Coming Complications of Nonalcoholic Fatty Liver Disease: Time to GNASH Your Teeth

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Nonalcoholic fatty liver disease (NAFLD), the leading cause of chronic liver disease in the USA and in other developed nations, is associated with metabolic risk factors including obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, hypertension, and “non-classical” risk factors such as obstructive sleep apnea and gout [1]. In the USA, the true prevalence of NAFLD is 25–40%, depending on the modalities used to diagnosis NAFLD, and is in parallel with the rising tide of obesity and T2DM [2, 3]. As cardiovascular disease and extrahepatic cancers are the most common causes of death among those with NAFLD [4, 5], NAFLD is now considered a multi-systemic metabolic disease.

Hepatocellular carcinoma (HCC), the fifth most common cancer worldwide, is a leading cause of cancer-associated death [6]. Although the vast majority of HCCs develop on a background of liver cirrhosis, cumulative data suggest that up to 20% of patients with HCC do not have preexisting cirrhosis [7]. Cases of NAFLD-related HCC have overtaken hepatitis C virus (HCV)-related HCC with the number of liver transplants for NAFLD-related HCC increasing almost tenfold in the last decade [8, 9]. Furthermore, among US veterans, it was recently demonstrated that NAFLD-related HCCs were less likely to have underlying liver cirrhosis compared with HCCs complicating other types of liver disease [10] and that NAFLD and the metabolic syndrome were key risk factors for HCC development [11]. In this issue

of *Digestive Disease and Sciences*, Nguyen and colleagues used the California Patient Discharge Database to quantify inpatient NAFLD encounters over a 7-year period [12]. Of clinical significance, the authors reported an increase in the number of cases of HCC and found that renal disease was associated with increased mortality among those hospitalized for a liver-related indication (adjusted hazard ratio = 1.5). Nguyen and colleagues observed that despite the increase in the number of NAFLD-associated HCCs, the number of patients transplanted for HCC has decreased [12], explained in part by the delayed presentation of HCC since individuals without cirrhosis are not routinely screened for HCC. Furthermore, those with NAFLD are also likely to harbor multiple metabolic risk factors and complications that may preclude them for undergoing liver transplantation. Although the pathogenic mechanisms by which HCC arises from a non-cirrhotic liver remain unclear, preclinical studies suggest that loss of tumor suppressor genes (e.g., phosphatase and tensin homolog and p53 [PTEN]) and dysregulation of the inflammatory pathways (i.e., nuclear factor [NF]- κ B, NF- κ B essential modulator [NEMO], and TGF- β activated kinase [TAK1 β]) may be responsible [13–15]. More studies are needed to elucidate putative pathways in humans and to identify those at risk of non-cirrhotic HCC and who may need screening. Although not specifically discussed in this report [12], non-HCC malignancy is the second most common cause of death among those with NAFLD [4, 5]. The specific association between NAFLD and colorectal cancer has been the subject of several studies, but the majority of the studies were cross-sectional, and as such, no causal relationship could be assessed. In a more recent report by Huang et al. [16], investigators reported that among 1522 asymptomatic individuals who had routine metabolic phenotyping and had received paired colonoscopies (all index colonoscopies were negative), NAFLD (as diagnosed by ultrasound) was an independent risk factor for new colonic adenoma development (adjusted OR 1.45) even after adjustment for metabolic confounders.

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The prevalence of chronic kidney disease (CKD) is 4–13% in the general population and is expected to increase by up to 7% each year [17]. Several studies have reported an association between NAFLD and chronic kidney disease (CKD) [4, 18], and in four prospective studies, NAFLD was independently associated with an increased risk of CKD and/or microalbuminuria [4, 19, 20]. In the meta-analysis, authors also reported a twofold increased incidence of CKD among NAFLD patients after adjustment for covariate risk factors [18]. Strikingly, those with biopsy-proven nonalcoholic steatohepatitis (NASH) were over twice as likely to develop CKD as those with only simple steatosis. Although these studies did not use isotopically measured glomerular filtration rate (GFR) to confirm the presence of CKD, or renal biopsy to exclude other causes of renal disease, the observations in this inpatient cohort [12] highlight the importance of large prospective population-based studies to clarify the association between NAFLD and incident CKD. NAFLD is also associated with an increased risk of developing incident T2DM (up to twofold), even after adjusting for lifestyle and metabolic risk factors [4, 5], and interestingly, the regression of NAFLD appears to mitigate the risk of new-onset T2DM [21]. Other associations with NAFLD include osteoporosis, obstructive sleep apnea, and endocrinopathies including growth hormone deficiency and hypothyroidism [4], and may need to be evaluated as part of NAFLD-associated comorbidities and charges for NAFLD-related outpatient and inpatient encounters.

In the same study [12], Nguyen and colleagues also described a significant increase in NAFLD inpatient encounters ($n = 8153$ in 2006 to $n = 16,457$ in 2013) and estimated the mean annual increase in inflation-adjusted inpatient charges of 9.8% per year. Although the authors had assumed an inflation rate of 3% per year, they had not provided a justification for this number. An alternative method would be to utilize the US Department of Labor Bureau of Labor Statistics Inflation Calculator to adjust for inflation each year in order to convert the 2006–2013 charges to a common year (https://www.bls.gov/data/inflation_calculator.htm). Hospital charges can also vary widely for the same type of care based on hospital ownership and mission, hospital location, and source of reimbursement. Thus, in order to standardize charges and remove the influence of hospital profit margins and insurer differences, a method has been developed to sum charges across hospitals by the Medicare Severity Diagnosis Related Groups (MS-DRGs) and to estimate the mean charge per MS-DRG. The mean charge per MS-DRG can then be used as a standardized estimate of the cost per discharge based on its MS-DRG [22].

Limitations notwithstanding, this study provided a snapshot of the projected increase in clinical burden and revealed the potential catastrophic economic impact. These findings are consistent with prior studies of resource utilization [23].

For example, in a study of 29,528 Medicare beneficiaries with NAFLD, investigators found a significant increase in annual outpatient charges from over \$2500 in 2005 to over \$3500 in 2010, and projection models estimate an increase in annual economic burden to over \$100 billion from direct medical costs and a further \$188 billion in societal costs [24]. Other limitations of this study [12] included possible inaccurate coding of disease states, the use of multivariate logistic regression for the assessment of hospitalizations and charges as opposed to a generalized linear model with appropriate family and link functions based on distribution of the charge data [25], and the use of the Charlson score instead of Elixhauser comorbidities for hospital resource use and hospital charges [26].

Nevertheless, the report by Nguyen and colleagues is sobering, warning of the likely *tsunami* of NAFLD cases, and the staggering personal and public health costs associated with NAFLD (and NAFLD-related conditions). Future studies of both the general population and among US veterans will be needed to better appreciate the type and burden of encounters and the potential economic costs. Prospective studies which incorporate more accurate diagnostic modalities (e.g., transient or shear wave elastography) will be needed to confirm the link between NAFLD and multiple medical conditions and to identify those at risk of developing non-cirrhotic HCCs. Studies will also be needed to understand the reasons for racial disparity in NAFLD outcomes and costs.

Compliance with ethical standards

Conflict of interest None.

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