Increased Risk of Mortality in Nonalcoholic Fatty Liver Disease/Nonalcoholic Steatohepatitis (NAFLD/NASH) Patients: Real-World Analysis of 2007-2015 Medicare Data

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Background

- NAFLD/NASH is projected to be a major cause of mortality in the coming decades.[1]
- Although prior studies have found that NAFLD/NASH patients' risk of all-cause mortality is higher with increasing fibrosis stage, these studies have not adjusted for patient demographics or comorbidities, have not evaluated risk associated with end-stage liver disease, and have studied a limited number of patients: n<1,500 in meta-analysis of previous mortality studies.[2,3]
- In addition, a recent nationally representative study of NHANES data reported that the metabolic comorbidities of diabetes, hypertension, and BMI ≥ 30 kg/m^2 were independent predictors of significant and advanced fibrosis in NAFLD/NASH patients.[4]

Aim

- To evaluate Medicare NAFLD/NASH patients' risk of all-cause mortality and disease progression, while adjusting for patients demographics and comorbidities, in a large real-world cohort.

Study Design and Methods

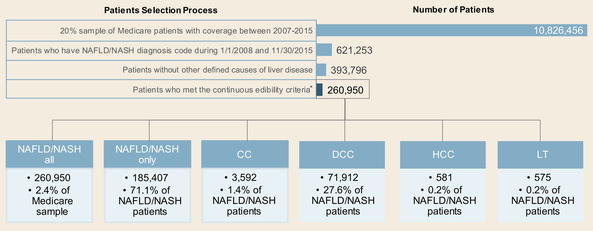
- Design: this was a retrospective, observational cohort study.
- Data source: 20% US Medicare sample with fee-for-service coverage. Data maintained by the Centers for Medicare and Medicaid Services (CMS), which insures 97% of US population ≥65 years.
- Inclusion criteria:
  - NAFLD/NASH diagnosed patients (patients with ≥ 1 claim of ICD-9-CM [571.8, 571.9] or ICD-10-CM [K76.0, K75.81] diagnosis codes for NAFLD/NASH) aged ≥18 years between 1/1/2008 and 11/30/2015.
  - Among NAFLD/NASH patients, 5 study cohorts identified: (1) NAFLD/NASH only (patients with no further liver disease progression), (2) compensated cirrhosis (CC), (3) decompensated cirrhosis (DCC), (4) hepatocellular carcinoma (HCC), (5) and liver transplant (LT).
  - The first NAFLD/NASH or advanced liver disease (CC, DCC, HCC, LT) diagnosis marked the index date. Cohorts were not mutually exclusive.
  - Patients required to have ≥6 months coverage prior to each cohort index date to assess baseline comorbidities.
  - Eligible patients followed from index date of each diagnosis to end of Medicare coverage, 31 December 2015, index for more severe disease, or death, whichever was earliest, and maximum follow-up was 8 years.
- Exclusion criteria:
  - Patients with other defined causes of liver disease were excluded (alcoholism, alcoholic liver disease, viral hepatitis, mumps hepatitis, HIV, Wilson's disease, autoimmune hepatitis, chronic toxic hepatitis, Gaucher, lysosomal acid lipase deficiency, primary biliary cholangitis, hemochromatosis and primary sclerosing cholangitis).
- Statistical analysis:
  - Kaplan Meier survival analyses
  - Cox regression model to assess the risk of mortality progression adjusted for patient demographics and comorbidities.
  - Cumulative incidence of liver disease progression in NAFLD/NASH and NAFLD/NASH CC patients.
  - Student's t-tests and chi-square test of independence were used to determine if and sample proportions were significantly different between cohorts.
  - P-values < 0.05 were deemed significant.

Study Outcomes

- Outcomes - the following were reported for each severity cohort:
  - Baseline demographics and comorbidities
  - All-cause mortality or time to event

Results

Table 1. Patient Selection Flowchart and Disease Severity Groups



*≥6 months coverage prior to each cohort index date

- 2.4% of the Medicare patients in the study had NAFLD/NASH.
- At the time of first cirrhosis diagnosis, 93% were first identified with a decompensation event (DCC).

Results

Table 2. NAFLD/NASH Patient Demographics by Disease Severity

	NAFLD/ NASH only (n=185,407)	CC (n=3,592)	DCC (n=71,912)	HCC (n=581)	LT (n=575)
Female, %	60.1%	63.4%*	59.5%*†	53.7%*†	49.5%
Age mean (SD)	66.7 (11.7)	66.8 (10.9)	70.8 (12.4)*†	73.1 (9.7)*†	67.2 (11.5)
Age group, %					
18-64	27.2%	30.9%*	22.5%*†	13.6%*†	26.3%*
65-69	33.4%	28.8%*	19.5%*†	21.2%*†	27.7%*
70-74	19.8%	20.5%*	19.9%*†	25.0%*†	24.3%*
75-79	10.8%	11.5%*	16.1%*†	16.4%*†	13.2%*
80+	8.9%	8.3%*	21.9%*†	23.9%*†	8.5%*
Race, %					
White	84.4	86.7*	86.2*†	82.4*†	86.3
Black	7.2	4.6*	7.3*†	5.9*†	6.6
Other	8.4	8.7	6.5	11.7	7.1

*P<.05 vs. NAFLD/NASH. †P<.05 vs. CC.
Note: NAFLD/NASH only (patients with no further liver disease progression)

- DCC (70.8) and HCC (73.1) patients were significantly older than CC (66.8) and NAFLD/NASH (66.7) only patients.
- Across disease severity groups, patients were primarily white (82.4 – 86.7%) and generally a higher proportion were female.

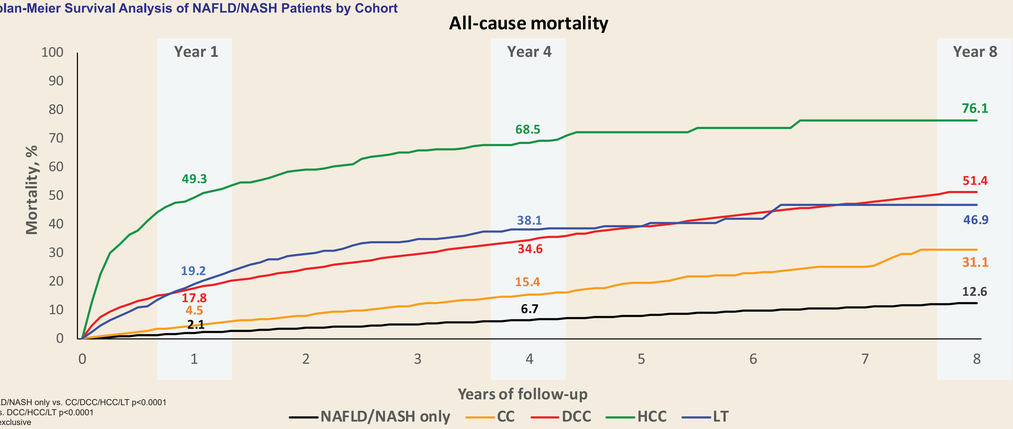
Table 3. NAFLD/NASH Patient Comorbidities by Disease Severity

	NAFLD/ NASH only (n=185,407)	CC (n=3,592)	DCC (n=71,912)	HCC (n=581)	LT (n=575)
CVD, n (%)	120,093 (64.8)	2,657 (74.0)*	63,238 (87.9)*†	487 (83.8)*†	478 (83.1)*†
Diabetes mellitus, n (%)	100,098 (54.0)	2,520 (70.2)*	45,881 (63.8)*†	384 (66.1)*	408 (71.0)*
Dysrhythmia, n (%)	53,566 (28.9)	1,291 (35.9)*	40,770 (56.7)*†	300 (51.6)*†	324 (56.3)*†
Hyperlipidemia, n (%)	156,254 (84.3)	3,114 (86.7)*	63,430 (88.2)*†	508 (87.4)*	494 (85.9)
Hypertension, n (%)	156,116 (84.2)	3,213 (89.4)*	66,584 (92.6)*†	530 (91.2)*	525 (91.3)*
Renal impairment, n (%)	39,299 (21.2)	1,044 (29.1)*	33,489 (46.6)*†	261 (44.9)*†	289 (50.3)*†
Smoking, n (%)	46,792 (25.2)	1,125 (31.3)*	28,584 (39.7)*†	215 (37.0)*†	259 (45.0)*†
Diabetes mellitus **AND** hypertension **AND** hyperlipidemia, n (%)	85,535 (46.1)	2,208 (61.5)*	41,839 (58.2)*†	345 (59.4)*†	357 (62.1)*
Diabetes mellitus **OR** hypertension **OR** hyperlipidemia, n (%)	176,073 (95.0)	3,465 (96.5)*	70,006 (97.3)*†	565 (97.2)*	559 (97.2)*

*P<.05 vs. NAFLD/NASH. †P<.05 vs. CC.

- NAFLD/NASH patients had a high metabolic comorbidity burden across all disease severity groups: 64.8 – 87.9% with CVD, 54.0 – 71.0% with diabetes mellitus, and 84.3 – 88.2% with hyperlipidemia.
- At least 58% of patients with CC or more severe liver disease also had all three comorbidities of diabetes mellitus and hypertension and hyperlipidemia.
- DCC and CC patients had significantly higher rates of comorbidities than NAFLD/NASH only patients, including CVD, diabetes mellitus, hyperlipidemia, hypertension, and renal impairment.

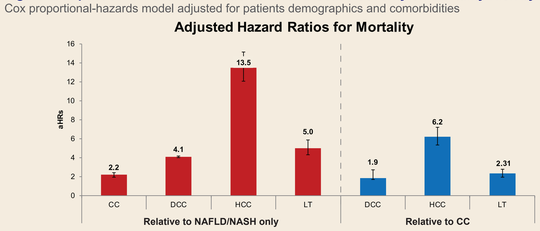
Figure 1. Kaplan-Meier Survival Analysis of NAFLD/NASH Patients by Cohort



Mortality rate in NAFLD/NASH only vs. CC/DCC/HCC/LT p<0.0001
Mortality rate in CC vs. DCC/HCC/LT p<0.0001
Groups not mutually exclusive

- NAFLD/NASH patients experienced a high rate of mortality, with an overall mortality rate of 26.3% in the study period, a higher than expected mortality rate for a similarly aged general population of 12.7% (Social Security life table). As expected, mortality increased in patients with more progressive liver disease.
- 1 year mortality for CC patients was significantly more than 2-times higher than NAFLD/NASH only patients (4.5 vs. 2.1%). In addition, DCC patients had 4-times significantly higher mortality than CC patients (17.8% vs. 4.5%).
- This trend continued over the study period, with mortality in NAFLD/NASH only, CC and DCC after 4 years of follow-up of 6.7%, 15.4%, and 34.6%, respectively, and 8 years of follow-up of 12.6%, 31.1%, and 51.4%.

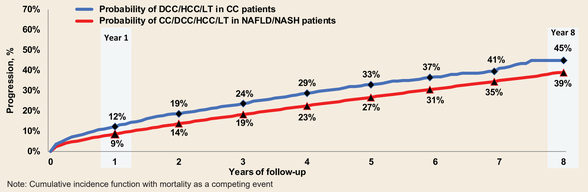
Figure 2. Impact of NAFLD/NASH Patients Liver Disease Severity on Mortality Risk by Cohort
Cox proportional-hazards model adjusted for patients demographics and comorbidities



All comparisons to NAFLD/NASH or CC statistically significant at p<0.001
Cox proportional-hazards regression model adjusted for patient age, race, gender, and the comorbidities of cardiovascular disease, renal impairment, diabetes, dysrhythmia, smoking, hyperlipidemia, and hypertension

- After adjustment for patient demographics and comorbidities, during the full study period, NAFLD/NASH patients' mortality risk significantly increased with liver disease progression from NAFLD/NASH and from CC to more advanced liver disease.
- Specifically, the risk of mortality for CC patients was significantly 2.2 times higher than NAFLD/NASH patients and 4.1 times higher for DCC than NAFLD/NASH patients. In addition, the risk of mortality for DCC patients was significantly 1.9 times higher than CC patients.

Figure 3. Cumulative Incidence of Liver Disease Progression for NAFLD/NASH and NAFLD/NASH CC Patients



Note: Cumulative incidence function with mortality as a competing event

- The probability of liver disease progression was high in NAFLD/NASH patients.
- For NAFLD/NASH patients, the probability of progression to advanced liver disease (CC, DCC, HCC, or LT) after 1 year of follow-up was 9% and this probability increased to 39% over the 8 year study period.
- For NAFLD/NASH CC patients, the probability of progression to ESLD (DCC, HCC, or LT) after 1-year of follow-up was 12%, and this probability increased to 45% over the 8-year study period.

Conclusions

- This study of Medicare NAFLD/NASH patients found:
  - NAFLD/NASH patients with advanced liver diseases had significantly higher comorbidities than NAFLD/NASH only patients, including higher rates of CVD, DM, and renal impairment.
  - Mortality due to NAFLD/NASH was high and increased from 13% in those with NAFLD/NASH only to 51% in those with DCC patients, who also had a significantly higher burden of comorbidities than NAFLD/NASH patients.
  - In the first year following diagnosis, patients' mortality was over 4-times significantly higher in DCC than CC patients and 2-times significantly higher in CC than NAFLD/NASH only patients. This trend remained after adjustment for patient demographics and comorbidities.
  - Over the 8 year study period, the probability of liver disease progression in NAFLD/NASH patients to CC or more severe disease was 39% and probability of progression in patients with CC due to NASH to ESLD was 45%.
  - Early identification and effective treatments for NAFLD/NASH patients are needed to reduce the rate of mortality.

Limitations

- NAFLD/NASH patient group may include F0-F3 patients as well as undiagnosed F4 (CC) patients due to under coding and lack of ICD code for F0-F3.
- Results are limited to the US Medicare population.
- As with any claims database, these data were subject to data coding limitations, data entry error, and misclassification of NAFLD/NASH.
- Results characterized all-cause mortality rather than liver-specific mortality.

Disclosures

- Study funded by Gilead Sciences, Inc.

References:
1. Golabi, Pegah, et al. "Current complications and challenges in nonalcoholic steatohepatitis screening and diagnosis." Expert review of gastroenterology & hepatology 10.1 (2016): 63-71.
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4. Wong, R. J., B. Liu, and T. Bhuket. "Significant burden of nonalcoholic fatty liver disease with advanced fibrosis in the US: a cross□sectional analysis of 2011□2014 National Health and Nutrition Examination Survey." Alimentary pharmacology & therapeutics 46.10 (2017): 974-980.

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