Nonalcoholic Fatty Liver Disease and Renal Function Impairment: A Cross-Sectional Population-Based Study on Its Relationship From 1999 to 2016

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There is growing evidence that links nonalcoholic fatty liver disease (NAFLD) with impairment of renal function. As such, we aimed to demonstrate the trend of NAFLD, NAFLD with renal insufficiency (RI), disease awareness, and mortality over time. Patient data were extracted from the National Health and Nutrition Examination Survey (NHANES) 1999-2016. A total of 14,255 adult study participants without competing liver disease or heavy drinking and with complete laboratory data were included. NAFLD was defined using the U.S. Fatty Liver Index (USFLI) and RI was defined using the Chronic Kidney Disease Epidemiology Collaboration equation and urine albumin:creatinine ratio. Death data were obtained from the National Death Index (up to December 31, 2015). Prevalence of NAFLD in participants was 31.2% (95% confidence interval [CI], 30.01-32.46); of these participants, 22.05% (95% CI, 20.34-23.85) had RI. From 1999 to 2016, prevalence of both NAFLD without RI (*P* = 0.048) and NAFLD-RI (*P* = 0.006) increased significantly. Among those with NAFLD-RI, awareness of kidney disease was 8.56% (95% CI, 6.69-10.89), while awareness of liver disease among all NAFLD was 4.49% (95% CI, 3.17-6.33). Among those with NAFLD, mortality incidence per 1,000 person years was highest among those with severe RI in all-cause mortality (104.4; 95% CI, 83.65-130.39) and other residual causes of mortality (mean, 50.88; 95% CI, 37.02-69.93). *Conclusion:* Prevalence of NAFLD and NAFLD-RI has increased over the past 2 decades in the United States. Low kidney disease and liver disease awareness are major public health issues as those with NAFLD-RI have significantly higher mortality than those with only NAFLD. (*Hepatology Communications* 2019;3:1334-1346).

Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of liver disease in the world, affecting approximately 24% of the global population.[1] Prevalence has been observed to be higher in patients with metabolic abnormalities, such as obesity and diabetes mellitus.[2] NAFLD is currently the second leading indication for liver transplantation in the United States and is foreseen to become the leading indication if the prevalence of NAFLD increases significantly, as predicted, over the next 10 years.[3,4] Additionally, NAFLD represents a significant clinical burden due to its association with metabolic syndrome, renal disease, and increased overall and cardiovascular-related mortality.[5-8] Recent literature has also reported a significant association between NAFLD and the development

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; CVD, cardiovascular disease; GGT, gamma-glutamyltransferase; NAFLD, nonalcoholic fatty liver disease; NFS, nonalcoholic fatty liver disease fibrosis score; NHANES, National Health and Nutrition Examination Survey; RI, renal insufficiency; USFLI, U.S. Fatty Liver Index.

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of kidney disease.[9] As such, it has become increasingly important to characterize the population having NAFLD and kidney disease and to evaluate the impact that kidney disease may have on the long-term outcomes of these individuals.

In addition, outcomes from chronic diseases, such as NAFLD and renal disease, are impacted by a person's health literacy, defined as an interplay of finding, understanding, and acting on health-related information to improve one's health; this involves both the patient and the caregivers.[10] Consistent research has shown that the poorer ones' health literacy is, the poorer the health outcomes are and the higher the health care costs.[11] It is essential now that as our knowledge of NAFLD and its associated comorbidities expand, we gain an understanding of the current state of NAFLD-related health literacy.[1,12] Therefore, this study aims to compare the trends of patients with NAFLD with and without renal disease, determine awareness of liver and kidney disease, and to assess the rate and predictors of mortality (overall, cardiovascular, cancer, and other residual) in participants with NAFLD.

Participants and Methods

This current study represents an analysis of the National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2016. NHANES is a cross-sectional survey conducted in the United States by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC); this has been a continuous survey in 2-year cycles since 1999. NHANES consists of a cross-sectional interview, examination, and laboratory data collected from a complex multistage, stratified, clustered probability sample representative of the civilian noninstitutionalized U.S. population in which all participants provide informed written consent to participate. The survey is approved by the institutional review board of the CDC, and all NHANES data and documentation are made publicly available by the CDC (https://www.cdc.gov/nchs/nhanes/index.htm).

All included participants were aged 18 years and older, participated in a medical examination at a mobile center, and underwent fasting blood work during their examination. We excluded participants <18 years old, those who had missing laboratory data needed to calculate the noninvasive indices (age, race/ethnicity, waist circumference, gamma-glutamyltransferase [GGT], fasting insulin, fasting glucose, serum creatinine, urine creatinine, and urine albumin), those who had a diagnosis of viral hepatitis, and those with heavy alcohol use.

DEFINITIONS

NAFLD and Fibrosis

NAFLD status was determined using the U.S. Fatty Liver Index (USFLI) because ultrasound data were not available for most NHANES survey cycles.[13] The USFLI has been validated and shown to accurately correlate with the presence of NAFLD diagnosed through ultrasound in the multiethnic U.S. general population (area under the receiver operating characteristic curve, 0.80; 95% confidence interval [CI], 0.77-0.83).[10] A USFLI ≥30 was selected to rule in fatty liver. At this cutoff, the sensitivity is 62%,

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the specificity is 88%, the positive likelihood ratio is 5.2, and the negative likelihood ratio is 0.43.

Heavy alcohol use was defined using the CDC definition of more than seven drinks per week for women or more than 14 drinks per week for men.[14] Severity of liver fibrosis was assessed using the NAFLD Fibrosis Score (NFS).[15] An NFS >0.676 was used to rule in stage 3-4 fibrosis, while NFS <–1.455 was used to rule out stage 3-4 fibrosis.

Renal Insufficiency

Estimated glomerular filtration rate was determined by the Chronic Kidney Disease Epidemiology Collaboration equation.[16] The urine albumin:creatinine ratio was used as a secondary measure of renal disease. Because NHANES is a cross-sectional database, we were unable to establish if the renal disease was chronic or acute; therefore, for our study purposes, renal disease was defined as renal insufficiency (RI), and the severity of RI was adapted from the National Institute of Diabetes and Digestive and Kidney Diseases and the Kidney Disease: Improving Global Outcomes CKD Work Group definitions.[17,18] We divided RI into four stages: no RI, mild, moderate, and severe (Supporting Table S1).

Comorbidities

Hypertension was defined as systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥80 mm Hg, or if persons were taking any antihypertensive medications. Dyslipidemia was defined as serum low-density lipoprotein ≥160 mg/dL, serum high-density lipoprotein <40 mg/dL for men and <50 mg/dL for women, or serum total triglycerides ≥200 mg/dL. Metabolic syndrome was defined by the Adult Treatment Panel III of the National Cholesterol Education Program.[19] Participants were considered to have diabetes mellitus if fasting serum glucose was ≥126 mg/dL or if glycohemoglobin was ≥6.5%. Asthma, arthritis, cardiovascular disease (CVD), stroke, chronic obstructive pulmonary disease, and cancer were determined from participant-reported medical history.

Health Literacy of Liver and Kidney Disease

Health literacy of NAFLD was defined as awareness of having a liver disease that was assessed using the following question: "Has a doctor or other health professional ever told you that you had any kind of liver condition?" Participants answered yes or no. Health literacy of renal disease was defined as having a kidney disease that was assessed using the following question: "Have you ever been told by a doctor or other health professional that you had weak or failing kidneys?" Participants answered yes or no.

MORTALITY

Participants were passively followed from their date of survey through December 31, 2015. Mortality status was determined by linking NHANES participants to the National Death Index through probabilistic record matching. Mortality outcomes were determined by the reported underlying cause of death on the participant's death certificate, coded according to the International Classification of Diseases, Tenth edition (ICD-10), for deaths occurring between 1999 and 2015. Causes of death for this study comprised all-cause mortality, cause-specific mortality from diseases of heart (ICD-10 code I00-I09, I11, I13, I20-I51), and malignant neoplasms (C00-C97). Additionally, we identified participants with all other residual causes of death (which excluded the vast majority of non-liver-related causes). These deaths excluded those with the following underlying causes of death: diseases of heart (I00-I09, I11, I13, I20-I51), malignant neoplasms (C00-C97), chronic lower respiratory diseases (J40-J47), accidents (unintentional injuries; V01-X59, Y85-Y86), cerebrovascular diseases (I60-I69), Alzheimer's disease (G30), diabetes mellitus (E10-E14), influenza and pneumonia (J09-J18), and nephritis, nephrotic syndrome and nephrosis (N00-N07, N17-N19, N25-N27).

STATISTICAL ANALYSIS

Descriptive statistics were reported as mean ± SD for continuous variables and proportion and 95% CI for categorical variables. The Student *t* test was used to evaluate normally distributed continuous variables, while the chi-squared test was used to evaluate categorical variables. Population estimates were determined by multiplying the adjusted prevalence estimates by population data from the U.S. Census Bureau. Independent risk factors for RI were evaluated using univariable and multivariable logistic regression. Variables with $P < 0.1$ in stepwise logistic regression were included in the model as well as variables that

were deemed clinically relevant. Variance inflation factors and condition indices were used to assess multicollinearity. Those variables with high variance inflation factors or condition indices were excluded from the model. Kaplan-Meier curves were generated to determine cumulative incidence of mortality. The log-rank test of equality was used to evaluate mortality in the variables of interest. Cox regression was used to determine risk factors for mortality. Validation of Cox proportional hazards assumption was performed by graphically comparing the Kaplan-Meier survival curves with the Cox predicted curves and through examination of log–log plots. A two-tailed P value <0.05 was considered to be statistically significant. Statistical analyses were performed using Stata 15.1 (Stata Corporation, College Station, TX) as Stata allows for appropriate use of the NHANES survey weights to project the data to the U.S. population.

Results

PATIENT DEMOGRAPHICS

From 1999 to 2016, 92,062 participants were available for analysis from NHANES. After our inclusion and exclusion criteria were applied, there were 14,255 patients who were morning-fasted adults (>18 years old), had all required laboratory work, had no competing liver disease, and in the absence of heavy alcohol use were available for further analysis (Fig. 1).

After applying the USFLI and Chronic Kidney Disease Epidemiology Collaboration calculations, 4,680 participants were noted to have NAFLD, of whom 1,279 had RI. Adjusted prevalence of RI among those with NAFLD was found to be 22.1% (95% CI, 20.3-23.9). The demographic characteristics of the participants are described in Table 1. Patients with NAFLD-RI were noted to be older, more likely to be women, had more health care use, and less likely to be a college graduate. Participants with NAFLD and RI also had more abnormal laboratory work and comorbidities compared to those with NAFLD alone (Table 2).

PREVALENCE AND TRENDS IN NAFLD AND RI IN THE UNITED STATES

The prevalence in 1999-2000 for overall NAFLD was 29.2% (95% CI, 25.8-32.9), for NAFLD without RI was 23.5% (95% CI, 20.2-27.1) and for NAFLD-RI was 5.7% (95% CI, 4.3-7.6). By 2015-2016, the prevalence for overall NAFLD increased to 34.9% (95% CI, 31.4-38.7), NAFLD without RI increased to 27.3% (95% CI, 23.7-31.1), and NAFLD-RI increased to 7.7% (95% CI, 6.2-9.5). Trend analysis for the time period 1999-2016 showed that the prevalence of overall NAFLD, NAFLD without RI, and NAFLD-RI all significantly increased over time (P = 0.007, P = 0.048, P = 0.006, respectively) (Fig. 2A). Based on population data from the U.S. Census Bureau in 2015-2016, NAFLD was affecting 84.9 million persons, NAFLD without RI was affecting 66.2 million, and NAFLD-RI was affecting 18.7 million persons (Supporting Table S2). Population estimates for previous years can be found in Supporting Table S1; race/ethnic-specific population estimates from 2011 to 2016 can be found in Supporting Table S3.

Among those with NAFLD, prevalence of RI did not increase significantly from 1999 to 2016 (P = 0.221). No significant increases were observed in mild, moderate, or severe RI in those with NAFLD during this time period (P = 0.448, P = 0.222, and P = 0.478, respectively) (Fig. 2B).

PREDICTORS FOR RI IN PARTICIPANTS WITH NAFLD

Univariable and multivariable results for the predictors of RI for participants with NAFLD for the 14 predictors that were found to be significant on univariable analysis are displayed in Supporting Table S4. On multivariable analysis, age 65 years and older, history of hypertension, history of diabetes, history of dyslipidemia, history of CVD, and having a high probability of fibrosis stage 3 and 4 were significant independent factors associated with RI.

AWARENESS OF KIDNEY AND LIVER DISEASE

Among the 4,680 persons with NAFLD, 4,451 (95.1%) responded to the survey questionnaire regarding liver disease, while 1,257 (98.3%) of the 1,279 persons with NAFLD-RI responded to the kidney disease awareness questionnaire. Awareness of liver disease among those with NAFLD and awareness of kidney disease among those with NAFLD-RI were

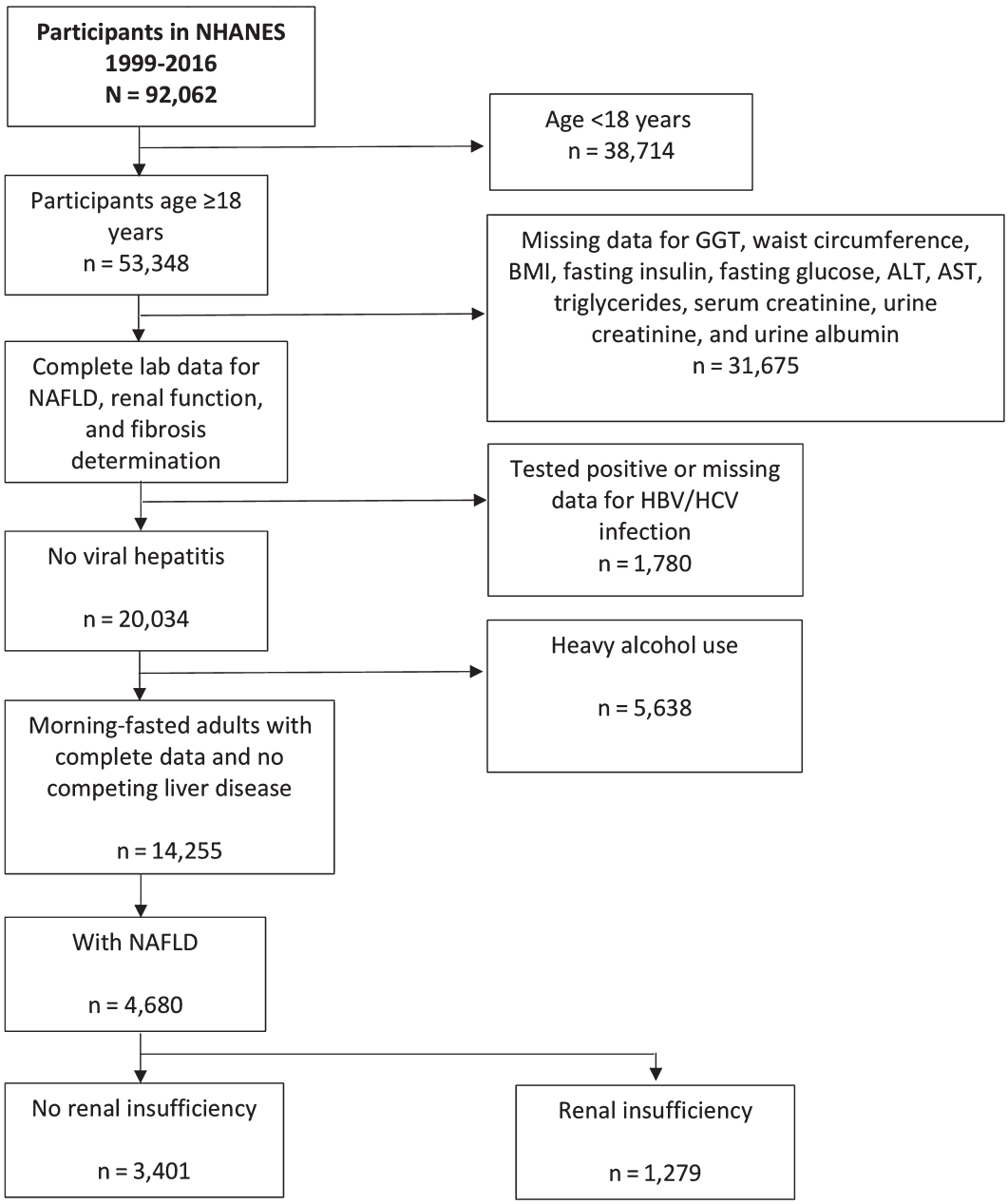


FIG. 1. Patient flowchart. Heavy alcohol use is defined as more than two drinks per day for men or more than one drink per day for women. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; GGT, gamma glutamyl trasferase; HBV, hepatitis B virus; HCV, hepatitis C virus; NHANES, National health and nutrition examination survey.

very low, with less than 10% awareness in both groups despite more than 90% of persons in both groups having used a health care service in the past year at least once. Awareness of liver disease among those with NAFLD was significantly higher in those with higher health care use in the past year. Among the NAFLD-RI population, kidney disease awareness was significantly higher in older persons, non-Hispanic blacks, and those with more severe RI (Supporting Table S5). In trends analysis, no significant increases in liver disease awareness among those with NAFLD ($P = 0.618$) were observed in 1999-2000 to 2015-2016 (Fig. 3A). Similarly, kidney disease awareness among those with NAFLD-RI did not significantly increase

TABLE 1. DEMOGRAPHIC CHARACTERISTICS IN PARTICIPANTS WITH NAFLD, WITH AND WITHOUT RI, FROM NHANES 1999-2016

Variable	Overall NAFLD (n = 4,680)	No RI (n = 3,401)	RI (n = 1,279)	*P* Value*
Age (years)	52.6 ± 16.3	50.0 ± 15.0	62.0 ± 17.0	<0.001
Male	56.3 (54.4-58.2)	58.0 (55.7-60.4)	50.2 (46.5-53.9)	<0.001
Ethnicity (%)				0.059
Non-Hispanic white	74.8 (71.9-77.4)	74.6 (71.7-77.3)	75.3 (71.4-78.9)	
Non-Hispanic black	6.3 (5.3-7.3)	5.9 (5.0-6.9)	7.7 (6.0-9.8)	
Hispanic/Mexican	16.5 (14.2-19.1)	17.0 (14.7-19.7)	14.5 (11.7-17.9)	
Other	2.5 (1.9-3.3)	2.5 (1.9-3.3)	2.5 (1.6-3.8)	
Foreign born	9.6 (8.3-11.0)	10.0 (8.6-11.6)	7.9 (6.5-9.7)	0.012
Income:poverty ratio <1.0	13.4 (12.0-15.0)	13.0 (11.4-14.9	14.6 (12.3-17.3)	0.28
Marital status				<0.001
Legally married	65.4 (63.1-67.6)	66.7 (64.2-69.0)	61.0 (56.8-65.0)	
Never married	11.7 (10.2-13.3)	12.7 (11.1-14.5)	8.1 (6.1-10.6)	
Other	23.0 (21.1-24.9)	20.6 (18.7-22.8)	30.9 (27.5-34.6)	
Smoking exposure				0.24
Never	55.0 (52.6-57.2)	55.6 (52.7-58.4)	52.7 (48.9-56.5)	
Current/former	45.0 (42.7-47.4)	44.4 (41.6-47.3)	47.3 (43.5-51.0)	
Education level				<0.001
No HS graduation	22.5 (20.8-24.3)	20.5 (18.7-22.5)	29.4 (26.4-32.5)	
HS graduate/some college	55.4 (53.0-57.8)	55.6 (52.8-58.4)	54.6 (50.9-58.2)	
College graduate or more	22.1 (20.0-24.3)	23.8 (21.4-26.4)	16.0 (13.2-19.4)	
Number of times used a health care service in the past year				<0.001
0	11.0 (9.8-12.3)	12.0 (10.6-13.5)	7.6 (5.7-10.1)	
1	13.9 (12.5-15.4)	15.0 (13.3-16.8)	10.2 (8.0-12.8)	
2-3	28.9 (27.0-30.9)	30.4 (28.1-32.8)	23.5 (20.3-26.9)	
4-9	29.6 (27.6-31.6)	28.0 (25.8-30.2)	35.2 (31.3-39.4)	
10+	16.6 (15.1-18.3)	14.7 (12.9-16.7)	23.5 (20.3-27.2)	

**P* value denotes comparison between participants with NAFLD with and without RI.
Abbreviation: HS, high school.

during this time period either (P = 0.403) (Fig. 3B). In the most recent time period of 2015-2016, awareness of liver disease among participants with NAFLD was 6.4% (95% CI, 4.0-10.0) while awareness of kidney disease among those with NAFLD-RI was 10.3% (95% CI, 5.8-17.7).

In multivariable logistic regression, we found that among participants with NAFLD, non-Hispanic blacks had lower odds of liver disease awareness and those with higher health care use had higher odds of awareness after adjusting for age, sex, ethnicity, birthplace, education level, insurance, income:poverty ratio, and health care use (Supporting Table S6). Additionally, after adjusting for the same variables, we found that the variables associated with higher odds of kidney disease awareness among those with NAFLD-RI were non-Hispanic blacks and those with higher health care use events (Supporting Table S7).

MORTALITY IN PATIENTS WITH NAFLD AND NAFLD-RI

The cumulative incidence of mortality among all participants with NAFLD by RI status is displayed in Fig. 4A. As noted at year 5, the cumulative mortality for those with NAFLD was 4.5%, with incidence increasing by RI status in mild (14.2%), moderate (21.2%), and severe (36.0%) RI (P < 0.001). The cumulative mortality incidence significantly increased over time at 15 years in NAFLD alone (19.9%), mild RI (42.4%), moderate RI (80.6%), and severe RI (85.5%) (P < 0.001).

The cumulative incidence of other residual causes of mortality among those with NAFLD by RI status is displayed in Fig. 4B. Those participants with NAFLD with moderate and severe RI had similar rates of mortality at 15 years, with 46.4% of those

TABLE 2. CLINICAL CHARACTERISTICS IN PARTICIPANTS WITH NAFLD BY RI STATUS, FROM NHANES 1999-2016

Variable	NAFLD (n = 4,680)	No RI (n = 3,477)	RI (n = 1,203)	*P* Value*
BMI (kg/m^2)	34.3 ± 6.8	34.3 ± 6.5	34.2 ± 7.8	0.74
BMI categories (kg/m^2)†				0.19
Underweight	0.0 (0.00-0.13)	0.0 (0.00-0.17)	0.0	
Normal weight	3.6 (2.9-4.4)	3.2 (2.4-4.2)	4.8 (3.6-6.4)	
Overweight	24.5 (22.7-26.4)	24.6 (22.6-26.7)	24.2 (20.8-27.8)	
Obese	71.9 (69.9-73.9)	72.2 (69.8-74.5)	71.0 (67.3-74.5)	
Albumin (g/dL)	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.4	<0.001
ALT (U/L)	32.1 ± 42.2	32.6 ± 23.1	30.3 ± 85.1	0.47
AST (U/L)	27.1 ± 19.8	27.3 ± 20.8	26.3 ± 13.9	0.11
Elevated ALT or AST (>1× ULN; %)	37.2 (35.0-39.5)	39.4 (36.9-42.0)	29.4 (25.7-33.5)	<0.001
Elevated ALT or AST (>2× ULN‡; %)	5.9 (5.1-6.9)	6.5 (5.4-7.7)	4.0 (2.7-5.8)	0.024
Alkaline phosphatase (U/L)	74.5 ± 26.10	73.7 ± 22.1	77.2 ± 38.6	0.043
GGT (U/L)	38.2 ± 39.9	37.1 ± 33.8	42.2 ± 59.2	0.009
Platelet (10^9/L)	254.8 ± 67.7	257.0 ± 65.0	246.8 ± 76.6	0.002
Total bilirubin (mg/dL)	0.7 ± 0.3	0.7 ± 0.3	0.7 ± 0.3	0.51
Serum creatinine (mg/dL)	0.9 (0.9-0.9)	0.8 ± 0.2	1.1 ± 0.5	<0.001
HbA1c (%)	6.00 ± 1.2	5.8 ± 1.0	6.6 ± 1.8	<0.001
Fasting glucose (mg/dL)	119.3 ± 40.3	114.2 ± 31.2	137.3 ± 62.7	<0.001
Fasting insulin (pmol/L)	136.1 ± 122.0	131.3 ± 83.2	152.9 ± 221.8	0.003
HOMA-IR (units)	6.9 ± 8.4	6.2 ± 4.9	9.2 ± 16.4	<0.001
Total cholesterol (mg/dL)	197.1 ± 42.4	198.1 ± 41.0	193.8 ± 47.2	0.025
HDL cholesterol (mg/dL)	45.3 ± 11.5	45.1 ± 10.7	46.0 ± 14.3	0.098
LDL cholesterol (mg/dL)	117.3 ± 35.7	118.9 ± 34.4	111.5 ± 39.6	<0.001
Triglycerides (mg/dL)	179.5 ± 139.7	176.0 ± 135.4	191.7 ± 153.5	0.011
eGFR§ (mL/minute/1.73 m^2)	90.5 ± 22.9	95.1 ± 18.3	74.2 ± 30.8	<0.001
eGFR categories§ (%, 95% CI)				<0.001
G1	51.9 (49.6-54.2)	57.3 (54.8-59.8)	32.8 (29.5-36.2)	
G2	38.7 (36.7-40.8)	42.7 (40.2-45.2)	24.7 (21.2-28.5)	
G3a	6.4 (5.5-7.5)	0	29.0 (25.3-33.1)	
G3b	2.2 (1.7-2.7)	0	9.9 (8.0-12.3)	
G4	0.7 (0.5-9.6)	0	3.2 (2.4-4.3)	
G5	0.1 (0.0-0.3)	0	0.4 (0.1-1.3)	
ACR§ (mg/mmol)	5.7 ± 36.1	0.9 ± 0.6	22.4 ± 81.4	<0.001
ACR categories (%, 95% CI)				<0.001
A1	84.0 (82.4-85.5)	100.0	27.4 (23.6-31.7)	
A2	13.3 (12.1-14.7)	0.00	60.4 (56.3-64.3)	
A3	2.7 (2.1-3.5)	0.00	12.2 (9.6-15.4)	
RI categories				<0.001
No RI	77.9 (76.2-79.7)	100.0	0.0	
Mild RI	15.8 (14.2-17.3)	0.00	71.3 (67.7-74.7)	
Moderate RI	3.9 (3.4-4.6)	0.00	17.8 (15.4-20.6)	
Severe RI	2.4 (1.9-3.0)	0.00	10.9 (8.7-13.5)	
Comorbidities (%)				
Hypertension	52.3 (50.0-54.6)	44.7 (42.0-47.4)	78.1 (74.3-81.4)	<0.001
Dyslipidemia	60.7 (58.4-62.9)	60.0 (57.4-62.6)	63.1 (59.4-66.8)	0.16
Metabolic syndrome	67.8 (65.3-70.1)	64.7 (62.1-67.3)	78.9 (74.6-82.6)	<0.001
Diabetes	24.4 (22.8-26.1)	19.3 (17.6-21.0)	42.4 (38.8-46.2)	<0.001

TABLE 2. *Continued*

Variable	NAFLD (n = 4,680)	No RI (n = 3,477)	RI (n = 1,203)	*P* Value*
Asthma	16.5 (15.0-18.2)	16.7 (14.9-18.7)	15.8 (13.3-18.7)	0.57
Arthritis	38.2 (36.1-40.4)	35.2 (32.8-37.6)	48.8 (45.2-52.4)	<0.001
CVD	13.3 (12.0-14.7)	9.7 (8.5-11.1)	25.8 (22.9-28.8)	<0.001
Stroke	4.6 (3.8-5.5)	3.4 (2.5-4.3)	8.9 (7.1-11.1)	<0.001
COPD	10.4 (8.9-12.1)	9.3 (7.6-11.2)	14.3 (11.6-17.5)	0.001
Cancer	12.6 (11.4-13.9)	11.3 (10.0-12.8)	16.8 (14.2-19.8)	<0.001
NAFLD fibrosis score‖				<0.001
Low probability	32.4 (30.4-34.4)	36.7 (34.4-39.0)	17.3 (14.5-20.4)	
Indeterminate	51.7 (49.9-53.5)	51.7 (49.5-53.9)	51.7 (48.1-55.2)	
High probability	16.0 (14.7-17.3)	11.6 (10.4-13.0)	31.1 (28.0-34.4)	

*P value denotes comparison between participants with NAFLD with and without RI.
†BMI categories: underweight BMI, <18.5; normal weight BMI, 18.5-24.9 (18.5-22.9 for Asian); overweight BMI, 25-29.9 (23-27.4 for Asian); obese BMI, ≥30 (≥27.5 for Asian).
‡ULN: ALT, ≥25 U/L for women, ≥35 U/L for men; AST, ≥40 U/L.
§See Supporting Table S1.
‖Low probability (NFS, <–1.455), indeterminate (NFS, –1.455 to –0.676), high probability (NFS, >0.676).
Abbreviations: ACR, albumin:creatinine ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; ULN, upper limit of normal.

with moderate and 49.4% of those with severe RI having died of other residual causes.

The cumulative incidence of cardiovascular-related mortality in participants with NAFLD by RI status is displayed in Supporting Fig. S1. As noted, the highest rate of mortality occurred in participants with NAFLD-severe RI, for which the 5-year cumulative incidence of mortality was 10.5%. This trend continued, with incidence of mortality reaching 36.7% at 15 years.

The cumulative incidence of cancer-related mortality in participants with NAFLD by RI status is displayed in Supporting Fig. S2. The highest incidence of mortality at 5 years was observed in NAFLD-severe RI at 5.7% (P < 0.001). At 15 years, NAFLD-moderate RI (17.5%) and NAFLD-severe RI (15.8%) had the highest cumulative incidence of mortality compared to mild and no RI (P < 0.001).

RISK FACTORS FOR MORTALITY IN PARTICIPANTS WITH NAFLD

On multivariable Cox regression analysis, being 65 years or older; being aged 50-64 years old; having mild, moderate, or severe RI; having a high probability of fibrosis; being a former or current smoker; and having a history of CVD were independent risk factors for all-cause mortality. Female sex as well as having a college degree or higher educational level were protective of all-cause mortality (Supporting Table S8). Older age, moderate and severe RI, and history of CVD were independent risk factors for CVD-related mortality, while being a woman was protective (Supporting Table S9). Older age and history of smoking were the only risk factors for cancer-related mortality in participants with NAFLD; being a female participant was again protective (Supporting Table S10). For other residual causes of mortality, older age, high probability of stage 3-4 fibrosis, past history of CVD, being a former or current smoker, and mild, moderate, or severe RI were significant risk factors for mortality (Supporting Table S11).

Discussion

Using data from NHANES, we found that the prevalence of NAFLD and NAFLD-RI has increased significantly from 1999 to 2016. We determined that age 65 years and older, hypertension, diabetes, history of CVD, and stage 3-4 fibrosis are all significant predictors for RI in participants with NAFLD. Additionally, we observed that in persons with NAFLD, incidence of all-cause, CVD-related, cancer-related, and other residual causes of mortality (including liver-related causes)

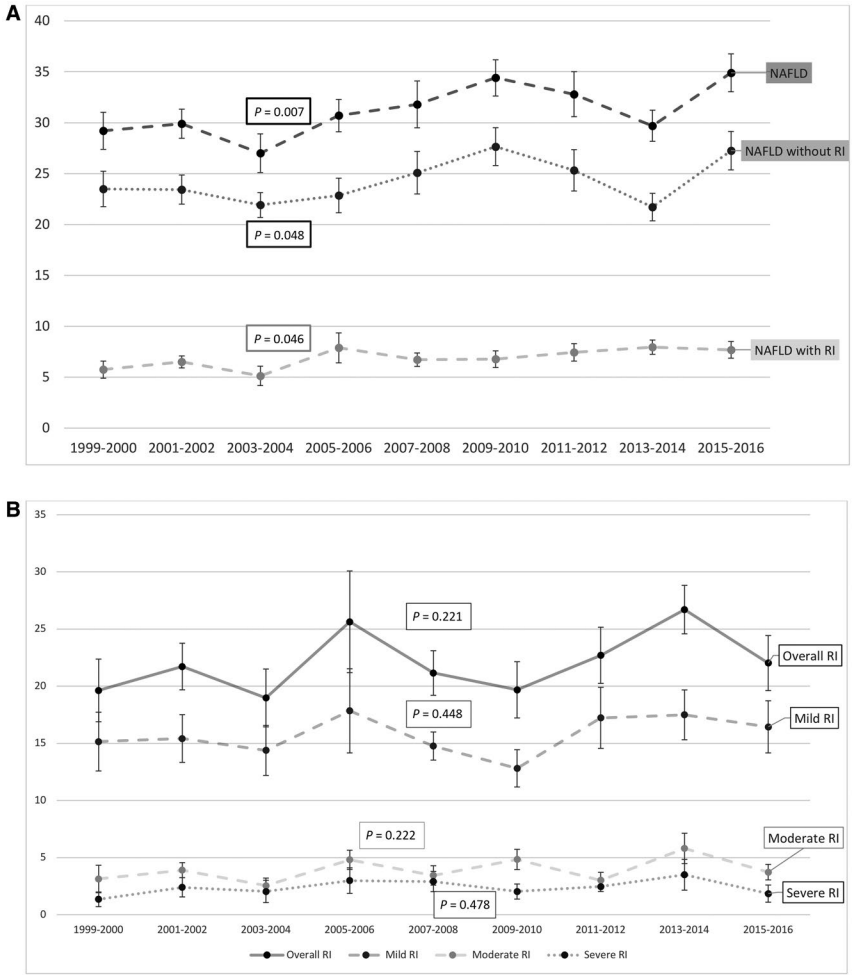


FIG. 2. Prevalence and trends from NHANES 1999-2016. (A) Prevalence and trends of NAFLD overall and NAFLD with and without RI. (B) Prevalence of RI among participants with NAFLD.

increased as severity of RI increased. Finally, this study emphasized the critically low participant awareness of both liver and kidney conditions. Despite health care use, more than 95% of persons with NAFLD were unaware of their liver condition and more than 90% of persons with NAFLD-RI were unaware of their kidney condition. However, those who had more encounters with a health care practitioner were more likely to be aware of their liver and or kidney disease.

As the prevalence of NAFLD increases, our study findings suggest that RI will increase accordingly; this is important as a recent modeling study determined that the number of prevalent cases of NAFLD in the United States will increase 21% by 2030, which could create an associated increase of RI.[4] Especially concerning is that NAFLD and RI each can pose many problems both clinically and economically. One study on NAFLD and RI using population-based data in the United States reported an increased risk for all-cause and cardiovascular-related mortality in patients with NAFLD and renal disease.[20] In our study, we found that participants with both NAFLD and RI experienced an increased risk for mortality; this was especially the case for those with NAFLD and severe RI who had the highest incidence of all-cause mortality (104.4 per 1,000 person years). Additionally, we found that the more severe the RI, the higher the incidence of cardiovascular-related, cancer-related, and other residual causes of mortality.

Furthermore, it is important to look more closely at the category of other residual causes of mortality. This is an area where many patients may have been

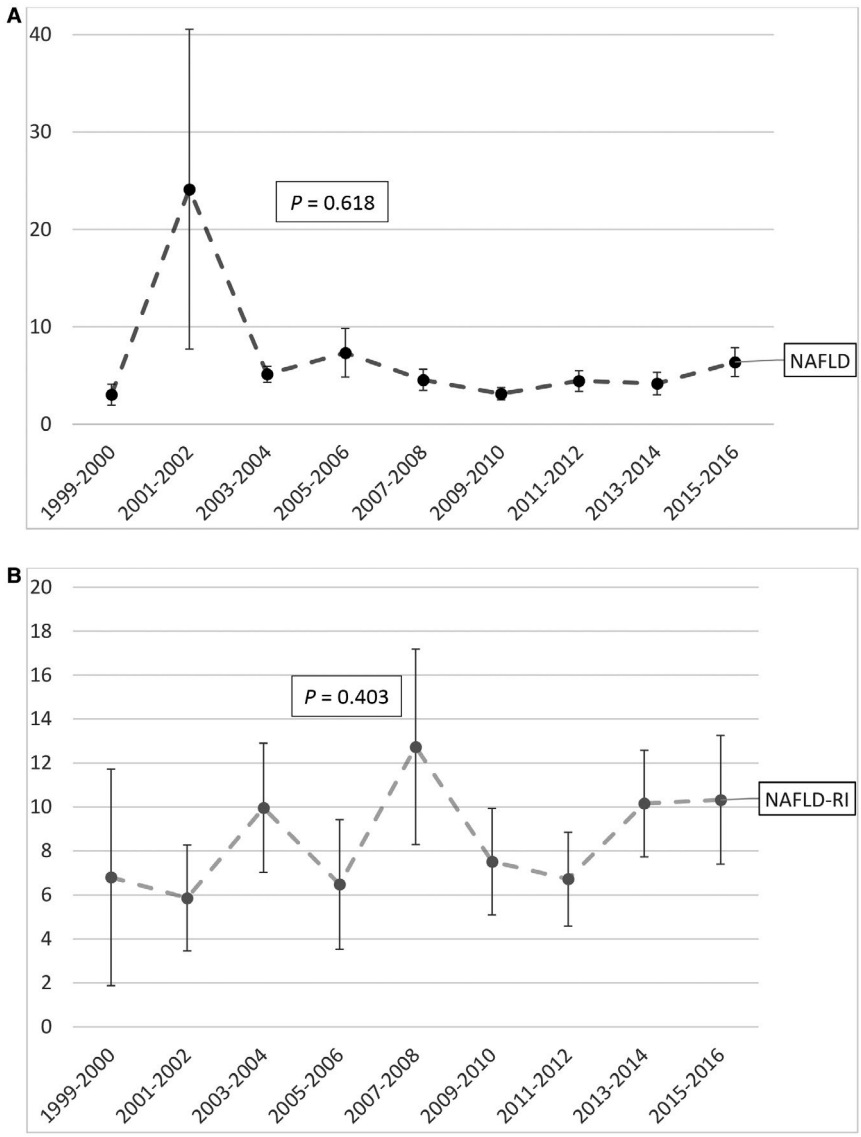
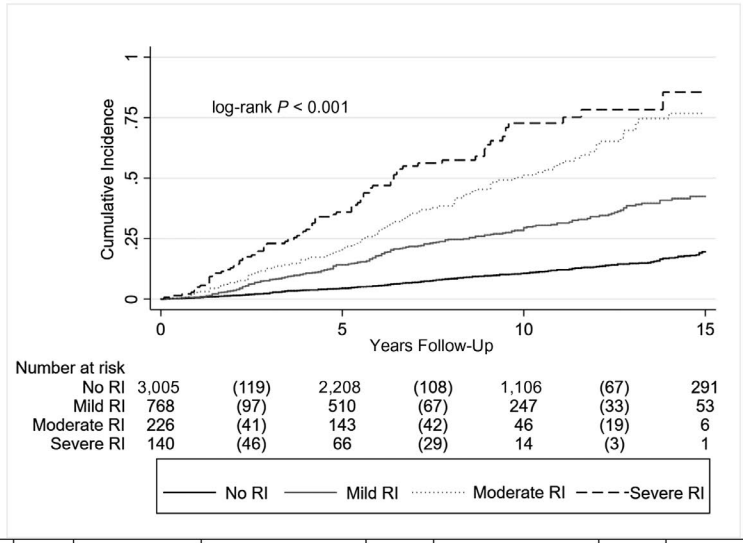


FIG. 3. Trends from NHANES 1999-2016. (A) Trends in liver disease awareness among participants with NAFLD. (B) Trends in kidney disease awareness among participants with NAFLD and RI.

classified when in fact their cause of death may have been related to their liver disease because this category excluded those who died of various common causes (heart disease, cancer, respiratory diseases, accidents, cerebrovascular disease, Alzheimer's disease, diabetes, influenza and pneumonia, nephritis, nephrotic syndrome, and nephrosis). In addition, we found that stage 3-4 fibrosis was also a significant predictor for other residual causes of mortality, providing further evidence that many of these patients may have died due to liver-related complications as it is now know that it is the stage of fibrosis that is the main independent predictor for liver-related mortality among those with NAFLD.[21] As such, it is vital for health care providers to identify patients with NAFLD early in their course of disease and provide appropriate treatment and care to prevent negative outcomes.

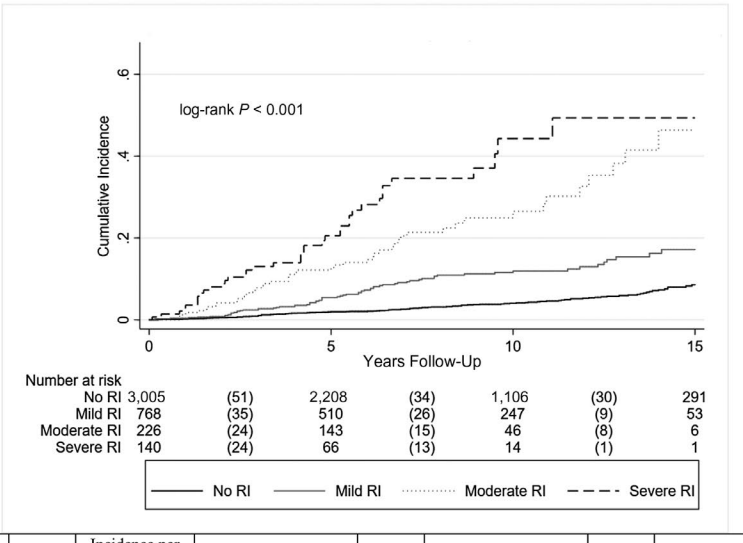
As noted in this study, the health literacy of patients with NAFLD and NAFLD-RI was very low, with only 5%-10% aware of their disease, although an encouraging finding was that the chance of patients becoming aware they had a liver and or kidney disease increased as their encounters with the health care system increased. As practitioners, one must be aware

A



Participant Status	Person Years	Cases	Incidence per 1,000 Person Years	5-Year Incidence (95% CI)	*P*5	10-Year Incidence (95% CI)	*P*10	15-Year Incidence (95% CI)	*P*15
NAFLD no RI	25,054	302	12.1 (10.8-13.5)	4.5 (3.8-5.3)		10.6 (9.4-12.1)		19.9 (17.4-22.6)	
NAFLD-mild RI	5,829	199	34.1 (29.7-39.2)	14.2 (11.8-17.0)		29.5 (25.8-33.7)		42.4 (37.1-48.1)	
NAFLD-moderate RI	1,487	104	69.9 (57.7-84.8)	21.2 (16.1-27.5)	**<0.001**	51.3 (43.3-59.9)	**<0.001**	80.6 (69.3-89.8)	**<0.001**
NAFLD-severe RI	747	78	104.4 (83.7-130.4)	36.0 (28.2-45.1)		72.7 (62.3-82.3)		85.5 (69.6-95.7)	

B



Participant Status	Person Years	Cases	Incidence per 1,000 Person Years	5-Year Incidence (95% CI)	*P*5	10-Year Incidence (95% CI)	*P*10	15-Year Incidence (95% CI)	*P*15
NAFLD no RI	25,054	115	4.59 (3.8-5.5)	2.0 (1.5-2.6)		4.0 (3.3-5.0)		8.6 (6.9-10.7)	
NAFLD-mild RI	5,829	71	12.18 (9.7-15.4)	5.5 (3.9-7.6)		11.9 (9.3-15.2)		17.2 (13.2-22.3)	
NAFLD-moderate RI	1,487	47	31.61 (23.8-42.1)	12.8 (8.8-18.4)	**<0.001**	26.6 (19.6-35.3)	**<0.001**	46.4 (33.0-62.1)	**<0.001**
NAFLD-severe RI	747	38	50.88 (37.0-69.9)	20.6 (14.1-29.4)		44.3 (32.1-58.7)		49.4 (35.2-65.6)	

FIG. 4. Cumulative incidence of mortality in participants with NAFLD by RI categories. (A) All-cause mortality. (B) Other causes of mortality, excluding diseases of heart, malignant neoplasms, chronic lower respiratory diseases, accidents, cerebrovascular diseases, Alzheimer's disease, diabetes mellitus, influenza and pneumonia, and nephritis, nephrotic syndrome, and nephrosis.

that part of the health literacy complex is dependent on the health care provider's knowledge and awareness of disease, which for NAFLD has been found to be low among general practitioners and other specialists.[22-24] Therefore, focused efforts need to be directed toward the development of a provider education program, realizing that this recommendation is not without its challenges due to the complexity of diagnosing and treating NAFLD.[25,26] Thus, increasing the health literacy of patients with NAFLD may take time. Nevertheless, practitioners should maintain a high index of suspicion that a patient may have NAFLD and potentially renal disease if they present being 65 years and older, have less than a college education, have a low income:poverty ratio, have hypertension and/or diabetes, have a history of CVD, and have stage 3-4 fibrosis so as to provide appropriate treatment with the goal to slow down or reverse disease progression. On the other hand, the very low liver disease awareness observed in this study may also be due to factors other than lack of patient health literacy. One factor is that many of these patients may not have been diagnosed with NAFLD due to the lack of an ultrasound test and/or awareness about NAFLD among health care providers, especially from the earlier survey cycles.

This current study has several limitations. First, as NHANES ceased abdominal ultrasound testing in 1994, we used the USFLI to identify individuals with NAFLD, and this may not be a perfect substitute for ultrasound. However, the USFLI has been found to be effective in determining the presence of ultrasound-confirmed NAFLD with high specificity (88%) and thus is useful for ruling in disease.[13] In fact, the ideal method should be liver histology, but this gold standard is neither feasible nor ethical in large observational studies of individuals who are asymptomatic. Second, the current study used cross-sectional data so we were unable to differentiate between chronic and acute kidney disease. Further studies are needed to study the individual effect of acute and chronic kidney disease on the clinical course of NAFLD. Third, participant awareness of kidney disease and liver disease is based on self-reported data, which are subject to recall bias. However, if patients are unable to recall that a physician has told them they have weak or failing kidneys or that they have a liver disease, then this highlights the increased need for health care providers to continually educate their patients on NAFLD, renal disease, and their associated risk factors. The low rate of disease awareness can also be due to the low disease diagnosis rates, especially for NAFLD and in the earlier survey cycles when awareness of NAFLD among health care providers was probably very low. Another limitation is the use of the public-use mortality files in NHANES, which prevented us from determining if patients died from liver-related causes or not. However, by including the other residual causes of mortality, which excludes many common causes of death, and based on the evidence we found in the Cox regression, we assume that many of these individuals died from liver-related complications.

In conclusion, prevalence of NAFLD and NAFLD-RI has increased significantly in the United States from 1999 to 2016, with an estimated 84.9 million and 18.7 million persons affected in 2015-2016, respectively. Awareness of kidney disease among those with NAFLD-RI and liver disease among those with NAFLD is suboptimal, with more than 90% of persons with kidney disease unaware that they have weak or failing kidneys and more than 95% of persons with NAFLD unaware that they are affected by a liver disease. We observed increased risk for all-cause and cardiovascular-related mortality in participants with NAFLD-RI; however, this increased risk for mortality was not different from those with RI alone. This current study highlights the need for both provider-level and patient-level educational programs to increase health literacy among patients with NAFLD and NAFLD-RI. Challenges remain due to limited options for diagnosing and treating NAFLD. Until further research provides answers to the best diagnostic and treatment methods to determine whether NAFLD or NAFLD-RI is present, health care providers need to maintain a high index of suspicion that a person who presents as 65 years and older, has an income:poverty ratio <1, has less than a college education, and has hypertension, CVD, stage 3-4 fibrosis, and/or diabetes is someone who is at high risk for NAFLD and NAFLD-RI. These individuals need to be treated accordingly to change the course of the disease and adverse outcome, which includes mortality.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1408/suppinfo.