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Editorial

Implications of comorbidities in nonalcoholic fatty liver disease

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Nonalcoholic fatty liver disease (NAFLD) affects around 30% of the global adult population and is becoming a major cause of cirrhosis, hepatic decompensation and hepatocellular carcinoma.[1] Ever since the initial characterization of NAFLD, we have known that obesity and insulin resistance are the main drivers of the disease. Numerous studies have confirmed a strong association between NAFLD and essentially all obesity-related metabolic disorders. Moreover, although as hepatologists we should pay attention to liver-related morbidity and mortality, it is clear that most NAFLD patients still die from cardiovascular disease (CVD) and extrahepatic cancers, with the exception of patients with cirrhosis in whom liver disease is the primary cause of death.[2]

In this issue, a narrative review by Manikat and Nguyen[3] explores the potential impact of NAFLD on the cardiovascular, renal, respiratory, endocrine systems as well as its association with non-hepatic cancer, infection and patient-reported outcomes. Some of these comorbidities can be alarming given that CVD and extrahepatic malignancies are the main culprits for mortality of NAFLD patients.[2] The link between NAFLD and extrahepatic malignancies is worth our great attention, considering that a recent meta-analysis suggests the link is independent of potential confounders including obesity and diabetes.[4]

However, the mechanisms underlying most of these associations remain unclear. As stated in the review and a previous study,[5] the close relationship between NAFLD and metabolic syndrome contributes to the predisposition to CVD. Although shared metabolic dysfunction among these comorbidities enables clinicians to implement treatment strategies (i.e., life simple 7 guidelines[6]) that may benefit both conditions, untraditional risk factors (i.e., fatigue and its driver sleep disturbances) may also affect NAFLD mortality through unknown pathways. Therefore, to clarify the nature of their associations, or whether and how NAFLD independently confers additional risk for other comorbidities may contribute to a more systematic management approach for NAFLD.

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IS THE ASSOCIATION BETWEEN NAFLD AND ITS COMORBIDITIES CAUSAL?

While the association between NAFLD and its comorbidities is firmly established, one interesting question is whether the relationship is causal. In clinical medicine, randomized controlled trials are the gold standard to establish causality. However, it is impossible (e.g., NAFLD) or unethical (e.g., smoking) to assign some exposures to people. In 1965, Sir Hill[7] published his nine-point criteria to support potential causality between environmental exposures and diseases. Since then, the criteria have often been used in epidemiological studies to infer causality. As illustrated in the Table 1, current studies have shown rather consistent correlation between NAFLD and comorbidities with a wide range of association strength depending on the condition. The bidirectional association (NAFLD preceding a comorbidity and vice versa) may be interpreted as both conditions contributing to the development of each other, or it may also mean the relationship is not causal. In some conditions (e.g., diabetes, chronic kidney disease, colorectal neoplasm), a dose-response relationship exists (i.e., the association with the comorbidity is stronger in patients with more severe liver disease). Finally, mechanistic studies to explain how NAFLD causes the extrahepatic conditions are largely lacking.

Another caveat looms large in the clinical association studies. Some studies defined NAFLD and fibrosis using formulae, which typically comprise liver enzymes plus metabolic risk factors. For example, fatty liver index, one of the most commonly used scores to define NAFLD in large registry studies, includes waist circumference, body mass index and triglycerides.[8] As such, it would be impossible to fully dissect the true effect of NAFLD from adiposity and metabolic dysfunction.

SOME EXAMPLES ON POTENTIAL CAUSAL RELATIONSHIPS

Type 2 diabetes (T2DM)

In a systematic review and meta-analysis of 80 studies, the global prevalence of NAFLD is estimated at 56% among patients with T2DM.[9] Over 10% of patients with T2DM may have liver fibrosis progression in 3 years.[10] NAFLD also increases the risk of incident diabetes by 2-fold.[11] Among patients with NAFLD and T2DM, age is a major determinant of adverse liver-related outcomes, whereas the use of aspirin, statins and some classes of anti-diabetic drugs (e.g., metformin and pioglitazone) has been shown to reduce the risk of hepatocellular carcinoma and cirrhotic complications.[12]

A number of mechanisms have been suggested to explain the increased risk of T2DM in patients with NAFLD. These include common dietary factors (e.g., fructose and saturated fat), gut microbiota dysbiosis (e.g., short-chain fatty acids produced by gut bacteria, such as butyrate, can modulate insulin sensitivity), increased gut permeability, adipose tissue dysfunction, changes in *de novo* ceramide synthesis, and increased hepatic glucose production (i.e., manifestation of hepatic insulin resistance).[13] A recent prospective study reported the prevalence of NAFLD among patients with T2DM to be 65.3%, and patients who developed NAFLD were more likely to have obesity and the metabolic syndrome.[14] Interestingly, NAFLD was also a risk factor in the development of T2DM in some prospective cohort studies,[15,16] and changes in steatosis status correlated with the incidence of T2DM through 15-year long-term follow-up,[16] adding the robustness of association between two diseases. However, with many metabolic confounders, a causative relationship remains unclarified.

Obstructive sleep apnea (OSA)

There is growing evidence that OSA severity manifested as intermittent hypoxia is dose-dependently associated with the development and progression of NAFLD. Various experimental evidence shows that intermittent hypoxia leads to glucose and lipid dysregulation, and hepatic inflammation, oxidative stress, and fibrosis, all of which are critical factors in NAFLD development.[17] OSA may increase the risk of NAFLD through its independent impact on insulin resistance, as supported by both clinical and animal studies.[18,19] Of note, the association between severe OSA and liver fibrosis evaluated by

Abbreviations:

NAFLD, nonalcoholic fatty liver disease; CVD, cardiovascular disease; OSA, obstructive sleep apnea; ALT, alanine aminotransferase; CAD, coronary artery disease; MR, Mendelian randomization; T2DM, type 2 diabetes

Table 1. Bradford Hill criteria for causation[7]

Criteria	Do studies reporting the association between NAFLD and comorbidities fulfill the criteria?
Strength of association	An odds ratio or relative risk of ≥2 is generally regarded as a strong association. This has been seen for some but not all comorbidities.
Consistency	The literature on the positive association is largely consistent.
Specificity	It would be difficult if not impossible to establish specificity in this case. Obesity-related metabolic disorders tend to occur together. Even if a causal relationship exists, NAFLD would unlikely be the sole cause of the comorbidity.
Temporality	Bidirectional relationship is more commonly reported. For example, patients with NAFLD are more likely to develop incident type 2 diabetes over time, whereas patients with type 2 diabetes also have increased risk of incident NAFLD and liver fibrosis. Another issue is that the onset of NAFLD is often inaccurate because the disease is largely silent before the development of liver-related complications.
Biological gradient	The severity of NAFLD (i.e., presence of NASH or the degree of liver fibrosis) has been shown to correlate with the risk of some comorbidities (e.g., type 2 diabetes, chronic kidney disease, colorectal neoplasm) in a dose-dependent manner.
Plausibility	Because of the well-established crosstalk between the liver and other organs (e.g., gastrointestinal tract and adipose tissue) and that adipose tissue is a major source of lipids to the liver, it is reasonable to consider obesity (or visceral adiposity) as a cause of NAFLD. The other way round (NAFLD causing the comorbidities), however, is more difficult to discern apart from the fact that NAFLD is a state of marked insulin resistance.
Coherence	There has not been serious conflict in the data interpretation with what is known about NAFLD and its comorbidities.
Experiment	The mechanisms underlying the association between NAFLD and comorbidities are not established in most cases. However, mechanistic studies exist in some conditions (e.g., hypoxia from obstructive sleep apnea causing NAFLD; NAFLD being a state of hepatic insulin resistance).
Analogy	There is no good analogy to suggest a similar condition may cause a similar disease.

NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

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liver stiffness measurement remains after multivariate adjustment for metabolic factors including insulin resistance.[20]

Although alanine aminotransferase (ALT) and aspartate aminotransferase levels are lowered with the continuous positive airway pressure treatment,[21] most related studies were limited by either small cohorts or short duration and failed to confirm its role in NAFLD progression.[22] Further studies are needed to clarify the underlying mechanisms as well as treatment strategies for these two disorders.

Coronary artery disease

As a top killer of NAFLD patients, CVD, particularly coronary artery disease (CAD) among its spectrum, is widely discussed for its close association with poor NAFLD prognosis. A meta-analysis of six studies with 25,837 patients reported that NAFLD patients had a 2.2-fold higher risk of developing CAD than those without NAFLD.[23] In a large cohort of asymptomatic individuals in South Korea, NAFLD was an independent risk indicator of subclinical coronary atherosclerosis with manifestation of having non-calcified coronary atherosclerotic plaques.[24] These vulnerable plaques suggest high risk of unexpected adverse cardiovascular events.

The association between CAD and NAFLD is well-established but rather intricate with both traditional and non-traditional metabolic risk factors involved, such as abnormal glucose metabolism, insulin resistance, hypoadiponectinemia, and hyperuricemia.[25] As mentioned, dysfunctional and ectopic lipid accumulation in NAFLD can be the damage-driver, causing lipoprotein abnormalities, initiation of inflammatory response and consequent development of atherosclerosis.[26] In this context, pericardial accumulation of ectopic fat represents another central pathogenesis for cardiometabolic disorders.[27] All these pathological hallmarks promote the development of CVD. However, the precise causative relationship is still under investigation.

MENDELIAN RANDOMIZATION STUDIES: A NEW TOOL TO ESTABLISH CAUSALITY?

A recent study contributes to inferring causality between NAFLD and CAD using an emerging method - Mendelian randomization study (MR).[28] MR is based on the assumption that certain genetic variants affect outcomes of interest (i.e., CAD) only through the exposure of interest (i.e., NAFLD) and independent of other confounders. By using MR, they demonstrated the interlink between genetically predicted NAFLD (defined as chronically increased ALT levels, imaging–based, or biopsy–confirmed NAFLD) and CAD after excluding generic variants involved in impaired very-low density-lipoprotein secretion. However, another MR study focusing on the association of NAFLD with CVD events observed no significant relationship between NAFLD and CAD, heart failure, or stroke.[29] Among different CVD events, only arterial stiffness was found to be causally associated with NAFLD. Wu et al.[30] also found no causal effect between NAFLD and stroke using the MR method, although a causal relationship might exist for ischemic stroke, large artery atherosclerosis and small vessel occlusion. This may be mediated by deranged adipokine profile and abnormal high-density lipoprotein cholesterol level in NAFLD patients. Further studies investigating the relationship between NAFLD and CVD are warranted.

Xie et al.[31] also sheds light on the complex relationships between NAFLD and its comorbidities using the MR method. Focusing on a number of modifiable risk factors, the widely reported associations between genetically predicted T2DM, hypertension and hypothyroidism with NAFLD were further confirmed. Notably, no significant association existed between hypothyroidism and NAFLD after adjusting for genetically predicted body mass index, suggesting that this relationship could be confounded by adiposity. Other causative risk factors for NAFLD including alcohol frequency, elevated serum levels of liver enzymes, obesity were also indicated in their integrated databases, which provides references for the public health intervention and the routine management for NAFLD. However, the database includes only European individuals, thus the generalizability of this study remains to be verified. In addition, pleiotropy is still a big challenge for all MR studies to overcome.

MANAGEMENT IMPLICATIONS

In summary, the excellent review by Manikat and Nguyen[3] is a timely reminder of the strong association between NAFLD and various comorbidities. While causality of the association remains a matter of debate, clinicians should be aware of the important comorbid conditions and arrange assessment and treatment as appropriate. Accordingly, the cur-

rent Asia-Pacific guidelines recommend routine assessment for adiposity, blood pressure, glucose and lipids in patients with NAFLD.[32] Accumulating data also support measurement of kidney function, and if symptomatic, assessment for obstructive sleep apnea and CVD. In addition, colorectal cancer and breast cancer are more common in patients with NAFLD, and screening has been shown to detect early cancers and lower mortality. Future studies should define whether a diagnosis of NAFLD should prompt earlier and more frequent screening for cardiometabolic conditions and related cancers.

Authors' contribution

Both authors contributed to the writing plan, literature review, and manuscript preparation. They approved the final version of this article.

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Conflicts of Interest

Vincent Wong has served as an advisor or consultant for AbbVie, Boehringer Ingelheim, Echosens, Gilead Sciences, Intercept, Inventiva, Novo Nordisk, Pfizer, Sagimet Biosciences, and TARGET PharmaSolutions; and a speaker for Abbott, AbbVie, Gilead Sciences, and Novo Nordisk. He has received a research grant from Gilead Sciences, and is a cofounder of Illuminatio Medical Technology Limited. Sherlot Song reports no conflict of interest.

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