having NAFLD and NASH. Further presence of the disease should be investigated even in non-obese individuals, as they are relatively more metabolically obese (Asian Paradox) and more prone to develop NAFLD as compared to other ethnic groups.

Therefore, the hepatic problem due to NAFLD needs to be addressed by each country in the region. Hence, understanding the magnitude of the problem is the first step towards the resolution of the problem which is at present, not available from almost all countries in the region. Therefore, ultrasound of

abdomen or other cost-effective non-invasive diagnostic tools should be included in the list of tests provided in government setup for early diagnosis of NAFLD. This will result in addressing the problem with necessary measures at an early stage in resource-constraint SEAR. Furthermore, early management of the disease will not only reduce the hepatic diseases but will also reduce the other metabolic disease in future.

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