

Review Article

Nonalcoholic Fatty Liver Disease Cirrhosis: A Review of Its Epidemiology, Risk Factors, Clinical Presentation, Diagnosis, Management, and Prognosis

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Cirrhosis is the common end stage of a number of chronic liver conditions and a significant cause of morbidity and mortality. With the growing epidemic of obesity and metabolic syndrome, nonalcoholic fatty liver disease (NAFLD) has become the most common cause of chronic liver disease worldwide and will become one of the leading causes of cirrhosis. Increased awareness and understanding of NAFLD cirrhosis are essential. To date, there has been no published systematic review on NAFLD cirrhosis. Thus, this article reviews recent studies on the epidemiology, risk factors, clinical presentation, diagnosis, management, and prognosis of NAFLD cirrhosis.

1. Introduction

Cirrhosis is the end stage of a wide number of chronic liver conditions that share common features of necroinflammation, fibrosis, and regenerative nodules, which modify the normal liver structure to reduce its functional mass and alter the vascular architecture [1]. Cirrhosis has become a major public health problem and a significant cause of morbidity and mortality [2]. It is the 13th most common cause of mortality worldwide [3]. Global cirrhosis deaths have increased from 1.54% of all deaths in 1980 to 1.95% in 2010 [4], causing more than one million deaths each year [5]. The most common primary etiologies for cirrhosis are chronic hepatitis B, alcoholic liver disease, chronic hepatitis C, and nonalcoholic fatty liver disease (NAFLD) [2]. Chronic hepatitis B is the most common cause of cirrhosis in most parts of Asia and sub-Saharan Africa [4], whereas alcoholic liver disease and chronic hepatitis C are the main causes in most developed countries. In recent years, with the rising incidence of obesity, NAFLD has become one of the leading causes of cirrhosis in some countries [6]. By 2020, the number of individuals with NAFLD cirrhosis is predicted to exceed that of those with hepatitis B- and C-related cirrhosis, and NAFLD cirrhosis will become the leading indication for liver transplantation [7].

2. Epidemiology

With the ongoing epidemic of obesity and metabolic syndrome, NAFLD has become the most common cause of chronic liver disease worldwide [8]. The global prevalence of NAFLD was estimated to be about 24% [9]. Cirrhosis is an important factor for liver-related morbidity and mortality in patients with NAFLD [10]. However, we still do not have a detailed understanding on how often NAFLD cirrhosis occurs. Existing studies with different study objects, diagnostic methods, and other variable parameters showed the inconsistent epidemiological results of NAFLD cirrhosis.

2.1. General Population Study. Kabbany et al. analyzed the National Health and Nutrition Examination Survey (USA) data between 2009 and 2012. Cirrhosis was diagnosed by an AST to platelet ratio index >2 and abnormal liver function tests. NAFLD cirrhosis was defined as cirrhosis that presented with at least one of the following: obesity, diabetes, insulin resistance, and metabolic syndrome. They reported that the prevalence of NAFLD cirrhosis was 0.178% [11]. Fung et al. performed a prospective cross-sectional study of 2493 volunteers recruited from the general population and the Red Cross Transfusion Center in Hong Kong (China). Cirrhosis was diagnosed by transient elastography (TE). They

found that the incidence of NAFLD cirrhosis was 0.17 % [12].

2.2. Diseases or Morbidity Patients Study. A study on 1799 patients with type 2 diabetes (T2DM) showed that the prevalence of NAFLD cirrhosis diagnosed by TE was 11.2% [13]. A review of 16 individual studies of 2,956 patients with severe obesity revealed that 5.8% of patients have NAFLD cirrhosis [8]. Those studies suggested that patients with T2DM or severe obesity have high incidence of NAFLD cirrhosis [14].

2.3. Hospitalized Patients with Cirrhosis Study. Xiong et al. performed a retrospective study of 1,582 patients with cirrhosis at Daping Hospital (China). Cirrhosis was diagnosed based on clinical symptoms, imaging data, and/or histological findings. This study found that the prevalence of NAFLD cirrhosis was 1.9% [15]. Michitaka et al. analyzed data from 33,379 patients with cirrhosis at 58 hospitals including all university and other major hospitals in Japan. Cirrhosis was diagnosed by autopsy, laparoscopy or abdominal imaging, laboratory findings, and clinical findings compatible with cirrhosis. This analysis showed that NAFLD cirrhosis constituted 2.1% of all cases of cirrhosis [16]. Karageorgos et al. studied 812 cases of cirrhosis from a liver disease center (Greece). The diagnosis of cirrhosis was confirmed by liver biopsy in compensated cirrhosis and clinical evidence in decompensated cirrhosis. They found that NAFLD cirrhosis constituted 15.5% of all cases of cirrhosis [17]. Hsiang et al. reported a retrospective study from a secondary care hospital in South Auckland (New Zealand). The diagnosis of cirrhosis was based on clinical, biochemical, histological, transient elastography, or radiological evidence accompanied by clinical signs of cirrhosis. The author found that NAFLD cirrhosis was prevalent in 16.4% of cirrhotic patients [18]. Those studies suggested that the prevalence of NAFLD cirrhosis is relatively lower in hospitalized patients with cirrhosis.

2.4. Liver Transplant Patient Studies. One study from the Nordic Liver Transplant between 2011 and 2015 reported that NASH cirrhosis was about 6.1% of adult patients (91/1476) listed for liver transplantation [19]. Another study from United Network for Organ Sharing database showed that NASH cirrhosis accounts for 5% of all young US patients listed for liver transplantation [20], and NASH cirrhosis increased from 1% to 16% from 2002 to 2016. The analysis of data from the Organ Procurement and Transplantation Network (OPTN) database from 2000 to 2014 also supported the increased tendency of NASH cirrhosis over time with an increase of 55.4% between 2016 and 2030 [21].

3. Risk Factor

3.1. Histological Subtype. Histological subtype is the greatest risk factor for the progression of NAFLD to cirrhosis. NAFLD has been divided into two main histological subtypes: non-alcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH) [22]. The incidence of progression to cirrhosis is higher in NASH than in NAFL. A longitudinal study with a mean of 15.6 years of follow-up showed that only 1% of

patients with NAFL developed cirrhosis, whereas 11% of those with NASH developed cirrhosis [23]. Moreover, NASH progressed more rapidly to cirrhosis. The annual fibrosis progression rate in patients with NASH was 0.14 stages, compared with 0.07 stages in patients with NAFL [24].

3.2. Metabolic Factors. Many studies suggested that diabetes is the strongest metabolic factor of progression of NAFLD to cirrhosis [25]. Porepa et al. used administrative health databases in Ontario (Canada) (1994–2006) to perform a population-based matched retrospective cohort study. 438,069 individuals with newly diagnosed diabetes were matched to 2,059,708 individuals without diabetes. After a median follow-up duration of 6.4 years, 1,119 (3.71%) patients with diabetes developed cirrhosis and 1,896 (1.34%) individuals without diabetes developed cirrhosis [26]. Nderitu et al. examined 509,436 participants from the Swedish Apolipoprotein Mortality Risk (AMORIS) cohort between 1985 and 1996 and found that 2,775 participants developed cirrhosis; diabetes and high blood glucose were associated with cirrhosis independent of obesity [27]. Other metabolic factors, including hyperlipidemia, obesity, and hypertension, were also important risk factors for NAFLD cirrhosis.

3.3. Genetic Polymorphisms. Genetic factors are believed to contribute to 30%–50% of the risk for high-prevalence diseases, such as obesity, T2DM, cardiovascular disease (CVD), and cirrhosis [28]. Genome-wide association studies (GWAS) and candidate gene studies have contributed greatly to our understanding of the genetic contribution to NAFLD progression. GWAS studies have identified some of the genetic variants associated with NAFLD progression. Among the loci identified, the nonsynonymous single-nucleotide polymorphism (SNP) in PNPLA3 (rs738409 c.444 C>G, p.Ile148Met), patatin-like phospholipase domain containing 3, has been validated across multiple patient cohorts. Notably, presence of this SNP has been robustly associated with the development of NAFLD cirrhosis [29]. One study of over 1000 individuals with biopsy-proven NAFLD demonstrated that the SNP in transmembrane 6 superfamily member 2 (rs58542926 c.449 C>T, p.Glu167Lys) was associated with increased risk for advanced fibrosis independent of gender, age at biopsy, BMI, T2DM, and PNPLA3 rs738409 genotype [30].

3.4. Age. In a retrospective cohort study from the United Kingdom, 351 patients with biopsy-proven NAFLD were divided into an older (≥ 60), a middle-aged (50 to 60), and a younger (≤ 50) group. Cirrhotic patients were significantly older than noncirrhotic patients. Older patients had significantly more risk factors, including hypertension, obesity, diabetes, and hyperlipidemia [31]. In a cross-sectional multicenter study from the United States, 796 patients with biopsy-proven NAFLD were classified into the elderly patients group (≥ 65) and the nonelderly patients group (18 to 65). Elderly patients with NAFLD had significantly higher rates of advanced fibrosis than nonelderly patients with NAFLD. Moreover, the elderly patients did not have more risk factors such as diabetes or insulin resistance [32]. However, the

association between age and cirrhosis in NAFLD may be related to the duration of disease rather than the age itself [33].

3.5. Other Factors. Other risk factors for progression to cirrhosis in patients with NAFLD include gender, ethnicity, and family history of metabolic traits. Data on gender differences in the development of cirrhosis in patients with NAFLD are discordant [34]. A longitudinal study of patients with NAFLD found that gender was not an independent risk factor for the progression of fibrosis. A few studies suggested that male gender is a strong independent risk factor for fibrosis. Some studies showed that the risk of advanced fibrosis is higher in females than in males. Although the risk of NASH was higher in Hispanics and lower in Blacks than Whites, the proportion of patients with significant fibrosis did not significantly differ among racial or ethnic groups in United States. Thus, ethnicity is not a risk factor for the development of cirrhosis in patients with NAFLD [35]. A recent study showed that 68.8% (779/1133) of patients with NASH cirrhosis have the family history of metabolic traits, and those patients have increased risk of cirrhosis diagnosis at an early age of <45 years. Those results suggested that the family history of metabolic traits is a risk factor for cirrhosis and associated with early age at diagnosis of NAFLD cirrhosis [36].

4. Clinical and Liver Function Features

The clinical presentations of NAFLD cirrhosis were analyzed from several early studies [37–39]. The majority of patients with NAFLD cirrhosis are female, older than 50 years, and frequently with obesity and/or T2DM. Patients with NAFLD cirrhosis are at risk of the same complications of cirrhosis as with any other etiology of liver disease [40]. Ascites is the first and most common clinical feature of decompensation, but occurs at a slower rate in patients with NAFLD cirrhosis than in patients with HCV cirrhosis [23]. Once ascites develops, the rate of hepatorenal syndrome in patients with NAFLD cirrhosis is similar to that in patients with HCV cirrhosis [41]. The incidences of variceal hemorrhage, hepatic encephalopathy, and hepatocellular carcinoma (HCC) were similar in NAFLD cirrhosis and HCV cirrhosis patients. Liver enzyme abnormalities are found in patients with NAFLD cirrhosis, but the degrees of liver enzyme abnormality are mild. The mean values of serum ALT, AST, AKP, and GGT are usually no more than three times of the upper limit of normal values.

5. Diagnosis

The diagnosis of decompensated cirrhosis is relatively easy for patients with NAFLD and is mainly based on (1) having risk factors for progression to cirrhosis, (2) excluding the other causes of cirrhosis, and (3) having cirrhosis complications. However, the diagnosis of compensated cirrhosis is difficult in patients with NAFLD due to absence of symptoms. Liver biopsy, imaging, and scoring systems for fibrosis are important methods for the diagnosis of compensated cirrhosis in patients with NAFLD.

5.1. Liver Biopsy. Liver biopsy represents the gold standard for diagnosis of cirrhosis. Key features of NASH, such as steatosis, ballooning, and Mallory-Denk bodies, are important histological features for the diagnosis of NAFLD cirrhosis. Steatosis is the histological feature that ties together all of the various forms of NAFLD. Steatosis may become inconspicuous in cirrhosis. However, a diagnosis of NAFLD cirrhosis can still be made if the critical features of ballooning and Mallory-Denk bodies are observed [42]. All histologic features of NASH may not be evident once it progresses to cirrhosis. Therefore, cirrhosis without features of NASH may be diagnosed as “cryptogenic cirrhosis”. T2DM and obesity are important factors for the development of NAFLD cirrhosis. In addition to excluding other known causes of cirrhosis, T2DM, obesity, and other comorbidities may help diagnose NAFLD cirrhosis without key NASH features in liver histology. Although liver biopsy is considered as the gold standard for the diagnosis of NAFLD cirrhosis, it is invasive and has several limitations, including sampling bias and complications (transient pain, anxiety and discomfort, hemorrhage, and rarely death) [43, 44].

5.2. Imaging Methods. In recent years, noninvasive alternative diagnostic imaging methods have been validated in comparison with liver biopsy and demonstrated good diagnostic accuracy for the diagnosis of cirrhosis. One of these techniques is TE, which produces a ‘liver stiffness measurement’ (LSM) using pulsed-echo ultrasound as a surrogate marker of fibrosis. A LSM >13.0 kPa is taken as the cut-off for clinically relevant cirrhosis [45]. A meta-analysis study of 7 articles showed that the sensitivity and the specificity of TE for the diagnosis of NAFLD cirrhosis were 96.2 % and 92.2%, respectively [46]. However, the failure rate of the M probe of TE is high in patients with BMI >30 kg/m² or T2DM [47]. The diagnostic accuracy for the liver fibrosis of XL probe of TE is similar to that of M probe [48]. As a result, in clinical practice, if the M probe is unreliable, the XL probe could be used [49]. Another noninvasive imaging technique for the diagnosis of cirrhosis is magnetic resonance elastography (MRE). Recent study showed that MRE has higher diagnostic accuracy in detecting liver fibrosis in patients with NAFLD compared to TE [50]. MRE may be a promising noninvasive technique for the diagnosis of NAFLD cirrhosis. The important limitation of TE and MRE is that they are not widely available.

5.3. Score Systems for Fibrosis. Based on demographic factors and blood tests, several scoring systems for the assessment of fibrosis or cirrhosis in NAFLD have been proposed: NAFLD fibrosis score (NFS), fibrosis-4-score (FIB-4), BARD (BMI-AST/ALT-Diabetes), enhanced liver fibrosis panel (ELF), Hepascore, Fibro Meter™, Fibro Test™, and so on [51]. NFS and FIB-4 are better than scoring systems in predicting advanced fibrosis in patients with NAFLD. NFS and FIB-4 have been recommended as screening tools to identify NAFLD patients with higher likelihoods of advanced fibrosis and/or cirrhosis in the NAFLD practice guideline from the American Association for the Study of Liver Diseases (AASLD) [52]. NFS is characterized by two cut-off values: lower cut-off value and higher cut-off value. The lower cut-off

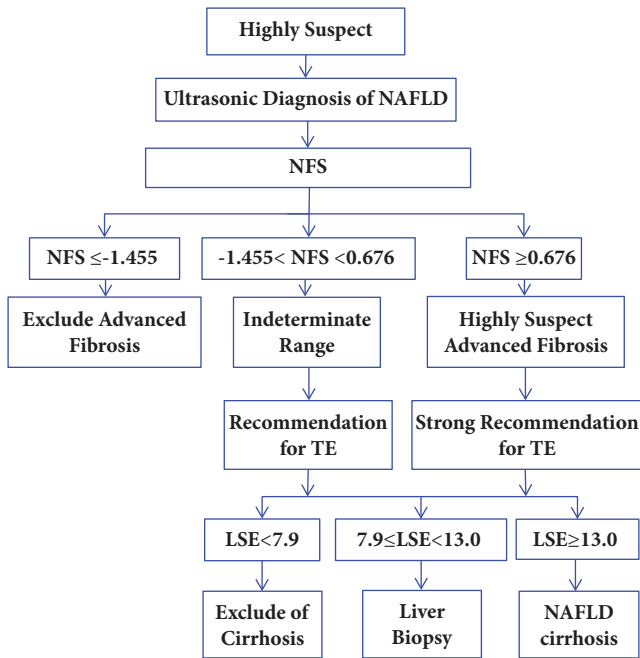


FIGURE 1: Proposal of diagnostic algorithm for classification of patients affected by NAFLD. NAFLD: nonalcoholic fatty liver disease; NFS: NAFLD fibrosis score; TE: transient elastography; LSE: liver stiffness measurement; kPa: kilopascal.

value has the highest negative predictive value to exclude advanced fibrosis. The higher cut-off value has the highest positive predictive value to identify patients with advanced fibrosis. The “gray area” between the two cut-off values is the indeterminate range [53]. FIB-4 also offers dual cut-off values as NFS: patients with score <1.45 are unlikely whereas patients with score >3.25 are likely to have advanced fibrosis.

Considering the different accuracy, cost, and availability of these diagnosis methods for cirrhosis, the selection of diagnostic approach for patients with suspected NAFLD cirrhosis could be suggested as follows: (1) NFS (or FIB-4) is first used for patients with diagnosed NAFLD. (2) Cirrhosis in patients with a NFS below the lower cut-off level can be excluded. Patients with a NFS above the indeterminate range or higher cut-off level require further diagnostic testing with TE. (3) Cirrhosis in patients with a TE <7.9 kPa can be excluded. Patients with a TE $7.9\sim 13.0$ kPa should consider liver biopsy. Patients with a TE >13.0 kPa are diagnosed as cirrhosis. A proposal of diagnostic algorithm is illustrated in Figure 1 (modified according to [45, 53]).

6. Management

Obesity is of great prognostic relevance to patients with cirrhosis, and weight loss is important in patients with NAFLD cirrhosis. However, weight loss should not be recommended in patients with decompensated end-stage liver disease due to the risk of protein calorie malnutrition [54]. Antifibrotic therapy is an important strategy for the prevention and reversion of NAFLD cirrhosis. Emerging drugs including activator of farnesoid X receptor (Obeticholic acid), antagonist of

C-C chemokine receptors type 2 and 5 (Cenicriviroc), and inhibitor of apoptosis signaling kinase-1 (Selonsertib) have been confirmed to have antifibrotic effect and will be expected to be developed as potential therapy for NAFLD cirrhosis [55]. Alcohol is a confirmed factor for liver injury. Alcohol should be prohibited in patients with NAFLD cirrhosis. Other conditions enhancing the development of cirrhosis in patients with NAFLD include diabetes, hyperlipidemia, and hypertension, which should be screened for and treated. The prevention, screening, and treatment of CVD and cirrhosis complications are critical for the prognosis of NAFLD cirrhosis. Liver transplant is an effective treatment for end-stage liver disease in patients with NAFLD cirrhosis.

6.1. Surveillance and Prevention of Cardiovascular Disease. Patients with NAFLD cirrhosis have a high prevalence of CVD. Careful attention should be paid to the surveillance of CVD. Noninvasive functional cardiac testing is recommended in patients with NASH cirrhosis, with progression to invasive tests when noninvasive testing is abnormal or inconclusive [54]. Hyperlipidemia is an important factor for the development of CVD. Statins, as drugs for lipid-reduction, are recommended for the prevention of CVD in patients with NAFLD cirrhosis who meet criteria based on current recommendations, but they should be avoided in patients with decompensated cirrhosis [52].

6.2. Screening and Management of Gastroesophageal Varices. Gastroesophageal variceal hemorrhage is a severe fatal complication of cirrhosis. Patients with NAFLD cirrhosis should be screened and managed for gastroesophageal varices according to AASLD practice guidelines [56]: (1) Patients with compensated cirrhosis (CC) without varices on screening endoscopy should have endoscopy repeated every 2 years; patients with CC with small varices on screening endoscopy should have endoscopy repeated every year; patients with CC without varices or with small varices who develop decompensation should have a repeat endoscopy when this occurs. (2) Traditional nonselective beta-blockers (NSBBs) (propranolol, nadolol, and carvedilol) or endoscopic variceal ligation (EVL) is recommended for the prevention of first variceal hemorrhage in patients with medium or large varices; NSBB is the recommended therapy for patients with high-risk small esophageal varices; the combination of NSBB and EVL is first-line therapy in the prevention of rebleeding.

6.3. Surveillance and Management of Hepatocellular Carcinoma. There is substantial evidence that cirrhosis is a common cause for the development of HCC [57]. Patients with NAFLD cirrhosis are at higher risk for HCC [58]. The cumulative incidence of HCC from NAFLD cirrhosis has been reported as 2.4% and 12.8% over a median follow-up of 3.2 to 7.2 years [59]. International societies recommend HCC surveillance in selected target populations, including patients with cirrhosis of any cause [60]. AASLD recommends that patients with NAFLD cirrhosis should be considered for HCC screening with ultrasound testing and with or without measurement of blood alpha-fetoprotein (AFP) levels, every 6 months [52, 61]. The treatment of HCC in patients with

NAFLD cirrhosis may be referred to the AASLD practice guidelines [61]. T2DM significantly increases the risk of developing HCC [62]. Metformin and statins significantly reduce the risk of HCC among patients with diabetes [63]. Statins and metformin have been suggested as potential strategies for the primary prevention of HCC in patients with NAFLD and diabetes [60, 62].

6.4. Liver Transplantation. Liver transplant is an effective treatment for end-stage liver disease, with an overall one-year survival of around 91% and a three-year survival of around 80%. Survival rates up to ten years are similar for patients receiving transplants for NAFLD cirrhosis and those receiving transplants for other indications, such as HCV cirrhosis and alcoholic cirrhosis. Guidelines for liver transplantation for patients with nonalcoholic steatohepatitis recommend that the indications for liver transplantation include NASH cirrhosis or HCC [54]. Studies of post-transplant survival outcomes suggested that NASH cirrhosis is associated with higher 30-day mortality, predominantly from an increase in CVD, and that severe obesity is likely to increase postoperative and long term mortality [64]. Thus, patients should undergo preoperative assessment and management of CVD and optimization of nutritional status. Following liver transplantation for patients with NAFLD cirrhosis, NAFLD recurs in at least 1/3 of patients [65]. Reduced mobility and commonly used immunosuppression regimens place those patients at higher risks of developing obesity, diabetes, and hypertension or exacerbating these conditions if previously present. As a result, body weight, hypertension, diabetes, and hyperlipidemia should continue to be monitored and managed in posttransplant patients.

7. Prognosis

Studies on the prognosis of NAFLD cirrhosis were reported mostly several years ago. The 5-year survival rate of 68 patients with NASH cirrhosis was 75.2% [48]. The death of patients with NAFLD cirrhosis is caused by complications. Once cirrhosis develops, prognosis is negatively impacted, with potential development of cirrhosis complications. The 5-year occurrence rates of ascites, varices, encephalopathy, and HCC of 68 patients with NASH cirrhosis were 19.1%, 28.2%, 16.1%, and 11.3%, respectively [38]. The 10-year occurrence rates of ascites, variceal hemorrhage, encephalopathy, and HCC of 152 patients with NASH cirrhosis were 14%, 12%, 15%, and 7%, respectively [66]. Bhala compared the natural history of NAFLD cirrhosis to HCV cirrhosis and found that patients with NAFLD cirrhosis appeared to have lower rates of liver-related complications and lower rates of HCC than patients with HCV infection of a similar disease stage, cardiovascular mortality was greater in patients with NAFLD related cirrhosis, and these two groups of patients had similar overall mortality [39]. NAFLD cirrhosis is the larger proportion of cryptogenic cirrhosis. The studies on the natural history of cryptogenic cirrhosis showed that the cumulated incidence of HCC in patients with cryptogenic cirrhosis was similar to that in patients with HCV cirrhosis, and patients with cryptogenic cirrhosis have a higher risk of

developing severe liver complications [67, 68]. These existing data strongly suggested that NAFLD cirrhosis has a poor prognosis.

8. Conclusions

NAFLD is becoming one of the leading causes of cirrhosis. Risk factors for the progression to cirrhosis in patients with NAFLD include NASH, metabolic factors, genetic polymorphisms, and older age. The clinical presentations of NAFLD cirrhosis are similar to those of cirrhosis caused by other etiology. The diagnosis of decompensated cirrhosis is relatively easy for patients with NAFLD. Liver biopsy, imaging, and scoring systems for fibrosis are important methods for the diagnosis of compensated cirrhosis in patients with NAFLD. Reducing weight, prohibiting drinking, managing other risk factors for progressing to cirrhosis, and antifibrosis are fundamental treatments. Screening, treatment, and prevention of cirrhosis complications and CVD are crucial for the management of NAFLD cirrhosis. Liver transplant is an effective treatment for end-stage liver disease in patients with NAFLD cirrhosis. The prognosis of NAFLD cirrhosis is poor. The prevention and treatment of NAFLD cirrhosis should be emphasized.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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