Economic and Clinical Burden of Nonalcoholic Steatohepatitis in Patients With Type 2 Diabetes in the U.S.

Zobair M. Younossi,[1,2] Radhika P. Tampi,[1] Andrei Racila,[1,2] Ying Qiu,[3] Leah Burns,[3] Issah Younossi,[4] and Fatema Nader[4]

OBJECTIVE

Nonalcoholic steatohepatitis (NASH) is a progressive form of nonalcoholic fatty liver disease (NAFLD) and is strongly associated with type 2 diabetes mellitus (T2DM). Patients with both T2DM and NASH have increased risk for adverse clinical outcomes, leading to higher risk for mortality and morbidity. We built a Markov model with 1-year cycles and 20-year horizon to estimate the economic burden of NASH with T2DM in the U.S.

RESEARCH DESIGN AND METHODS

Cohort size was determined by population size, prevalence of T2DM, and prevalence and incidence of NASH in 2017. The model includes 10 health states—NAFL, NASH fibrosis stages F0 through F3, compensated and decompensated cirrhosis, hepatocellular carcinoma, 1 year post–liver transplant, and post–liver transplant—as well as liver-related, cardiovascular, and background mortality. Transition probabilities were calculated from meta-analyses and literature. Annual costs for NASH and T2DM were taken from literature and billing codes.

RESULTS

We estimated that there were 18.2 million people in the U.S. living with T2DM and NAFLD, of which 6.4 million had NASH. Twenty-year costs for NAFLD in these patients were $55.8 billion. Over the next 20 years, NASH with T2DM will account for 65,000 transplants, 1.37 million cardiovascular-related deaths, and 812,000 liver-related deaths.

CONCLUSIONS

This model predicts significant clinical and economic burden due to NASH with T2DM over the next 20 years. In fact, this burden may be greater since we assumed conservative inputs for our model and did not increase costs or the incidence of T2DM over time. It is highly likely that interventions reducing morbidity and mortality in NASH patients with T2DM could potentially reduce this projected clinical and economic burden.

Nonalcoholic fatty liver disease (NAFLD) is characterized by hepatic steatosis (>5%) in the absence of excessive alcohol consumption or other causes of fatty liver disease and chronic liver disease (1). NAFLD ranges from simple steatosis (NAFL), which has a low likelihood of progression to advanced liver disease, to nonalcoholic steatohepatitis (NASH), which has greater potential for progression. NAFLD is recognized as one of the most common causes of chronic liver disease in the U.S. and worldwide (1–3). NAFLD is

highly prevalent in patients with components of metabolic syndrome (4,5). In fact, risk factors for NAFLD include visceral obesity, impaired insulin sensitivity, and type 2 diabetes mellitus (T2DM), as well as older age, male sex, and Hispanic ethnicity (4,6,7). The global prevalence of NAFLD is estimated to be 25.2%, and the prevalence of NASH is estimated at 1.5–6.45% in the general population (8,9). Patients with NASH are more likely to progress to advanced liver disease and die of liver-related causes, and all NAFLD patients, regardless of underlying liver pathology, are at risk for cardiovascular disease (10–13). In addition to clinical burden, NAFLD and NASH are associated with significant health care utilization (14–16).

Although the global prevalence of NAFLD in the general population is quite high, the prevalence is even greater in patients with T2DM, at 55.5% (95% CI 47.3–63.7) globally when diagnosed by ultrasound or proton MRS (^{1}H-MRS) and 59.7% (95% CI 52.8–66.5) when diagnosed using ultrasound or aminotransferase levels (17,18). In the U.S., the prevalence of NAFLD among patients with T2DM was 51.8% (95% CI 31.3–71.6) when using ultrasound or ^{1}H-MRS and 53.1% (95% CI 26.1–78.4) when using any diagnostic method. The prevalence of NASH among patients with T2DM was 37.3% (95% CI 24.7–50.0) when diagnosed via liver biopsy, and the prevalence of advanced fibrosis among biopsied patients with NAFLD and T2DM was 17.02% (95% CI 7.3–34.9) (17).

Additionally, the presence of T2DM in patients with NAFLD has been shown to adversely affect long-term outcomes. Patients with T2DM have higher rates of fibrosis progression, cirrhosis, hepatocellular carcinoma (HCC), and both liver-related and cardiovascular mortality than patients without T2DM (5,19–21). The growing global epidemic of T2DM can potentially fuel the future clinical burden of NASH and NASH-related liver complications. In 2015, 23 million adults in the U.S. had been diagnosed with T2DM, with another 7.2 million estimated to be undiagnosed, comprising over 12% of the adult U.S. population. An estimated 1.5 million more adults are expected to be diagnosed with T2DM each year (22). Medical expenditures for patients with diagnosed T2DM are ∼2.3 times higher than those of the general population, with an estimated one in four health care

dollars being spent on diabetes care and management (23). This growing global prevalence of T2DM will not only adversely influence the clinical burden of NAFLD but also its economic burden. Therefore, our aim was to estimate the overall economic burden, excess burden due to liver disease, and clinical outcomes of the 2017 adult population diagnosed with T2DM and NAFLD in the U.S. over the next 20 years.

RESEARCH DESIGN AND METHODS

Model Building

We constructed a Markov model with both an incidence and prevalence module using Microsoft Excel (Fig. 1). Both modules had a 20-year horizon, with a cycle length of 1 year. Starting with the diagnosed T2DM population in each age-group cohort, we modeled the incidence of NASH in patients with NAFLD without histologic evidence of NASH (NAFL or fatty liver/simple steatosis) and the prevalent NASH population as of 2017. NASH prevalence was reported for all stages of fibrosis using the Meta-analysis of Histological Data in Viral Hepatitis (METAVIR) scale, from F0 (no fibrosis) to F4 (cirrhosis; represented here as the compensated cirrhosis [CC] health state). The incidence model consisted of 10 health states; patients started with simple steatosis (NAFL) and progressed through the model to NASH fibrosis stages F0–F3, CC, decompensated cirrhosis (DCC), HCC, 1 year post–liver transplant (1yPLT), and PLT, with three absorbing mortality states (liver related, cardiovascular, and background mortality [BM]). The prevalence module excluded the NAFL state but otherwise had health states identical to the incidence module. The prevalence of NASH was defined as any degree of fibrosis from METAVIR stages 0–4, where stage 4 is represented in the model as CC. In both modules, patients transitioned to a different state (or remained in the same state) every year based on the associated transition prob!ability (Supplementary Table 1) and exited the model when they reached one of the three absorbing mortality states.

Transition probabilities were calculated from the literature and meta-analyses (Supplementary Table 1). We calculated the relative risk of advanced fibrosis and cirrhosis and cardiovascular mortality for patients with T2DM compared with the general population (24). We multiplied the annual transition rates (back calculated from our transition probabilities)

from our previous model by the relative risk (24,25). The relative risk for transitions from low fibrosis states (F0/F1) to higher fibrosis states (F2/F3) and from high fibrosis states (F2/F3) to cirrhosis (CC) was 1.78, and relative risk for transitions from low fibrosis states to cirrhosis was 1.2 for patients with T2DM based on a study assessing independent predictors of liver fibrosis in patients with NAFLD (24) (Supplementary Table 1). Our approach was supported by comparison with a recently published study in which progression to advanced fibrosis was measured in middle-aged Japanese patients with and without T2DM. This study found that the hazard ratio for fibrosis progression was 1.879 (95% CI 1.40–2.52). We calculated the annual transition probability from cumulative incidence reported over 3–10 years; the transition probability in patients without T2DM ranged from 1.02% to 1.37%, and annual transition probability to advanced fibrosis in patients with T2DM ranged from 2.08% to 2.71%. This closely mirrors the annual probabilities to advanced fibrosis used in this model (20) (Supplementary Table 1). Transition probabilities from DCC and HCC states to 1yPLT and from 1yPLT to PLT were adjusted according to the age of the cohort, as patients are less likely to receive and survive a transplant with increasing age, with 1-year survival for liver transplants due to metabolic disease at 89.2% according to the Organ Procurement and Transplantation Network (Supplementary Table 2). Age-related BM was calculated from life tables from the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics and applied in 5-year intervals (26) (Supplementary Table 3).

The overall prevalence of diagnosed T2DM in all age-group cohorts was 9.9%, or 24.7 million adults in the U.S., as determined from the 2017 CDC National Diabetes Statistics Report (22) (Table 1). We used the prevalence of diagnosed T2DM rather than total estimated diabetes population as we would not be able to estimate when (or if) patients would receive a definitive T2DM diagnosis during their lifetime, which is associated with significantly higher direct medical costs.

Incidence Module

In the incidence module, all patients enter the model in the NAFL state and progress to the NASH with F0 stage
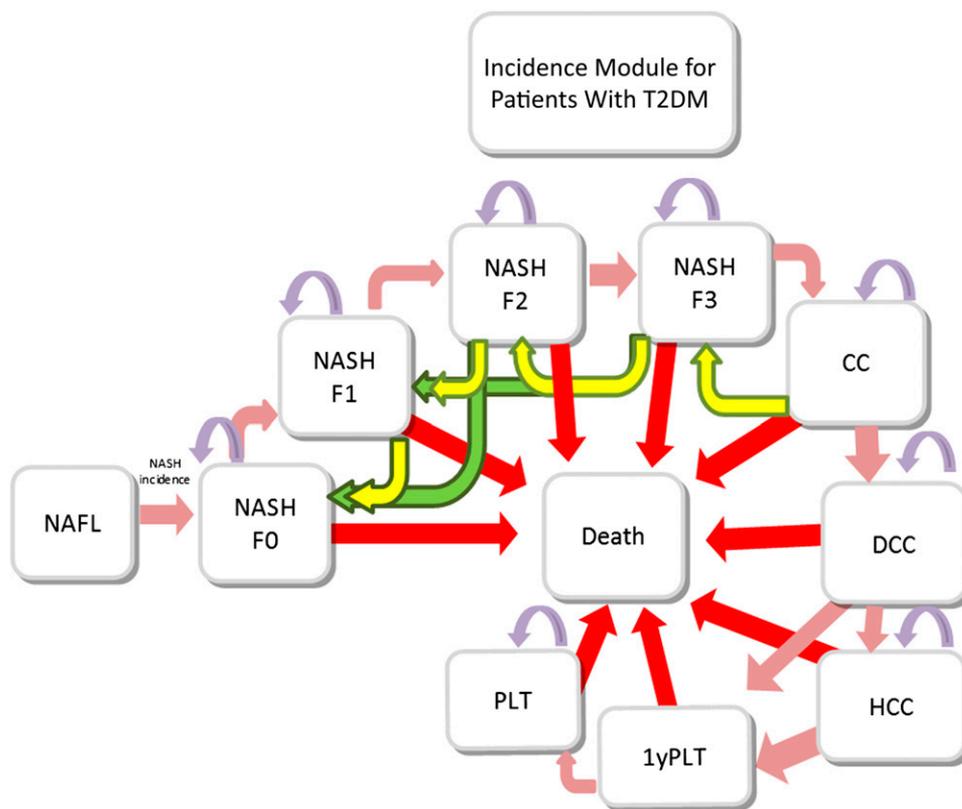
Figure 1—Model figure for incidence module.

according to the age-related annual incidence of NASH (Fig. 1 and Table 1). Each age-group cohort was modeled over a 20-year horizon; thus, we calculated the economic burden associated with the NAFL state, all NASH states, and diabetes costs for each age-group cohort over two decades.

Estimates for the prevalence of NAFL in patients with T2DM depend on the method of diagnosis, BMI, ethnicity, age, and hypertension status of patients involved in the study. As the prevalence of comorbidities associated with both NAFLD and T2DM increases with age, we assumed that the prevalence of NAFL also increased with age. The overall prevalence of overweight (BMI $\geq$25 and $<$30 kg/m^2), obesity (BMI $\geq$30 and $<$40 kg/m^2), and severe obesity (BMI $>$40 kg/m^2) in adult patients with T2DM was 26.1% (95% CI 23.2–29.2), 43.5% (95% CI 39.6–47.6), and 17.8% (95% CI 14.8–21.3), respectively (22). We used the prevalence of obesity among patients with T2DM as a proxy for hepatic steatosis/NAFL prevalence in each age-group cohort as liver triglyceride content has been positively associated with increasing BMI and age (although this is not to say that patients with BMI $<$30 kg/m^2 do not have significant hepatic triglyceride content) such that NAFL prevalence increased from 22% in the 18–34 age-group cohort to 58% in the 65+ age-group cohort (22,27–29) (Table 1).

The annual incidence rate of NASH in the general population was 20% of the annual incidence of NAFLD in the general population (5,30); however, the incidence of T2DM in patients with NAFLD is up to five times higher compared with the T2DM incidence in the general population (17,31). As the prevalence of NAFLD is high in patients with T2DM

Table 1—Demographic inputs for T2DM, NAFL, and NASH in the U.S. in 2017

Age-group (years)	U.S. population size	Diagnosed T2DM	Diagnosed T2DM cohort	NAFL prevalence in T2DM	Prevalent NAFL cohort	Annual incidence rate of NASH in T2DM with NAFL	NASH prevalence in T2DM	Prevalent NASH cohort	NAFLD (NAFL + NASH) prevalence in T2DM	Total prevalent NAFLD (NAFL + NASH) in T2DM
18–34	75,521,000	2.20%	1,661,462	22%	365,522	0.10%	10%	166,146	32.0%	531,668
35–49	61,419,000	8.10%	4,974,939	35%	1,741,229	0.21%	19%	945,238	54.0%	2,686,467
50–64	63,302,000	12.40%	7,849,448	47%	3,689,241	0.28%	26%	2,040,856	73.0%	5,730,097
65+	49,244,000	20.80%	10,242,752	58%	5,940,796	0.36%	32%	3,277,681	90.0%	9,218,477
Total	249,486,000	9.91%	24,728,601	47.46%	11,736,787	—	26.0%	6,429,922	73.5%	18,166,709

(and vice versa), we assumed that the incidence of NASH and NAFLD would also be two to five times higher in the population diagnosed with T2DM as compared with the general population and named this parameter the T2DM-NASH incidence factor. For our base case analysis, we set the T2DM-NASH incidence factor at 3.5 but varied this in our sensitivity analysis.

Prevalence Module

We estimated NASH prevalence with any degree of fibrosis (F0–CC). The use of certain diagnostic modalities tends to underestimate hepatic steatosis or have low sensitivity below 12.5% liver fat (28,32) or can overestimate the prevalence of NASH (percutaneous liver biopsy, as patients generally have a clinical indication for this invasive procedure or are diagnosed in tertiary care centers). The prevalence of NASH among patients with diagnosed T2DM in other studies has varied from 26% (by liver biopsy in patients with T2DM with normal plasma aminotransferase levels) to 52% using ^{1}H-MRS and liver biopsy (and reporting that 50% of NAFLD patients have NASH) to 96.8% using ultrasound and liver biopsy (with 100% of patients with T2DM having NAFLD) (28,29,33). A recent meta-analysis estimated the global prevalence of NASH among patients with T2DM at 37%; however, we believe that using liver biopsy alone would introduce a bias toward overestimation in our model (17).

The estimated prevalence of advanced fibrosis among biopsied patients with T2DM and NAFLD was 17.02% (95% CI 7.29–34.86); thus, we assumed that 80% of the prevalent NASH population would enter the model in stages F0–F2 and 20% of the prevalent NASH population would enter the model in stages F3/CC (17). Patients would then progress through the model according to appropriate transition probabilities until reaching one of the three absorbing mortality states.

Costs

We calculated the average total annual direct medical cost associated with each health state from the U.S. health system perspective. Costs for NAFLD states in the model were microcosted using 2017 Current Procedural Terminology (CPT) codes, assuming nonfacility prices, global service, and no modifiers (Supplementary Table 4).

Costs for fibrosis states included annual low to medium complexity coded physician consultations, transient elastography, lipid panel, liver profile, complete blood count, percutaneous liver biopsy to confirm NASH diagnosis, and one-time screening per patient for hepatitis B and C. Costs for advanced liver disease (states CC through HCC) were derived from the literature, validated by hepatology experts, and adjusted for our analysis (34–36). For those cost data imputed from studies on advanced liver disease in hepatitis C and nonalcoholic liver disease patients, we excluded the cost of antivirals and other disease-specific costs. For liver transplants and associated care for the year after (1yPLT state), we used the billed charges from the 2017 Milliman Research Report on U.S. organ and tissue transplant costs (37) multiplied by the average national cost-to-charge ratio across hospitals from the National Inpatient Sample, Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality (38). Charges for liver transplant and associated care were inclusive of care 30 days pretransplant, organ procurement, hospital transplant admission (facility charges), physician fees, the first 180 days posttransplant discharge, and necessary drugs. For the PLT state, we calculated the cost of antirejection medications and an annual visit with a transplant specialist team for blood draw and associated care using 2017 CPT codes. We did not include NAFLD treatment costs (such as pioglitazone, vitamin E, or intensive weight loss/ nutrition programs) or the cost of complications due to HCC or liver transplant, or vary state costs by age-group cohort for NAFLD.

The average annual direct medical costs attributed to diagnosed diabetes for each age-group cohort were taken from a 2017 paper released by the American Diabetes Association. These costs are the incremental costs incurred due to diabetes relative to the general population and are inclusive of institutional care, outpatient care, and outpatient medications and supplies, including insulin (23). As is standard, all future costs were discounted by 3% annually.

Sensitivity Analysis

We conducted a probabilistic sensitivity analysis (PSA) to assess the parameter and varied transition probabilities; costs; prevalence of T2DM, NAFL, and NASH; and incidence of NASH. Probability distributions and parameters for each model input included in the sensitivity analysis can be found in Supplementary Table 4. We used a gamma distribution for costs, beta-PERT (Program Evaluation and Review Technique) distribution for demographic inputs, and Dirichlet (multivariate beta distribution) for transition probabilities. Probability distribution parameters (α and β) for costs and transition probabilities were estimated using a method of moments approach. We used the average value found in the literature for the "most likely" value for beta-PERT probability distributions for demographic inputs. For inputs without a range of values, we set the lower and upper bounds to ±35% of the most likely value. Base case inputs for our probabilistic analysis included adults aged 50–64 years. We averaged results from 10,000 Monte Carlo microsimulations for all parameters in both the incidence and prevalence modules of the model histograms showing the frequency of select outcomes (liver transplants, liver-related mortality, and liver disease–related costs). The aggregated results of 10,000 Monte Carlo microsimulations have been provided in the Supplementary Data.

RESULTS

Deterministic Results

Clinical Burden of NASH With T2DM

The prevalence of diagnosed T2DM among adults in the U.S. was estimated to be 9.9%, comprising 24.7 million adults. The prevalence of NAFLD in the diagnosed T2DM population was estimated to be 18.2 million people out of 24.7 million diagnosed with T2DM. In fact, our model shows that the prevalence of NAFLD among patients with T2DM is 73.5%, which is slightly higher than the mean global prevalence estimated in recent meta-analyses but still within the 95% CI (17,18). The proportion of all adults with both diagnosed T2DM and NAFLD in 2017 is thus estimated to be 7.3%. The prevalence of NAFL in adults with T2DM was estimated to be 47.5%, or 11.7 million people. The prevalence of NASH in patients with T2DM in the U.S. was estimated to be 26%, or 6.4 million patients (Table 1).

We also estimated the clinical burden of NASH with T2DM. Using the incidence

module, we estimate that over two decades, there will be nearly 865 liver transplants, 27,000 person-years spent with DCC, and 10,900 person-years spent with HCC. Of patients in the incidence cohort, 55.8% will die of age-related mortality, 17,600 (0.15%) will die of liver-related complications, and 485,000 (4.1%) will die of cardiovascular mortality (Table 2). Although the nature of a Markov model makes it impossible to identify which proportion of cardiovascular deaths are attributable to NAFL versus NASH, adverse liver-related outcomes are entirely attributable to NASH patients as the probability of moving from the NAFL state to any other state except NASH F0, F1, cardiovascular mortality, or BM is not possible.

The prevalence module estimates that 64,000 liver transplants will occur over the next two decades of the prevalent NASH with T2DM cohort, comprising 29% of the total estimated liver transplants performed over that time period. In this cohort, liver-related mortality will account for 795,000 (12.4%) deaths, and cardiovascular mortality will cause 883,000 (13.7%) deaths. Finally, this cohort will experience 1.2 million and 468,000 person-years spent with DCC and HCC, respectively.

In summary, over the next 20 years, out of a cohort of 18.2 million people, NASH and T2DM will be potentially responsible for 64,900 liver transplants, 812,000 liver-related deaths, 1.37 million cardiovascular deaths, 1.27 million DCC person-years, and 479,000 HCC person-years (Table 2).

Economic Burden of NASH in T2DM

The total economic burden for the incident NASH cohort with T2DM was $25.4 billion. Of this cost, $22 billion (87%) was attributable to diabetes care and management and $3.4 billion (13%) related to NASH care. The per-person-per-year cost of incident NASH and T2DM for each age-group cohort in the incidence module is $5,100 for ages 18–34 years, $4,400 for ages 35–49 years, $5,700 for ages 50–64 years, and $10,800 for ages 65 years and over. The economic burden for NAFL was $1 trillion, with $990 billion (98.6%) attributable to diabetes care and $13.7 billion (1.4%) attributable to NAFL care.

The economic burden for the prevalent NASH cohort with T2DM was $642 billion, with $482.2 billion (75%) attributable to diabetes care and management and $160.3 billion (25%) to NASH-related liver care. The per-person-per-year cost of NASH and T2DM for each age-group cohort in the prevalence module is $7,700 for ages 18–34 years, $7,200 for ages 35–49 years, $7,700 for ages 50–64 years, and $13,100 for ages 65 years and over.

In summary, the total cost of NASH with T2DM is $667.9 billion, with $504.2 billion (75.5%) related to diabetes management and $163.7 billion (24.5%) related to NASH care. For all patients with NAFLD and T2DM, the total cost per-person-per-year is $7,700, with costs attributable to diabetes comprising $6,900 (89.4%) of total cost and NAFLD-attributable costs comprising $819 (10.6%) (Table 2).

PSA

Sensitivity analyses for our model showed that for adults aged 50–64 years with diagnosed T2DM in the U.S. and either NAFL or NASH, our model likely underestimates the number of liver transplants and liver-related deaths (Supplementary Table 5). Average results from our PSA were significantly higher than deterministic results for these two outputs and show a large spread when the frequency of each output is plotted (Supplementary Fig. 1A and B). The average lifetime cost calculated from our PSA is close to our deterministic results; however, the range of costs over 10,000 microsimulations in the incidence module has a large spread (Supplementary Fig. 1C). Overall, our model is robust in predicting future costs in the prevalence model but likely underestimates the clinical burden of NAFLD among patients with T2DM.

CONCLUSIONS

This is the first study to assess the economic and clinical burden of NASH and NAFLD in patients with T2DM. In this analysis, we used the most recent data from a meta-analysis to obtain the prevalence and transition probabilities for this cohort of patients with T2DM (Supplementary Table 4). We used the most recent cost data to determine the economic burden in the U.S. (Supplementary Table 4). To be complete, we used both prevalence and incidence modules to estimate future outcomes. To evaluate areas of uncertainty, extensive sensitivity analyses were performed.

Table 2—Results for incident and prevalent NASH populations, 2017

	Incident population		Prevalent population	
	Non-NASH NAFLD	NASH	NASH	All NAFLD
Total cost	$1,004,497,393,586	$25,384,714,465	$642,564,607,921	$1,672,446,715,972
Total liver-related care costs	$13,731,975,851	$3,407,540,732	$160,340,175,347	$177,479,691,930
Total diabetes-related care costs	$990,765,417,735	$21,977,173,733	$482,224,432,574	$1,494,967,024,042
Person-years accumulated	144,715,642	3,453,969	68,511,726	216,681,338
Total cost per person-year	$6,941	$7,349	$9,379	$7,718.46
NAFLD-attributable costs per person-year	$95	$987	$2,340	$819
Percent of total cost per person-year attributable to NAFLD	1.37%	13.4%	25.0%	10.6%
Diabetes-attributable costs per person-year	$6,846	$6,363	$7,039	$6,899
Percent of total cost per person-year attributable to diabetes	98.6%	86.6%	75.0%	89.4%
Liver transplants	865		64,013	64,878
Liver-related deaths	17,592		794,638	812,230
DCC person-years	26,942		1,242,662	1,269,604
HCC person-years	10,868		468,481	479,349
Cardiovascular deaths	485,486		883,469	1,368,955

Our data show that 7.3% of the adult population have NAFLD and T2DM in the U.S., with 6.4 million individuals with diabetes estimated to have underlying NASH. The most significant clinical burden in individuals with diabetes and NAFLD was seen in those with NASH. In fact, the population size of patients with NASH and T2DM was over 1.8 times smaller than the population with T2DM and NAFL but accounted for 43–74 times more adverse clinical outcomes (DCC person-years 46-fold higher, HCC person-years 43-fold higher, liver-related mortality 45-fold higher, and liver transplant 74-fold higher). These data are consistent with the evidence that NASH is the progressive form of NAFLD, and this progression may be exacerbated in the setting of T2DM (19,24,39).

It is also important to remember that cardiovascular mortality is the main cause of death in NAFLD. In our model, cardiovascular mortality is 1.7 times higher than liver mortality for the entire cohort, as both NAFLD and T2DM increase the risk of major adverse cardiac events (11–13,24,40). In contrast, NASH with T2DM also accounts for a large number of liver-related adverse outcomes, which is primarily limited to the progressive NASH.

Our cost data also provided some other interesting insights. As expected, the total cost of NAFLD with T2DM in the U.S. over the next two decades is estimated to be $1.67 trillion. In this context, the majority of costs are related to the diabetes care. This is expected because the majority of patients have NAFL and rarely develop severe liver disease; thus, their health care costs are mostly driven by T2DM management and care. Nevertheless, liver-related health care for this group still accounts for $13.7 billion, which is attributed to annual liver checkups and other related clinical evaluations.

In contrast, the population with NASH and T2DM accounted for substantial cost burden. The total liver-related costs of NASH with T2DM were almost 12 times higher ($163.7 billion vs. $13.7 billion) than NAFL with T2DM. The liver-related costs for NAFL were $95 per person-year, whereas liver-related costs for NASH were 24 times higher at $2,275 per person-year.

The major limitation of our study is the lack of prospective real-world natural history data to determine the true incidence and progression of NASH. Our model also does not take into account rising medical costs (particularly insulin), the costs associated with complications common in advanced liver disease, or the implementation of future costly treatments or technologies to treat NASH or T2DM. Finally, our model does not take into account the pool of NAFLD patients with newly diagnosed diabetes (incident T2DM) or the rising incidence of NAFLD (higher than current rates), which would significantly increase future costs. As our approach was conservative and based on present-day standards, we limited our time horizon for the model to 20 years to reduce uncertainty in model outcomes. Nevertheless, our in-depth approach of performing a meta-analysis prior to establishing this model and updating transition probabilities and cost data with the latest evidence brings substantial strength to our approach.

This model focuses on the incidence of NAFLD in patients with T2DM and the subsequent costs and health outcomes associated with these two conditions. However, the authors recognize that there exists an intricate relationship and dual causality between T2DM and NAFLD and that the mechanisms underlying both diseases are uniquely intertwined. Although we did not focus on the incidence of T2DM in NAFLD subjects in this model, we do believe that NAFLD, as the hepatic manifestation of the metabolic syndrome, plays an important role in the development of and exacerbation of diabetes and other metabolic conditions in a unique, "multiple hit" combination of genetics and environmental factors.

In summary, this analysis suggests that the clinical and economic burden of NASH in patients with T2DM is currently substantial, and as the prevalence of T2DM increases globally, this burden will continue to rise. It is critical that clinicians, payers, policy makers, and the pharmaceutical industry not only understand the clinical burden of NASH in patients with T2DM but also the economic and patient-reported outcomes burden. These multiple assessments provide a more complete outlook of the potential burden of NAFLD and NASH in the U.S.

References

1. Chalasani N, Younossi Z, Lavine JE, et al.; American Gastroenterological Association; American Association for the Study of Liver Diseases; American College of Gastroenterology. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012;142:1592–1609
2. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol 2018;15:11–20
3. Younossi ZM. Non-alcoholic fatty liver disease - a global public health perspective. J Hepatol 2019;70:531–544
4. Younossi ZM, Otgonsuren M, Venkatesan C, Mishra A. In patients with non-alcoholic fatty liver disease, metabolically abnormal individuals are at a higher risk for mortality while metabolically normal individuals are not. Metabolism 2013;62:352–360
5. Golabi P, Otgonsuren M, de Avila L, Sayiner M, Rafiq N, Younossi ZM. Components of metabolic syndrome increase the risk of mortality in non-alcoholic fatty liver disease (NAFLD). Medicine (Baltimore) 2018;97:e0214
6. Duseja A, Chalasani N. Epidemiology and risk factors of nonalcoholic fatty liver disease (NAFLD). Hepatol Int 2013;7(Suppl. 2):755–764
7. Zelber-Sagi S, Nitzan-Kaluski D, Halpern Z, Oren R. Prevalence of primary non-alcoholic fatty liver disease in a population-based study and its association with biochemical and anthropometric measures. Liver Int 2006;26:856–863
8. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016;64:73–84
9. Le MH, Devaki P, Ha NB, et al. Prevalence of non-alcoholic fatty liver disease and risk factors for advanced fibrosis and mortality in the United States. PLoS One 2017;12:e0173499
10. Misra VL, Khashab M, Chalasani N. Non-alcoholic fatty liver disease and cardiovascular risk. Curr Gastroenterol Rep 2009;11:50–55
11. Mellinger JL, Pencina KM, Massaro JM, et al. Hepatic steatosis and cardiovascular disease

outcomes: an analysis of the Framingham Heart Study. J Hepatol 2015;63:470–476

12. Targher G, Bertolini L, Rodella S, et al. Non-alcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. Diabetes Care 2007;30:2119–2121

13. Drapkina OM, Yafarova AA. Non-alcoholic fatty liver disease and cardiovascular risk: scientific problem state. Ration Pharmacother Cardiol 2017;13:645–650

14. Sayiner M, Otgonsuren M, Cable R, et al. Variables associated with inpatient and outpatient resource utilization among Medicare beneficiaries with nonalcoholic fatty liver disease with or without cirrhosis. J Clin Gastroenterol 2017; 51:254–260

15. Younossi ZM, Zheng L, Stepanova M, Henry L, Venkatesan C, Mishra A. Trends in outpatient resource utilizations and outcomes for Medicare beneficiaries with nonalcoholic fatty liver disease. J Clin Gastroenterol 2015;49:222–227

16. Younossi ZM. Patient-reported outcomes and the economic effects of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: the value proposition. Hepatology 2018;68:2405–2412

17. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. J Hepatol 2019;71:793–801

18. Dai W, Ye L, Liu A, et al. Prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus: a meta-analysis. Medicine (Baltimore) 2017;96:e8179

19. Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. Clin Gastroenterol Hepatol 2004;2:262–265

20. Tada T, Toyoda H, Sone Y, et al. Type 2 diabetes mellitus: a risk factor for progression of liver fibrosis in middle-aged patients with nonalcoholic fatty liver disease. J Gastroenterol Hepatol 2019;34:2011–2018

21. El-Serag HB, Tran T, Everhart JE. Diabetes increases the risk of chronic liver disease and hepatocellular carcinoma. Gastroenterology 2004;126:460–468

22. Centers for Disease Control and Prevention. *National Diabetes Statistics Report, 2017*. Atlanta, GA, Centers for Disease Control and Prevention, 2017

23. Yang W, Dall TM, Beronjia K, et al.; American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. Diabetes Care 2018;41:917–928

24. Hossain N, Afendy A, Stepanova M, et al. Independent predictors of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2009;7:1224–1229, 1229.e1-2

25. Younossi ZM, Tampi R, Priyadarshini M, Nader F, Younossi IM, Racila A. Burden of illness and economic model for patients with non-alcoholic steatohepatitis (NASH) in the United States. Hepatology 2019;69:564–572

26. Arias E, Heron M, Xu J. United States life tables. National Vital Statistics Reports 66(4) [Internet], 2017. Available from https://www.cdc.gov/nchs/data/nvsr/nvsr66/nvsr66_04.pdf. Accessed 17 April 2018

27. Iglay K, Hannachi H, Joseph Howie P, et al. Prevalence and co-prevalence of comorbidities among patients with type 2 diabetes mellitus. Curr Med Res Opin 2016;32:1243–1252

28. Portillo-Sanchez P, Bril F, Maximos M, et al. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. J Clin Endocrinol Metab 2015;100:2231–2238

29. Bril F, Millán L, Kalavalapalli S, et al. Use of a metabolomic approach to non-invasively diagnose non-alcoholic fatty liver disease in patients with type 2 diabetes mellitus. Diabetes Obes Metab 2018;20:1702–1709

30. Allen AM, Therneau TM, Larson JJ, Coward A, Somers VK, Kamath PS. Nonalcoholic fatty liver disease incidence and impact on metabolic burden and death: a 20 year-community study. Hepatology 2018;67:1726–1736

31. Mantovani A, Byrne CD, Bonora E, Targher G. Nonalcoholic fatty liver disease and risk of incident type 2 diabetes: a meta-analysis. Diabetes Care 2018;41:372–382

32. Bril F, Ortiz-Lopez C, Lomonaco R, et al. Clinical value of liver ultrasound for the diagnosis of nonalcoholic fatty liver disease in overweight and obese patients. Liver Int 2015; 35:2139–2146

33. Masarone M, Rosato V, Aglitti A, et al. Liver biopsy in type 2 diabetes mellitus: steatohepatitis represents the sole feature of liver damage. PLoS One 2017;12:e0178473

34. Kaplan DE, Chapko MK, Mehta R, et al.; VOCAL Study Group. Healthcare costs related to treatment of hepatocellular carcinoma among veterans with cirrhosis in the United States. Clin Gastroenterol Hepatol 2018;16:106–114.e5

35. McAdam-Marx C, McGarry LJ, Hane CA, Biskupiak J, Deniz B, Brixner DI. All-cause and incremental per patient per year cost associated with chronic hepatitis C virus and associated liver complications in the United States: a managed care perspective. J Manag Care Pharm 2011;17:531–546

36. Allen AM, Van Houten HK, Sangaralingham LR, Talwalkar JA, McCoy RG. Healthcare cost and utilization in nonalcoholic fatty liver disease: real-world data from a large U.S. claims database. Hepatology 2018;68:2230–2238

37. Bentley TS, Phillips SJ, Hanson SG. 2017 U.S. organ and tissue transplant cost estimates and discussion [Internet], 2017. Available from http://us.milliman.com/uploadedFiles/insight/2017/2017-Transplant-Report.pdf. Accessed 15 December 2018

38. HCUP National Inpatient Sample (NIS). Cost-to-charge ratio files (CCR). Healthcare Cost and Utilization Project (HCUP) [Internet], 2016. Rockville, MD, Agency for Healthcare Research and Quality (AHRQ). Available from https://www.hcup-us.ahrq.gov/db/state/costtocharge.jsp. Accessed 25 April 2019

39. Angulo P, Kleiner DE, Dam-Larsen S, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. Gastroenterology 2015;149:389.e10–397.e10

40. Younossi ZM, Otgonsuren M, Henry L, et al. Association of nonalcoholic fatty liver disease (NAFLD) with hepatocellular carcinoma (HCC) in the United States from 2004 to 2009. Hepatology 2015;62:1723–1730