Recent Epidemiology of Nonalcoholic Fatty Liver Disease

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INTRODUCTION

Fatty infiltration of the liver was only sporadically recognized in early literature and generally felt to be a benign condition. Until the 1990s, most studies recognized nonalcoholic fatty liver disease (NAFLD) as an “innocent bystander” rather than the “guilty party” in patients with cryptogenic cirrhosis,¹ which was commonly used for end-stage liver disease in which the underlying etiology remains unidentified. The landmark comment by Ludwig et al.² in 1980 first described the term “nonalcoholic steatohepatitis (NASH)” after identifying 20 nonalcoholic patients with liver biopsies showing changes similar to alcoholic hepatitis. Caldwell et al.³ recognized that the risk factors for cryptogenic cirrhosis paralleled those for NASH and NAFLD. Subsequent studies found that cirrhosis tends to occur at an older age in obese patients, further suggesting cryptogenic cirrhosis as a downstream effect of NASH and NAFLD.⁴

A major limitation in understanding the epidemiology of NAFLD has been the lack of a distinct classification of the disease. For example, under the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9 CM), NAFLD has been grouped under cryptogenic cirrhosis or “other chronic nonalcoholic liver diseases” or “unspecified chronic liver disease without alcohol,” underestimating at least 42.1% of individuals with NAFLD that were otherwise diagnosed by chart review.⁵ The misclassification of nomenclature has been an inherent problem in understanding pathophysiology and the prevalence of NAFLD, and its impact on downstream health outcomes. This review on NAFLD will further explore the current trends in epidemiology, recognize the importance of establishing the diagnosis of NAFLD in the context of chronic liver disease, and explore the diagnostic nuances in tracking the progression of NAFLD over time.

DEFINITIONS

The diagnosis of NAFLD requires more than or equal to 5% of hepatic fat accumulation and exclusion of other etiologies of liver disease such as viral hepatitis, autoimmune liver disease, hemochromatosis, Wilson’s disease, drug-induced liver disease as well as significant alcohol consumption.⁶ The American Association for the Study of Liver Diseases Practice Guideline for NAFLD defines significant alcohol consumption as current or recent alcohol

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consumption of >21 standard drinks per week in men and >14 drinks per week in women over 2 year period. Diagnosis of NAFLD needs to be ruled out secondary causes of fatty infiltration, including lipodystrophy, starvation, Cushing’s disease, and steatogenic medications (corticosteroids, amiodarone, methotrexate, tamoxifen, and anti-retroviral therapy). As seen in Table 1, NAFLD refers to a broad array of histological variety from nonalcoholic fatty liver (NAFL) to NASH, which may or may not present with fibrosis that can progress to end-stage liver diseases such as cirrhosis or hepatocellular carcinoma (HCC). NASH is defined as the presence of over 5% of hepatic fat accumulation and lobular inflammation with hepatocyte ballooning degeneration, with or without any fibrosis. NASH cirrhosis is defined as the presence of cirrhosis with current or previous histological evidence of NAFL or NASH.

### 1. Incidence of NAFLD

There are scattered and limited data regarding the incidence of NAFLD in the general population. With the recent transition to ICD-10-CM with a specific diagnostic code for NAFLD, a study in England showed the incidence rate of NAFLD of 29 per 100,000 person-years with significant underestimated rates due to ICD-10 code. A meta-analysis published in 2016 showed that the pooled regional incidence rate estimates for Israel and Asia were 28.0 per 1,000 person-years (95% confidence interval [CI], 19.3 to 40.6) and 52.3 per 1,000 person-years (95% CI, 28.3 to 96.8) and respectively. A recent meta-analysis in Asia during 1999 to 2019, described the overall pooled incidence rate was 50.9 per 1,000 person-years (95% CI, 28.0 per 1,000 person-years (95% confidence interval [CI], 19.4 to 22.0) subjects had suspected steatosis, with 10.0% presenting having severe steatosis. Interest-

### 2. Prevalence of NAFLD

The true prevalence of NAFLD is hard to measure accurately due to the lack of consistent diagnostic criteria. NAFLD can be diagnosed using a radiologic assessment, while the degree of fibrosis and diagnosis of NASH requires a liver biopsy. The prevalence of NAFLD could be defined by histology, imaging, and blood tests, which are a much less reliable method of diagnosing NAFLD.

A systematic review and meta-analysis on the global epidemiology of NAFLD estimated prevalence of NAFLD by imaging to be 25.2% (95% CI, 22.1 to 28.7) with an estimated prevalence of NASH to be lower ranging from 3 to 5%. It is noted that the Middle East and South America have the highest prevalence of 32% (95% CI, 13.5 to 58.2) and 30.5% (95% CI, 22.7 to 39.4), respectively, and the lowest prevalence in Africa at 13.5% (95% CI, 5.9 to 28.7).

Table 2 summarizes the recent prevalence of NAFLD from across the world. Based on the United States (US) Third National Health and Nutrition Examination Survey (NHANES III), an extensive representative survey of the US civilian population, the prevalence of NAFLD by ultrasonography is estimated to be 34.0% in the US.

### 3. Current trends and future projections in NAFLD

Based on the serial NHANES dataset, the prevalence of NAFLD using noninvasive panels by US Fatty Liver Index, increased from 20.0% (1988–1994) to 28.3% (1999–2004) to 33.2% (2009–2012) and 31.9% (2013–2016) over 30 years. According to numerous studies which combined liver biopsy, noninvasive radiologic modalities as well as liver enzymes, 3% to 5% of NAFLD can progress to NASH with advanced fibrosis or cirrhosis, which is 1.25% of all

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**Table 1. Definition of Nonalcoholic Fatty Liver Disease**

| Condition                                      | Description                                                                 |
|------------------------------------------------|-----------------------------------------------------------------------------|
| Nonalcoholic fatty liver disease               | -Greater than 5% of hepatic fat accumulation                                |
|                                                | -Exclusion of other etiologies of liver diseases (i.e., infection, alcohol)  |
| Nonalcoholic fatty liver                       | -Hepatic steatosis without any histological manifestation of ballooning degeneration or fibrosis |
| Nonalcoholic steatohepatitis (NASH)            | -Hepatic steatosis with histological manifestation of ballooning degeneration, lobular inflammation with or without fibrosis |
| NASH cirrhosis                                 | -NASH with the presence of cirrhosis                                         |

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population,

as described in Fig. 1. The prevalence of NAFLD-related advanced fibrosis increased from 2.6% (2005–2008) and 4.4% (2009–2012) to 5.0% (2013–2016) among subjects with NAFLD defined as the hepatic steatosis index; and from 3.3% (2005–2008) and 6.4% (2009–2012), to 6.8% (2013–2016) among those with NAFLD defined as US Fatty Liver Index (p < 0.01). In this study, advanced fibrosis was defined as having at least one of the high probabilities for advanced fibrosis using three non-invasive fibrosis markers.

Among type 2 diabetics from 1989 to 2018, the global prevalence was 55.5% for NAFLD, 37.3% for NASH and 17.0% for advanced fibrosis. A recent study using the Markov prediction model reported that NAFLD is projected to increase by 21% from 83 million in 2015 to 101 million in 2030. NASH is forecasted to grow 63% from 17 million in 2015 to 27 million in 2030. Incidence of decompensated cirrhosis is predicted to increase 168% by 2030, while the incidence of HCC is projected to increase by 137%. Using Markov modelling of the burden of NAFLD-related disease in eight countries including China, France, Germany, Italy, Japan, Spain, United Kingdom, and United States, prevalence of NASH will increase 15% to 56%, while liver-related mortality and advanced liver disease will more than double due to an aging population and the projected rising prevalence of diabetes.

![Fig. 1. Estimated number of individuals in the US population affected by nonalcoholic fatty liver disease (NAFLD). All numbers are estimated by the current prevalence of NAFLD, nonalcoholic steatohepatitis (NASH), NASH cirrhosis.](image-url)

**Table 2. Global Incidence and Prevalence of NAFLD**

| Author (year)       | Country                                      | Description of study                                      | Diagnostic method                                                                 | Incidence or prevalence of NAFLD (%) |
|---------------------|----------------------------------------------|------------------------------------------------------------|-----------------------------------------------------------------------------------|--------------------------------------|
| Incidence           |                                               |                                                            |                                                                                   |                                      |
| Younossi et al. [2016] | Asia and Israel                              | 5 Studies                                                  | Ultrasonography, computed tomography scan OR magnetic resonance spectroscopy OR blood testing | For Asia, 52.3 per 1,000 (95% CI, 28.31–96.77); Israel, 28.01 per 1,000 person-years (95% CI, 19.34–40.57) |
| Li et al. [2019]    | Asia                                          | 18 Studies                                                 | Ultrasonography, computed tomography scan OR magnetic resonance imaging/spectroscopy OR liver biopsy OR blood testing/predictive indices (fatty liver index or hepatic steatosis index) or ICD-9-CM codes | 50.9 per 1,000 person-years (95% CI, 44.8–57.4) |
| Allen et al. [2018] | USA                                           | Community cohort study (n=3,869 subjects)                   | ICD-9-CM codes                                                                   | 329 per 100,000 person–years in 2014 |
| Prevalence          |                                               |                                                            |                                                                                   |                                      |
| Younossi et al. [2016] | Africa, Asia, Europe, Middle East, North America, South America | 86 Studies included in meta-analysis from 22 countries, 1989-2015 (n=8,515,431) | Ultrasonography, computed tomography scan OR magnetic resonance spectroscopy       | 25.2% [95% CI, 22.1–27.9]             |
| Li et al. [2019]    | Asia                                          | 237 Observational studies included in meta-analysis 1999-2019 (n=13,044,518) | Ultrasonography, computed tomography scan OR magnetic resonance imaging/spectroscopy, serum based indicies, OR liver biopsy | 30.5% [95% CI, 29.3–30.9]             |
| Kim et al. [2013]   | USA                                           | US national representative samples (n=11,154)               | Ultrasonography                                                                   | 34.0%                                |
| 3.2% [advanced fibrosis] |
| Abeysekera et al. [2020] | UK                                             | UK Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (n=4,021) | Transient elastography with controlled attenuation parameter (CAP) score         | 20.7% [95% CI, 19.4–22.0] for steatosis 2.7% [95% CI, 2.2–3.2] for suspected fibrosis (F2-F4) |

NAFLD, nonalcoholic fatty liver disease; CI, confidence interval; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.
4. Hospitalizations and economic burdens in NAFLD

The National Inpatient Sample is the largest publicly available, all-payer database of national hospital discharges in the US. It contains a 20% stratified and weighted sample of the US community and academic hospital. Hospitalization rates for decompensated cirrhosis and HCC increased approximately 1.5-fold from 2005–2006 to 2013–2014 in the US. Hospitalization rates with NAFLD-related decompensated cirrhosis increased from 13.4 per 100,000 hospitalizations to 32.1 per 100,000 hospitalizations with an annual increase of 10.6%, a magnitude 2-fold higher than chronic hepatitis C virus infection or alcoholic liver disease. The proportion of NAFLD among hospitalizations with decompensated cirrhosis steadily increased from 12.7% to 20.1% while the percentage of chronic hepatitis C infection (39.3% to 27.6%) and alcoholic liver disease decreased (39.0% to 37.4%) from 2005 to 2014. Hospitalizations for NAFLD-related HCC also increased with an annual rate of 8%. Other studies have also exhibited similar trends indicating NASH cirrhosis is the fastest-growing etiology of liver cirrhosis to contribute to hospitalizations. This trend echoes the idea that there is a subset of NAFLD patients who may be “rapid progressors” and need closer monitoring.

The burden of NAFLD on healthcare costs and resource utilization remains significant nowadays. A study based on real-world data from a US medical claims determined that the long-term cumulative healthcare cost of NAFLD is 80% higher than that of a non-NAFLD of similar age and metabolic comorbidities, although this study only considered private insurance and Medicare Advantage health plans. Patients limiting with healthcare access are less likely to have private insurance or Medicare Advantage plans and may be diagnosed with NAFLD at a later stage; there may be a considerable difference in healthcare costs for the management for these populations. This hypothesis raises the concern that NAFLD will impact minorities and patients who experience health disparities. A recent study in Sweden showed that healthcare costs were approximately twice as high in biopsy-confirmed NAFLD patients than in matched controls, which were primarily attributed to higher rates of hospitalizations and outpatient visits.

5. Risk factors and the extrahepatic manifestation of NAFLD

Although NAFLD has been considered as the hepatic manifestation of the metabolic syndrome, a growing body of evidence suggests that NAFLD may be a key driver in metabolic syndrome. The hepatic manifestations of NAFLD are merely one component of a multi-organ systemic disease, which impacts on the cardiovascular, endo-

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Hispanic whites and non-Hispanic blacks based on the third NHANES. A study using the recent 2011 to 2016 NHANES showed that prevalence was highest among Hispanic Americans (42.4%), followed by non-Hispanic whites (28.4%), Asian Americans (18.3%) and non-Hispanic blacks (17.4%). Regarding advanced fibrosis, the NAFLD-related advanced fibrosis increased steadily in non-Hispanic whites. However, it leveled off during 2013 to 2016 in non-Hispanic blacks. Underlying genetic components are likely to play a role in the differences in the prevalence of NAFLD among race/ethnic groups. Genetic factors are further discussed below.

### MORTALITY IN NAFLD

#### 1. All-cause mortality

The first community-based study regarding the survival of patients (n=435) diagnosed with NAFLD using imaging or histology was conducted in Olmsted County, Minnesota, from 1980 to 2000. The study reported a significant decrease in survival for patients with NAFLD compared to the general Minnesota population of the same age and sex at 7.6 years of follow-up (standardized mortality ratio, 1.34; 95% CI, 1.003 to 1.76). Some of studies show similar findings with increased all-cause mortality with ranges of standardized mortality ratio of 1.34 to 2.6 and hazard ratio (HR) of 1.004 to 1.038. However, several other studies showed no difference in all-cause survival between subjects with or without NAFLD. A study using the third NHANES data with linked mortality data reported no significant difference in the all-cause mortality of US-diagnosed NAFLD compared with the non-NAFLD. The most important reasons for this inconsistency among studies might be due to diversity in the NAFLD spectrum according to the study population and consideration for metabolic abnormalities as confounders. A recent study using 27 years follow-up data of the third NHANES, NAFLD was associated with the increased risk for all-cause mortality (HR, 1.20; 95% CI, 1.08 to 1.34), while this study did not consider any metabolic variables as confounders. In this study, the population attributable fraction of NAFLD for all-cause mortality is 7.5% (95% CI, 3.0 to 12.0), while those of diabetes was 38.0% (95% CI, 13.1 to 63.0). This discrepancy sheds light on the importance of identifying high-risk populations within NAFLD that correlates with decreased survival. Compared to subjects without advanced fibrosis, those with a high probability of advanced fibrosis had a 69% increase in mortality after adjustment for other known predictors of mortality. These increases in mortality were almost entirely from cardiovascular causes. An international longitudinal study based on the liver biopsy determined that the fibrosis stage was independently associated with all-cause and liver-related mortality regardless of the presence or severity of other histologic features. In this study, the NAFLD scoring system did not provide any long-term prognostic information. Therefore, defining the presence of advanced fibrosis and the rate of fibrosis progression correlates with survival guides the development of diagnostic pathways that aim to stratify low-risk NAFLD patients from those that will progress to fibrosis or cirrhosis. While liver biopsy remains the gold standard, noninvasive fibrosis markers have been developed (Table 3), including fibrosis-4 (FIB-4), NAFLD fibrosis score as well as aspartate aminotransferase (AST) to platelet ratio index (APRI). A retrospective analysis using the NASH Clinical Research Network database validated the diagnostic performance of FIB-4 score (C-statistics: 0.80) and NAFLD fibrosis score (0.78) for advanced fibrosis. While stratification by fibrosis using NAFLD fibrosis score, FIB-4, and APRI at baseline proved to be a significant predictor of all-cause mortality, discussed previously, this study demonstrated that changes in FIB-4, APRI or NAFLD fibrosis score were significantly associated with disease progression including progression to advanced fibrosis. Further study is needed to confirm the longitudinal association between dynamic changes in noninvasive fibrosis panels and all-cause mortality in NAFLD. Similarly, vibration-controlled transient elastography and magnetic resonance elastography could identify advanced fibrosis with superior accuracy, however, limitation remains for clinical use for primary physician or epidemiologic study.

In addition to the fibrosis stage, several other factors

### Table 3. Formulas of Noninvasive Fibrosis Marker Panels

| Formula                      | Equation                                                                 |
|------------------------------|--------------------------------------------------------------------------|
| Fibrosis-4                   | [(Age [years] × AST [U/L]/platelet [10^12/L] × ALT [U/L])^0.99] + 0.75   |
| NAFLD fibrosis score         | =1.675+0.037×age [years]+0.094×BMI [kg/m^2]+1.13×IFG or diabetes [yes=1, no=0] +0.99×AST/ALT–0.031×platelet count [10^12/L]–0.66×albumin [g/dL] |
| APRI                         | [(AST/upper limit of normal)/platelet count [10^12/L]] × 100             |

AST, aspartate aminotransferase; ALT, alanine transferase; NAFLD, nonalcoholic fatty liver disease; BMI, body mass index; IFG, impaired fasting glucose; APRI, AST to platelet ratio index.
should be considered in predicting outcomes of patients with NAFLD. First, the inclusion of age in the scoring systems may increase predictive power but create biases, especially in the setting of rising rates of childhood obesity. Secondly, race/ethnicity and genetic factors may play a pivotal role in all-cause mortality. A single variant of phospholipase domain-containing 3 or PNPLA3 (rs738409) gene was strongly associated with NAFLD, NASH, and decompensated cirrhosis. The highest frequency of this allele was in Hispanics, followed by non-Hispanic whites and least in non-Hispanic blacks. While we may be able to obtain static measurements of the presence or absence of

| Study design: | 72 weeks, multicenter, randomized, placebo-controlled study by NASH Clinical Research Network (CRN) to assess 25 mg obeticholic acid compared to placebo in NASH (n=283). All had liver biopsy within 90 days of start and at end of study. | Summary: | Patients who had histological improvement had reductions in liver biochemistry at week 12 and 24 compared to those who did not achieve histological improvement. | Risk factors: | Baseline NAS, triglycerides, INR, AST and ALT reduction at week 24. |
| Study design: | Analysis of data from a multicenter phase II study of selonsertib to assess NASH patients with fibrosis stage 2 and 3 on liver biopsy. Pre and post treatment (24 weeks) assessments with magnetic resonance elastography (MRE), MR estimated proton density fat fraction (MRI-PDFF) were studied to assess correlation to histology on liver biopsy | Summary: | MRE and MRI-PDFF both correlated with histology. 15% had fibrosis progression. | Risk factors: | Liver stiffness by MRE was significantly correlated with fibrosis stage as assessed by liver biopsy and non-invasive serum markers. Correlations at 24 weeks were more reliable than at baseline. |
| Study design: | Analysis of data from two phase 2b, placebo-controlled trials of simtuzumab assessing predictors of fibrosis progression in patients with NASH and bridging cirrhosis. | Summary: | 22% of patients with baseline F3 fibrosis progressed to cirrhosis. Factors significantly associated with progression to cirrhosis included higher baseline values of and greater increases in hepatic collagen content, level of alpha-smooth muscle actin, and enhanced liver fibrosis score. | Risk factors: | Enhanced liver fibrosis score >9.8, platelet count, FIB-4/NFS/APRI, platelet count predict progression to cirrhosis. |
| Study design: | Prospective longitudinal cohort study of biopsy proven NAFLD paired with MRE in 2011 and 2018. | Summary: | Liver stiffness on MRE had positive correlation with fibrosis stage. At follow up biopsy, 25% of patients without cirrhosis at baseline had fibrosis progression on histology. More than 15% increase in MRE was strongest predictor in progression to advanced fibrosis. | Risk factors: | Increase in MRE (liver stiffness measurement >15%), AST, platelet count. |
| Study design: | Prospective cohort substudy from NASH CRN who underwent 2 liver biopsies, at least 1 year apart | Summary: | 33.9% progressed by at least 1 stage of fibrosis. 16.8% showed progression from stage 0 to 2 on initial biopsy to stage 3 and 4 on follow up. This group were more likely to have metabolic syndrome. | Risk factors: | Baseline and change in AST, fibrosis stage, ballooning, portal inflammation, change in NAS. |
| Study design: | Systematic search of multiple databases, paired liver biopsy at least 1 year apart. | Summary: | 33.6% progressed by at least 1 stage of fibrosis. 1 stage of progression over 14.3 years for patients with NAFL and 7.1 years for patients with NASH. | Risk factors: | Presence of hypertension (OR 1.94; 95% CI, 1.00–3.74) and low AST:ALT ratio at the time of baseline biopsy. |

Fig. 2. Recent literature summarizing risk factors for nonalcoholic fatty liver disease (NAFLD) progression.
fibrosis, the level of disease activity is difficult to ascertain. Genetic variants may have underpinnings of understanding NAFLD disease activity. PNPLA3 and another common genetic variation called transmembrane 6 superfamily member 2 (TM6SF2) combined with lipoprotein insulin resistance index and age, were able to predict advanced fibrosis with a receiver operative characteristic curve of 0.82. A recent population-based study showed that the homozygous PNPLA3 I148M (rs738409) GG genotype was longitudinally associated with the increased risk for all-cause mortality in the general population and NAFLD.55 Thirdly, not enough data exists to determine the frequency and duration of monitoring for NAFLD. A meta-analysis of patients with NASH with no fibrosis on biopsy indicates the mean rate of progression was 0.13 stage (95% CI, 0.07 to 0.18 stage) per year.51 However, in subgroup analysis, 21.2% of patients progressed four stages of fibrosis over a mean 5.9 (±3.7) years.51 The heterogeneity in “rapid progressors” indicates a need for further investigation for factors that may determine fibrosis or all-cause mortality. Fig. 2 identifies risk factors such as fibrosis stage, biochemical markers, as well as imaging findings that predict the risk of progression to fibrosis and/or cirrhosis in recent literature. Overall, noninvasive fibrosis algorithms, platelet count, and AST have been consistently identified as predictors of fibrosis progression. The risk for progression of fibrosis in NAFLD consists of an interplay between genetic factors, biochemical markers, as well as intrinsic microbial factors.56

In terms of mortality trends in chronic liver disease in the US, age-standardized hepatitis C virus infection-related mortality increased from 2007 to 2013, followed by a marked decrease after the introduction of direct-acting antiviral agents (from 2014 to 2016).57 The annual percentage changes (APC) in hepatitis C virus infection-related mortality increased 2.0% per year (2007–2014) but decreased 6.4% per year (2014–2016).57 In contrast, age-standardized mortality increased for NAFLD (APC 6.1% [2007–2013] and APC 11.3% [2013–2016]).57 Mortality for cirrhosis (APC, 15.4%; 95% CI, 14.1 to 16.7) from NAFLD also increased over the previous decade.58 Fig. 3 shows an increase in the risk of all-cause mortality, with increasing stage of fibrosis among subjects with NAFLD irrespective of the presence of NASH.59 The magnitude of increasing relative risk appeared identical between subjects with NAFLD with/without NASH, with overlapping 95% CI of relative risk estimates.59

2. Cause-specific mortality and complications
Cardiovascular disease is the leading cause of mortality in patients with NAFLD. Compared with other chronic liver diseases, the cause of death in NAFLD was more likely to be cardiovascular disease (approximately 20%).60 In addition, cardiovascular mortality is highest in NAFLD patients with metabolic syndromes.61 Traditional cardiovascular risk factors such as dyslipidemia, smoking, insulin resistance, hypertension, and abdominal obesity, share a substantial overlap with risk factors for NAFLD.62 Association between cardiovascular diseases and NAFLD cannot be attributable to shared risk factors between two diseases.63 Among patients with NAFLD, advanced fibrosis by noninvasive panels was a statistically significant predictor of cardiovascular mortality (HR, 3.46; 95% CI, 1.91 to 6.25 for NAFLD fibrosis score; HR, 2.53; 95% CI, 1.33 to 4.83 for APRI; HR, 2.68; 95% CI, 1.44 to 4.99 for FIB-4).15 An international study with biopsy-proven NAFLD with bridging fibrosis or cirrhosis determined that NAFLD with bridging fibrosis had non-hepatic malignancies and car-
diovascular events predominantly, while NASH cirrhosis had mostly liver-related events. A meta-analysis including 34,043 adults showed that subjects with NAFLD more likely to develop non-fatal and/or fatal cardiovascular disease events than those without NAFLD (odds ratio, 1.64; 95% CI, 1.26 to 2.13) over a median 7 years. In addition, subjects with more severe NAFLD, including advanced fibrosis were had a higher risk of non-fatal and/or fatal cardiovascular events (odds ratio, 2.58; 95% CI, 1.78 to 3.75).

The second most common cause of death is malignancy. Historical Korean cohort study including 25,947 subjects (NAFLD: 33.6%) during the median 7.5 years follow-up reported that the cancer incidence rate of NAFLD was higher than that of non-NAFLD (782.9 vs 592.8 per 100,000 person-years: HR, 1.32; 95% CI, 1.17 to 1.49). NAFLD was associated with the incidence of colorectal cancer in males (HR, 2.01; 95% CI, 1.10 to 3.68) and breast cancer in females (HR, 1.92; 95% CI, 1.15 to 3.20). Another cohort study from Olmsted County, Minnesota, demonstrated that NAFLD was associated with a nearly 2-fold increase in the overall risk of incident cancers during a median 8 years (incidence rate ratio, 1.9; 95% CI, 1.3 to 2.7). The highest risk increase was noted in uterine, followed by stomach, pancreas, and colon cancer.

Liver disease is also an essential contributor to death among patients with NAFLD, being the third most common cause and accounting for 13% of all deaths in a study by Adams et al. In contrast, “chronic liver disease and cirrhosis” is the 13th leading cause of death among the Minnesota general population, accounting for <1% of all deaths. This implies that the increased overall mortality rate among NAFLD patients compared with the general population is at least partly due to complications of NAFLD. Due to second-generation direct-acting antiviral agents approved late 2013, there has been a significant reduction in the waitlist burden related to chronic hepatitis C virus infection; however, the number of total registrants awaiting liver transplantation continues to rise. In 2016, for the first time, both alcoholic liver disease and NASH had surpassed chronic hepatitis C virus infection as the leading indications of liver transplantation in the US. HCC is the third leading cause of cancer-related deaths in the world. There is an increase in the rate of HCC reported by Surveillance, Epidemiology, and End Results-Medicare linked database from 2004 to 2009, which is not explained by the increase of incidence in NAFLD. Data suggest a poorer prognosis with HCC from NAFLD-cirrhosis as 62% of patients with NAFLD-related HCC died within 1 year than those with HCC related to viral hepatitis and a majority (84.3%) of patients with NAFLD-related HCC died of their primary liver cancer. A study using the US national mortality data showed that there was a linear increase in the age-standardized HCC-related mortality rates for NAFLD (19.1%; 95% CI, 14.0 to 24.5). Among patients with NAFLD, cardiovascular disease increased at a gradual pace (APC, 2.0%; 95% CI, 0.6 to 3.4), whereas liver-related mortality increased rapidly (APC, 12.6%; 95% CI, 11.7 to 13.5) based on the US national mortality data from 2007 to 2017.

CURRENT HEALTH POLICY

Even though the prevalence of NAFLD is already 30% and projected to increase substantially, there is no clear consensus currently on the most cost-effective to identify the approximately 100 million NAFLD patients in the US general population that will progress to the 1.5% who experience fibrosis and cirrhosis. In fact, no clear national policies exist regarding identifying high-risk populations and monitoring for progression to cirrhosis. In 2018 and 2019, a comprehensive survey of the national policy in 29 European countries showed an absence of written national strategies or action plans for NAFLD and a small portion of countries had national clinical guidelines (34%) and recommended screening for NAFLD (38%) in all patients with either diabetes, obesity, and/or metabolic syndrome. This could indicate the lack of appreciation for the high prevalence and the lack of clear guidelines in identifying and following high-risk patients using current diagnostic methods and classification scores.

CONCLUSIONS

This review summarizes the worldwide incidence and prevalence of NAFLD, discusses diagnostic nuances in determining subjects with NAFLD who progress to cirrhosis, and quantifies downstream impacts on the healthcare economy in the context of all-cause and cause-specific mortality. Currently, the estimated prevalence of NAFLD by imaging was 25.2%, with an estimated prevalence of NASH to be lower, ranging from 3% to 5%. NAFLD can progress to NASH with advanced fibrosis or cirrhosis in about 3% to 5% of NAFLD. The fibrosis stage is independently associated with all-cause and liver-related mortality regardless of the presence or severity of other histologic features. Further study is needed to confirm the longitudinal association between dynamic changes in noninvasive fibrosis panels and all-cause mortality. Age, race/ethnicity, sex, metabolic comorbidities, and genetics were associated with outcomes of NAFLD. Cardiovascular disease, extra-
hepatic malignancy, and end-stage liver disease are the leading cause of mortality in patients with NAFLD. This review identifies that screening guidelines for NAFLD to identify high-risk populations and monitoring for progression to cirrhosis remains a significant unmet need in the field.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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