Magnitude of Nonalcoholic Fatty Liver Disease: Western Perspective

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The incidence of nonalcoholic fatty liver disease (NAFLD) is continuing to rise worldwide, and it is estimated that this disquieting trend will continue for another 10–15 years before prevalence begins to decrease. NAFLD is the hepatic manifestation of metabolic syndrome. As obesity, diabetes, and other lifestyle-related diseases continue to rise, the spectrum of NAFLD, e.g., nonalcoholic steatohepatitis, liver fibrosis, liver cirrhosis, liver-related morbidity, and mortality, will increase in parallel. Its widespread prevalence and associated economic burden have drawn significant attention, and a multitude of pharmaceutical companies are participating in active research trying to find a "cure". Unfortunately, as of now, no targeted treatment exists to treat this condition, and therefore, emphasis has been on its prevention. The current review focuses on the epidemiology, clinical characteristics, risk factors, and clinical outcomes of NAFLD in Western countries. It is important to understand the magnitude of NAFLD and its risk factors in Western countries where the prevalence of NAFLD has now reached epidemic proportions to identify the best strategy to prevent and possibly control this epidemic. (J Clin Exp Hepatol 2019;9:497–505)

With the advent of highly effective medications to eradicate hepatitis C and control hepatitis B, nonalcoholic fatty liver disease (NAFLD) is marching ahead unabated to become the most common chronic liver disease throughout the world. With prevalence of obesity reaching around 40% in the United States, NAFLD, an obvious by-product of obesity, is increasing in parallel and will have far-reaching consequences that will put increased stress on the health-care system in the years to come.[1] This review article will focus on the magnitude, prevalence, racial distribution, long-term outcomes, rising economic/health-care burden, and impact of NAFLD on liver transplantation and mortality associated with it in the Western world. Worldwide prevalence of NAFLD diagnosed through imaging is 25%, and nonalcoholic steatohepatitis (NASH) is estimated to be around 3–4%. Highest prevalence is found in the Middle East (32%) and South America (31%), while its lowest prevalence is in Africa (14%).[2] NAFLD prevalence varies significantly depending on the country, race, and ethnicity.

Prevalence of NAFLD in the Western World

In the United States, 64 million people are estimated to have NAFLD; of which, 6.65 million have NASH.[2,3] There were estimated 232,000 cases of incident NASH reported in 2017 in the United States.[3] In a smaller study conducted in Manitoba, Canada, incidence of NASH was reported to be between 28 and 36%.[4] Prevalence of NAFLD in South America is 30.4%, with up to a third of these individuals progressing to NASH.[2,5] Depending on the country, the prevalence of NAFLD varies from as low as 13% in Peru to as high as 30% in Brazil.[2,6] Most of these studies used abdominal ultrasound and transaminases to estimate the prevalence of NAFLD. Prevalence of NAFLD diagnosed by ultrasound and liver enzymes in Italy was noted to be 23%, the Netherlands 34%, Hungary 23%, and Finland about 41%.[7] Prevalence of NAFLD seem to be more in UK (46.2%) among all European countries compared to Germany (about 30%), Romania 20%, and Spain 25.8%.[8]

As per recent estimates, prevalence of NAFLD in the United States based on liver ultrasound in general population is around 24%.[2] However, NAFLD is more prevalent in Hispanics (24.1%) compared to African Americans (13.5%), and even among Hispanics, incidence varies based on their country of origin (Mexican 33% vs Dominican 16%).[6,9] Bambha *et al.*[10] described that Latinos with NASH earned

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Abbreviations: CKD: chronic kidney disease; NAFLD: nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis; BMI: body mass index; OSA: obstructive sleep apnea; PNPLA3: patatin-like phospholipase domain–containing protein 3; TM6SF2: transmembrane 6 superfamily 2
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a lower income, ate more carbohydrates, and were less physically active than non-Latino whites.

Risk Factors for NAFLD and Their Prevalence

1) Diet

The rising prevalence of NAFLD in Western countries has been incriminated to its association with food habits and sedentary lifestyles. Patients with NAFLD often consume a high-fat diet that may be an independent risk factor for the development of NASH.[11] Additionally, the quality of dietary fats plays a key role in the pathogenesis of NAFLD as shown by the beneficial effect of monounsaturated fatty acids and polyunsaturated fatty acids.[12,13] Westernized dietary patterns, characterized by a high consumption of red meat products, refined grains, pastries, and sugar-sweetened beverages, are associated with higher likelihood or risk of metabolic syndrome, whereas adherence to dietary patterns that are rich in whole grains, fruits, vegetables, legumes, and fish appears to exert a beneficial effect.[14,15] Much of the data support beneficial effect of Mediterranean diet on both prevention and resolution of the metabolic syndrome[16] and reducing risk and severity of NAFLD.[17] Further studies are warranted to confirm these early findings in a larger population of patients and potentially use Mediterranean dietary pattern as an adjunct for treatment of NAFLD in Western population.

2) Obesity

Obesity is defined by a body mass index (BMI) > 30 kg/m^2, and morbid obesity is defined as a BMI > 40 kg/m^2.[18] Prevalence of obesity is increasing in adults and children and has been described by the World Health Organization as a global epidemic with an estimated 500 million obese adults and 1.5 billion overweight or obese individuals worldwide.[19,20] Prevalence of obesity as per the Centers for Disease Control and Prevention is 39.8% in adults in the USA.[21] Mean BMI in US adults has increased from 25.7 to 28.7 for men and from 25.1 to 28.7 for women from 1960s to 2000s with a threefold increase in rates of obesity over this time period.[22] As per the CDC, up to 9.8% of US adults have diabetes and 34% are prediabetic.[23] NAFLD has been strongly linked to obesity, with a reported prevalence as high as 80% in obese patients and only 16% in individuals with a normal BMI and without metabolic risk factors.[24,25] Prevalence of nonalcoholic liver disease in patients with obesity undergoing bariatric surgery is >95% and is about 33–66% in patients with diabetes.[26] Patients with lean NAFLD share similar metabolic profile with insulin resistance and dyslipidemia as in obese patients.[27] The prevalence of NAFLD in the US in lean individuals is about 7%.[28] Visceral adiposity has been linked to susceptibility to NAFLD in nonobese subjects as opposed to subcutaneous fat and BMI.[29] In a recent study, bariatric surgery resulted in improvement in histopathologic features of disease and resolution of NASH in nearly 85% of patients after 1 year of follow-up.[30] In a recently published systematic review and meta-analysis, bariatric surgery was found to result in complete resolution of NAFLD in obese patients.[31] Randomized controlled trials are needed to confirm the therapeutic benefits of bariatric surgery in NAFLD.

3) Type 2 diabetes

The intricate role of the liver in systemic metabolism, insulin resistance, and type 2 diabetes mellitus (T2DM) cannot be overemphasized. Patients with NAFLD are commonly insulin resistant. On the other hand, a large number of patients with T2DM develop NASH as an inflammatory complication of NAFLD. The high incidence of NASH in patients with T2DM leads to further complications, such as cirrhosis and hepatocellular carcinoma, which are increasingly being recognized.[32] Both personal and family history of diabetes increases the risk of NASH and fibrosis among patients with NAFLD.[33] In fact, family history of diabetes has been proposed as a potential marker for risk stratification of patients with NAFLD (especially among nondiabetics).[33] Several prior studies from the NASH Clinical Research Network cohort and several other independent cohorts have consistently shown that diabetes is associated with NASH and advanced fibrosis among patients with NAFLD.[34–37] The presence of diabetes has long-term prognostic significance in patients with liver disease because it is an independent predictor of cirrhosis and hepatocellular carcinoma (HCC).[38–40]

4) Obstructive sleep apnea

Obstructive sleep apnea (OSA) affects over 4% of the general population and 35–45% of obese individuals.[41,42] There is evidence to suggest that OSA is an independent risk factor for NAFLD.[43] Meta-analysis done by Musso *et al.*[44] showed that OSA is associated with increased risk of NAFLD and that all patients with OSA should be screened for NAFLD and liver fibrosis. Several cohort studies have demonstrated a high incidence of fatigue and OSA symptoms in those with NAFLD.[45,46] The pathophysiological mechanism leading NAFLD in OSA has been extensively reviewed.[47] Evidence suggests that the pathophysiological alteration in gas exchange (repetitive hypoxemic and hypercapnic events), called chronic intermittent hypoxia (CIH), can lead to increased proinflammatory cytokine production, endothelial dysfunction, oxidative stress, metabolic dysregulation, and insulin resistance.[48–50] Additionally, CIH may trigger liver injury, inflammation, and fibrogenesis.[51] In alignment with this evidence, OSA has also been shown to promote the evolution of NAFLD from steatosis to NASH in an animal model.[52] Several studies have suggested a robust relationship between

OSA and NASH.[43,53–58] A recent study also found association of OSA with advanced NASH histology.[59] In summary, there is evidence to suggest that presence of OSA might alter the natural history of NAFLD, development of NASH, and fibrosis progression.

5) Genetic factors

Epidemiological and genetic studies provide a solid example of heritability of NAFLD and also help clarify some of the variability in NAFLD phenotype and risk of its progression. To date, at least three common genetic variants in the patatin-like phospholipase domain–containing protein 3 (PNPLA3), transmembrane 6 superfamily 2 (TM6SF2), and glucokinase regulatory protein genes have been robustly linked to NAFLD.[60] PNPLA3, also known as adiponutrin, is a member of the patatin-like phospholipase family. The rs738409 C-> G single-nucleotide polymorphism, encoding the Ile148Met variant protein of PNPLA3, is a well-described genetic determinant of hepatic steatosis.[61] Several studies have established a strong link between PNPLA3 and the development of NAFLD.[62,63] A recent meta-analysis showed significant association between risk of NAFLD and NASH and rs738409 polymorphism in all genetic models.[64] PNPLA3 polymorphism rs738409 has been associated with NASH as well as with severity of necroinflammatory changes independent of metabolic factors.[65] Additionally, PNPLA3 has been associated with an increased risk of advanced fibrosis among patients with liver disease and is an independent risk factor for HCC among patients with NASH.[66] NASH was more frequently observed in GG than CC homozygous variant of the gene.[62] The rs738409 GG genotype versus the CC genotype was associated with a 28% increase in serum alanine aminotransferase levels. Although its exact biological function is debated, PNPLA3 is highly expressed on the surface of lipid droplets of hepatocytes and adipose tissue. Aberrant function of *PNPLA3* rs738409 results in an absence of lipase activity, thus leading to intracellular triglyceride or retinol accumulation in hepatocytes and hepatic stellate cells, respectively.[67–69]

Long-Term Outcomes of NAFLD

The fundamental function of the liver is glucose and lipid metabolism, which is altered in the setting of NAFLD, resulting in pathophysiological effects that extend beyond the liver with significant increase in prevalent and incident cardiovascular disease (CVD), chronic kidney disease (CKD), and T2DM. The magnitude of risk of developing these extrahepatic manifestations parallels the underlying severity of NAFLD, such that patients with NASH appear to be at a greater risk of incident CVD, CKD, and T2DM than those with simple steatosis. PNPLA3, visceral adipose tissue accumulation, dietary intake, and the gut microbiome further modify the risk of developing these extrahepatic manifestations. More recently, NAFLD has been associated with risk of developing colonic neoplasia and reduced bone mineral density.

1) Chronic kidney disease

Prevalence of CKD in the US is 6.9%.[70] The presence and severity of NAFLD are associated with an increased risk and severity of CKD.[71] Musso *et al.*[71] found a strong correlation between CKD and NASH/NAFLD after adjusting for other traditional risk factors for NASH. Patients with NAFLD have a 40% increased risk of developing CKD.[72] CKD is also a known independent predictor of increased mortality (18.5% in 17 years) in patients with NAFLD.[73] NAFLD increases the risk of cardiovascular events independent of the effect of CKD on the same.[74] The implication is that routine screening for NAFLD may be warranted in populations with CKD to enable targeted interventions for CVD prevention in higher risk patients. Additionally, the impact of renal function at the time of transplant has shown to have an impact on graft survival. In a recent study, Molnar *et al.*[75] showed that simultaneous liver-kidney (SLK) recipients with NASH with preserved renal function before liver transplantation had a lower risk of death and functioning graft compared to patients with pretransplant severe renal dysfunction and patients who were SLK recipients.

2) Cardiovascular disease

NAFLD has been associated with both increased CV and all-cause mortality.[76] One Italian study performed with a ten-year follow-up via prospective case–control design demonstrated that patients with NAFLD were at increased risk for CV events, such as acute coronary syndrome and cerebrovascular accident as compared to controls.[77] The presence of carotid plaques and hepatic steatosis were the strongest predictors for such events. Most recently, in analysis of the Multi-Ethnic Study of Atherosclerosis study, 728 American NAFLD subjects were prospectively observed and found to have an increased incidence of nonfatal myocardial infarction, cardiac arrest, angina with or without revascularization, and all-cause mortality after median 7.6-year follow-up as compared to controls.[78] Among a Finnish cohort observing 268 patients with NAFLD and 720 controls, there was an increase in CV events proportional to the amount of hepatic steatosis as quantified by ultrasound.[79] A subsequent retrospective American study identified NAFLD patients with increased frequency of CV events after five- and ten-year follow-up.[80] In a recent cross-sectional study involving the third-generation offspring from the Framingham Heart Study, no association existed between CV events and NAFLD, as diagnosed via CT.[81] However, the study included significantly more diabetic patients within the CV group, and the ages of these patients were also much older than those of controls who did not develop CV events, limiting interpretation of this study.

There was also a low prevalence of CV events overall, as defined by nonfatal MI, heart failure, CVA, transient ischemic attack and peripheral arterial disease in this selective patient population. Despite these drawbacks, there was still an association found between hepatic steatosis and subclinical CV disease, which included coronary artery calcium and abdominal artery calcium, especially among male subjects. A retrospective American study concluded that increasing severity of NAFLD histology correlated with increased liver-related mortality but not all-cause mortality.[82] These 132 NAFLD cases were almost exclusively analyzed in a Caucasian cohort. Moreover, the prevalence of T2DM was lower in patients with isolated hepatic steatosis versus patients with steatohepatitis. A later Swedish prospective cohort study found that NASH was associated with both increased liver-related and all-cause mortality as compared to controls.[83] Another prospective American study stated that NASH increases liver-related mortality but not overall mortality when compared to all NAFLD patients.[84] Independent risk factors for liver-related mortality included T2DM, older age, lower albumin, and elevated alkaline phosphatase levels. In contradiction to these studies, one retrospective, American study revealed that hepatic steatosis has no correlation with liver-related or CV-related outcomes among diabetic patients after five years of follow-up.[85]

3) Colorectal neoplasia

Most of the data linking colorectal neoplasia and NAFLD has come out of Asian countries.[86–88] A recent study from the USA found a higher rate of polyp (43%) and adenoma (22%) detection (almost ~twofold higher risk) in patients with NAFLD undergoing liver transplantation.[89] Similar reports have emerged from Europe as well.[90] Whether the increased risk of colorectal neoplasia is related to NAFLD or its association is related to diabetes is a matter of debate, and hopefully, future research in this area will answer these and other mechanistic questions.[91] A recent meta-analysis of observational studies (involving asymptomatic individuals of predominantly Asian descent undergoing screening colonoscopy) suggested that NAFLD (detected by imaging or biopsy) is independently associated with a moderately increased prevalence and incidence of colorectal adenomas and cancer.[92] However, the observational design of these studies does not allow for inferring a causal relationship as the possibility of residual confounding by some unmeasured factors cannot be ruled out. More prospective studies, particularly in European and American individuals, and mechanistic studies are required to better understand the association between NAFLD and colonic carcinogenesis.

4) Osteoporosis/osteopenia

Although deterioration of bone homeostasis in patients with NAFLD is commonly observed, its etiology has not been fully elucidated yet. A recent study from the USA showed relationship between NAFLD with high alanine aminotransferase and lower BMD in the general US population.[93] Chronic inflammation, vitamin D3, growth hormone, insulin-like growth factor 1, osteopontin, fetuin-A, irisin, osteocalcin, and osteoprotegerin from osteoblasts have been proposed as mediators of mutual interactions among the skeleton, fatty tissue, and liver leading to osteoporosis.[94] A study from Italy has shown independent associations between (a) low BMD and PNPLA3 CG + GG genotype; (b) low BMD and NASH; and (c) PNPLA3 CG + GG genotype and NASH, providing support for a causal relationship between NASH and low BMD.[95] An earlier meta-analysis concluded that there is controversy regarding the effect of NAFLD on BMD. Further longitudinal studies that assess the effects of these two conditions are required to exclude the confounding effect of BMI on BMD. Although to date there are still many issues that have not been elucidated, growing evidence suggests that screening and surveillance for low bone mineral density in patients with NAFLD should be considered in future strategies and guidelines for NAFLD management.

Economic Impact and Health-care Burden of NAFLD

Estes *et al*. used the Markov model and METAVIR fibrosis stage of advanced liver disease to study the progression of liver disease in patients with NAFLD and NASH. According to this study, the total estimated cases of NAFLD is likely to increase from 83.1 million (2015) to 100.9 million by 2030 in the United States and NASH cases from 16.52 million (2015) to 27 million in 2030. A cross-sectional study using National Health and Nutrition Examination Survery data showed that among individuals with NAFLD, there was 23.8% prevalence of ≥F2 fibrosis and 2.3%–9.7% prevalence of ≥F3 fibrosis.[96] As the liver fibrosis cases increase, patients needing liver transplants are expected to increase as well. Lifetime costs of all patients with NASH in the US in 2017 were estimated to be $222.6 billion, and the cost of the advanced NASH population was estimated around $95.4 billion.[3] Cirrhosis-related mortality secondary to NAFLD increased from 2007 to 2016 with an annual percentage change (APC) of 15.4%.[97] The number of patients with NAFLD-related liver disease presenting to the emergency department has nearly doubled from 6% in 2005 to 11.9% in 2011.[98]

A population-based cohort study in Olmsted County, Minnesota, including patients with NAFLD confirmed that survival in patients with NAFLD was lower than the expected survival for the general population. Higher mortality was associated with age (hazard ratio per decade 2.2), impaired glucose (hazard ratio of 2.6), and cirrhosis (hazard ratio of 3.1).[99] Liver disease was the third leading

cause of death in this patient population.[99] As per US Census and National Center for Health Statistics mortality records, age-standardized mortality increased in patients with nonalcoholic liver disease from an APC of 6.1% in 2007–2013 to APC of 11.3% from 2013–2016.[100] Usually, in patients with NAFLD, CVD represents the leading cause of death, followed by cancer-related and then liver-related mortality. Patients with NASH have higher risk of liver-related mortality than patients without NASH.[101] Patients with cryptogenic cirrhosis had more admission days in hospital for nonliver-related events like cardiovascular, cerebrovascular, and endocrine diseases compared to patients with noncryptogenic cirrhosis.[102] A population-based cohort study conducted in Finland included 3 groups of patients with nonfatty liver disease, moderate fatty liver disease, and severe fatty liver disease, wherein patients with severe fatty liver disease had higher mortality and morbidity related to coronary artery disease independent of all traditional risk factors.[79] The Framingham Risk Score accurately predicts coronary heart disease risk in patients with NAFLD and could help patients get an early intervention to reduce coronary events.[103]

Hepatocellular Carcinoma in Patients with NAFLD

Hepatocellular carcinoma is the fourth deadliest cancer in the United States, and its annual incidence and death rate has been increasing by approximately 2.5% per year for the last two decades.[104] NAFLD/NASH is becoming a major cause of hepatocellular carcinoma in the United States and is associated with more advanced presentation and higher mortality.[105] However, regrettably, patients with NASH-HCC are significantly less likely to receive Model for End-stage Liver Disease (MELD) exception points than patients with other etiologies of hepatocellular carcinoma.[106] Several factors play a role in carcinogenesis and progression of NASH to HCC.[107] Insulin resistance, damage of hepatocytes due to free fatty acids and adipokines, oxidative stress,[108] and inflammatory cytokines causing suppression of p53 tumor suppressor genes[109] all cause progression of NAFLD to hepatocellular carcinoma. Interestingly, these pathophysiologic processes start at the stage of steatosis, and many Western studies have found hepatocellular carcinoma in early stages of steatosis even in noncirrhotic patients. A study conducted at the V.A. health system in Texas, United States, involving 1500 patients showed a strong association of NASH without cirrhosis with hepatocellular carcinoma.[110]

Liver Transplant in Patients with NAFLD

Per a recent report, NASH has become the number one reason for liver transplantation in women and remains the second most common etiology in general for patients on liver transplant waitlist in the United States.[111,112]

Table 1 Magnitude of NAFLD—Summary of Western Perspective.

Magnitude of NAFLD	Frequencies[a]	Reference
Prevalence of NAFLD in the USA	24%	2, 6
Prevalence of NAFLD in South America	31%	2, 6
Prevalence of NAFLD in Europe	23.71%	2, 6
NAFLD prevalence in Hispanic-Americans	24.1%	2, 6
NALFD prevalence in African Americans	13.5%	2, 6
Lifetime cost of patients with NASH (in 2017 US$)	222.6	3
Prevalence of NAFLD risk factors		
Obesity	39.8%	21
Diabetes	9.8%	23
Chronic kidney disease	6.9%	70
Obstructive sleep apnea	6.5%	41, 42
Leading indication for liver transplantation in women in the USA	NAFLD	112
Second leading cause of liver transplantation in the USA	NAFLD	111
Post-LT survival for NASH at 1 year	88%	114
Post-LT survival for NASH at 3 years	82%	114
Post-LT survival for NASH at 5 years	77%	114
NAFLD recurrence after LT	15–100%	119

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.
[a]Frequencies reported unless stated otherwise.

The number of new waitlist registrants with NASH increased by 170% (804–2174) from 2004 to 2013. However, these patients have a lower 90-day survival and are less likely to receive a liver transplant.[111] Patients with NASH have significant diabetes, hypertension, and obesity and also seem to be older, which puts them at increased risk of mortality while waiting for a liver transplant.[113]

The post-LT survival rate in NASH seems to be excellent with 88% survival at 1 year, 82% at 3 years, and 77% at 5 years, which is comparable to LT performed for other liver diseases.[114] Patients with normal renal function are at lower risk of mortality after liver transplant compared to patients with severe renal dysfunction in NASH group.[115] On the other hand, a German group reported higher mortality, postoperative complications, and decreased graft survival in patients transplanted for NASH as they are associated with obesity and diabetes.[116] Despite this complex relation between metabolic risk factors and graft survival, it is very important to optimize risk factors as they play a significant role in post-LT cardiovascular events and development of recurrent NASH after liver transplant. Cardiovascular events, although common in the postoperative period in patients with NASH after liver transplant, do not seem to affect overall mortality.[117,118]

NAFLD recurrence after liver transplantation is a vexing problem, and its incidence has been reported to be anywhere between 15 and 100%.[119] Post-transplant metabolic syndrome has multifactorial etiologies, although adverse effect profile of immunosuppressive agents (steroids, calcineurin inhibitors, mTOR inhibitors, and so on) and lack of adherence to lifestyle modifications are its major contributors. Physicians ought to educate their patients on the pivotal role of diet and exercise after liver transplantation and attempt risk factor modification (e.g., control of high blood pressure, diabetes, dyslipidemia, obesity, CKD) with appropriate counseling and pharmacotherapy.

Burning Issues in NAFLD Care

With a lack of widespread awareness among primary care physicians of its existence, associated complications and impact on health care and absence of screening guidelines from major medical societies such as American Association for the Study of Liver Diseases and European Association for the Study of the Liver, hitherto, which recognized incidence of NAFLD are likely the tip of the proverbial 'iceberg'. The problem gets compounded by the lack of Food and Drug Administration–approved treatment for this condition and our sole reliance on human/patient behavior to practice lifestyle modifications which require lifelong dietary self-control and unremitting self-discipline to participate in regular physical activity, which fails too often to be relied upon as the principal treatment option for this entity. Lastly, given rising rates of NAFLD in general Western population, there is growing concern that we will soon run out of 'suitable donors' for deceased or living donor liver transplantation for NAFLD as hepatic steatosis is associated with risk of primary nonfunction/early allograft dysfunction. A summary of the magnitude of NAFLD is presented in Table 1.

In summary, NAFLD represents a spectrum of diseases varying from hepatic steatosis to cirrhosis and hepatocellular carcinoma which is taking the shape of a rapidly rising epidemic, which will substantially encumber the healthcare system in the United States and all over the world. Rising trends of metabolic risk factors will further worsen the magnitude of NAFLD, leading to further complications and increasing economic burden. Public health efforts should be aimed at forming policies and guidelines to control and prepare for the imminent onslaught of this pervasive noncommunicable disease.

AUTHOR CONTRIBUTIONS

Sanjaya K. Satapathy conceptualized the manuscript, and along with Naga Swetha Samji, and Rajanshu Verma drafted the manuscript. All other authors participated in the critical revision of the manuscript for important intellectual content.

CONFLICTS OF INTEREST

The authors have none to declare.

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