Do Patients With NASH-related Cirrhosis Have Better Overall Survival Compared With Other Etiologies of Cirrhosis? A Population-based Study

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Goals and Background: Nonalcoholic steatohepatitis (NASH) is a leading cause of cirrhosis. We aim to explore the clinical outcomes of NASH cirrhosis compared with other etiologies of cirrhosis.

Methods: We utilized an EHR-based database (TriNetX) to study the outcomes of NASH cirrhosis. Patients diagnosed with NAFLD or NASH and cirrhosis between January 2016 and December 2019 were identified utilizing appropriate ICD-10-CM codes. The primary outcome was 3-year overall survival. Secondary outcomes were decompensated cirrhosis, hepatocellular carcinoma, and liver transplantation. The Control group was patients with other etiologies of cirrhosis than NASH. Study and control groups were matched for demographic characters and comorbidities using propensity score matching.

Results: We identified 45,063 patients with NASH cirrhosis. The NASH cirrhosis cohort comprised older (61 vs. 59 y) White (78% vs. 64%) women (58% vs. 38%) with more comorbidities (diabetes mellitus, obesity, ischemic heart disease, history of cancer, chronic kidney disease). After propensity score matching, patients with NASH cirrhosis had a better 3-year survival (78% vs. 74%, HR 0.79, 95% CI 0.77-0.82) compared with patients with non-NASH cirrhosis. Hepatocellular carcinoma was diagnosed less commonly in patients with NASH cirrhosis (6.7% vs. 10.6%, $P < 0.001$), and liver transplantation was performed more often for NASH cirrhosis compared with non-NASH cirrhosis [Risk ratio 1.13 (1.08–1.18)].

Conclusions: Patients with NASH cirrhosis probably have better 3-year overall survival than other etiologies of cirrhosis. This is an interesting finding, as patients with NASH are older and have more comorbidities. Improved survival can be partly explained by a higher probability of liver transplantation and improvements in cardiovascular outcomes.

Key Words: nonalcoholic fatty liver disease, NASH, cirrhosis, outcome, database

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The rising prevalence of obesity-related liver diseases—nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH), is rising worldwide, parallel with the obesity pandemic.[1] It is estimated that 25%–30% of the general population in the United States have NAFLD, and about 14% have NASH.[1,2] It is projected that the prevalence of NAFLD, notably NASH with advanced fibrosis, will increase substantially over the next decade. This will translate into an increased incidence of decompensated cirrhosis, hospitalizations for decompensated cirrhosis and hepatocellular carcinoma (HCC) by 2-fold to 3-fold by 2030, and increased demand for liver transplant for NASH-related cirrhosis and HCC.[3–5] The most common causes of death in patients with NAFLD/NASH are cardiovascular disease (CVD) and nonhepatic malignancies.[6] With improvement in CVD-related mortality, we can expect further rise in end-stage liver disease and liver-related mortality. However, there is a dearth of data comparing the clinical outcomes of patients with NASH-related cirrhosis with other etiologies of cirrhosis. Thus, we aim to explore the clinical outcomes of patients with NASH-related cirrhosis of the liver compared with other etiologies of cirrhosis.

METHODS

This is a population-based, multicenter, retrospective cohort study utilizing TriNetX (Cambridge, MA), "a global federated health research network that provides deidentified data from electronic medical records." (*https://www.trinetx.com/page/4/#home-slider-3-copy*) "To fortify protected health information, TriNetX rounds up the number of patients to the nearest 10 for analytic purposes".[7] We accessed the TriNetX platform to obtain aggregated health records of 75 health care organizations (HCO) from January 2016 to December 2019. This period was selected to ensure the unambiguous use of ICD-10-CM codes across all HCOs. Additional assistance was obtained from the technical team at TriNetx to develop the queries and run the analysis.

Study Population and Comparison Groups

Adult patients ($\geq$18 y) diagnosed with NAFLD or NASH were identified using ICD-10-CM codes (K76.0, K75.81). We identified patients with the diagnosis of cirrhosis using ICD-10-CM codes (K74.0, K74.2, K74.6). Two cohorts of patients were selected, one with the diagnosis of NASH cirrhosis and the other with other etiologies of cirrhosis (non-NASH cirrhosis). NASH cirrhosis was defined as the presence of NAFLD or NASH and cirrhosis of the liver. Non-NASH cirrhosis was defined as cirrhosis of the liver from other etiologies, and patients with a diagnosis of NAFLD or NASH were excluded. Other etiologies of cirrhosis include—alcohol, chronic hepatitis C, chronic hepatitis B, Wilson disease, autoimmune hepatitis, alfa-1 antitrypsin deficiency, biliary cirrhosis, and these

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etiologies of cirrhosis were excluded from the NASH cirrhosis cohort (Fig. 1). The 2 groups were compared for baseline demographic characteristics (age, gender, race, ethnicity) and common comorbidities (diabetes mellitus, obesity, malnutrition, chronic kidney disease, chronic pulmonary diseases, coronary artery disease, and heart failure), and primary and secondary outcomes.

Follow-up and Clinical Outcomes

The study and comparison cohorts were followed up for 3 years following the diagnosis of cirrhosis. The primary outcome was 3-year mortality in patients with NASH cirrhosis compared with non-NASH cirrhosis. Secondary outcomes were the development of hepatic decompensation and hepatocellular carcinoma and the frequency of liver transplantation between the 2 groups. Decompensated cirrhosis was defined as the development of ascites, variceal gastrointestinal (GI) bleeding, hepatic encephalopathy, hepatorenal syndrome, or hepatopulmonary syndrome. The Control group was patients with other etiologies of cirrhosis than NAFLD (Fig. 1). Study and control groups were matched for demographic characters and comorbidities using propensity score matching.

Ethical Considerations

This study involves human subjects; however, the Western institutional review board has provided a waiver to TriNetX since it utilizes aggregate counts, and investigators do not have access to protected health information from the participating HCOs. Thus, written patient consent is not required. Specific geographical and institutional data of participating centers are kept anonymous.[8]

Statistical Analyses

The mean and SD were calculated for continuous variables, and proportion and percentage were calculated for dichotomous and categorical variables. Propensity score matching was performed. To generate a propensity score, the first step was logistic regression (where the outcome was exposure). Then factors associated with the exposure were determined by evaluating (Table 1) (before matching) for variables significantly different between the study and control groups. Age (at the time of study enrolment), gender, and common comorbidities (diabetes mellitus, obesity, malnutrition, chronic kidney disease, chronic pulmonary diseases, coronary artery disease, and heart failure) that were significantly different before matching were controlled.[9] Age and the above comorbidities were also assessed as a proxy for the Charlson comorbidity index since the Charlson comorbidity index of individual patients cannot be calculated in the database (Table 1). The "greedy nearest neighbor matching" approach was used, wherein a patient in the study groups whose propensity score was the closest to that of a patient in the control group was selected as the match without replacement.[10] Cohorts were considered well-matched if there was a standardized mean difference of less than 0.1 for continuous variables. Propensity score density graph and table have been provided as supplement files 1, Supplemental Digital Content 1, http://links.lww.com/JCG/B67, and 2, Supplemental Digital Content 2, http://links.lww.com/JCG/B68.

For clinical outcomes, risk ratio (RR) and risk difference were calculated, and Kaplan-Meier analysis with survival curve was obtained for 3-year mortality (Supplement files 3, Supplemental Digital Content 3, http://links.lww.com/JCG/B69, and 4, Supplemental Digital Content 4, http://links.lww.

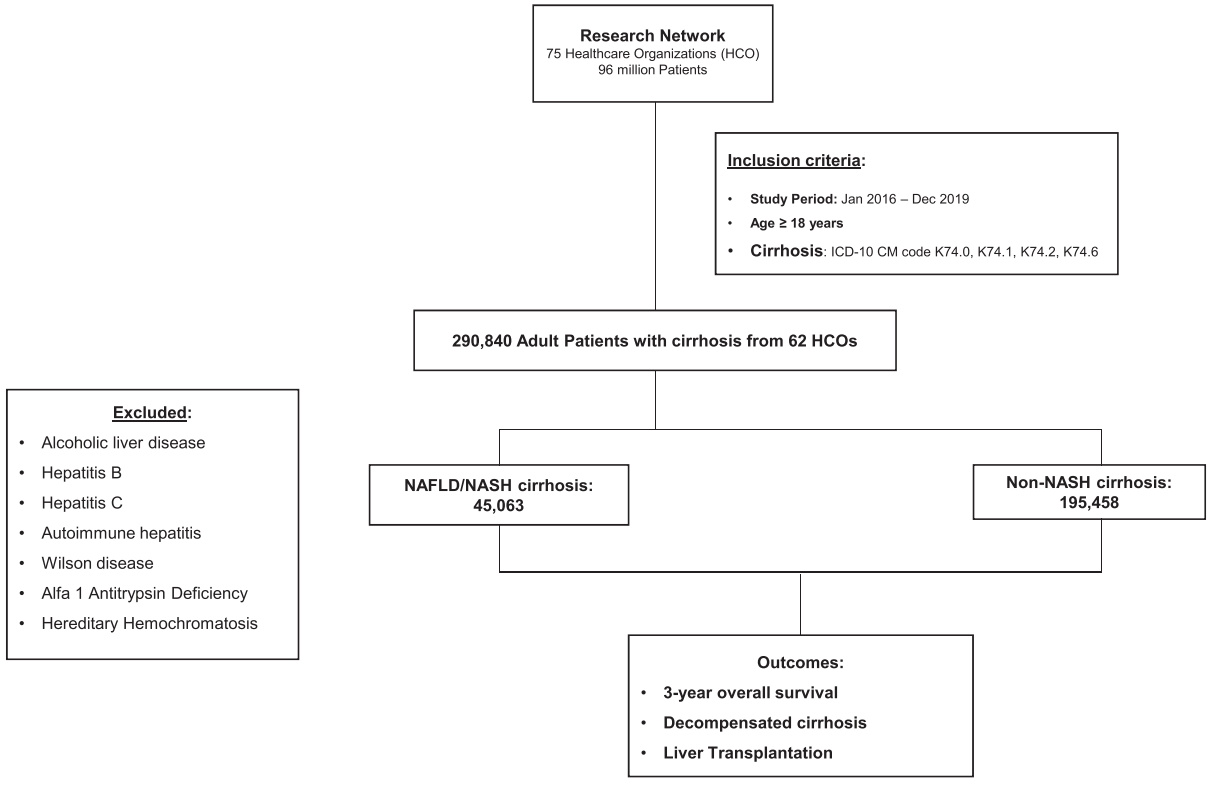

FIGURE 1. Consort diagram showing the selection of study and control populations in the database. HCO indicates health care organizations; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis.

TABLE 1. Baseline Characteristics of Patients With NASH Cirrhosis and non-NASH Cirrhosis

	Mean (±SD)		No. patients (%)			
	NASH cirrhosis (45,063)	Non-NASH cirrhosis (195,458)	NASH cirrhosis (45,063), n (%)	Non-NASH cirrhosis (195,458), n (%)	*P*	Standard difference
Demographic characteristics						
Age (y) (mean)	61 ± 12.8	59 ± 13	—	—	< 0.001	0.15
Female	—	—	25,725 (58)	72,930 (38)	< 0.001	0.41
White	—	—	34,654 (78)	122,935 (64)	< 0.001	0.14
Black	—	—	1921 (4.3)	27,022 (14)	< 0.001	0.22
Comorbidities						
Diabetes Mellitus	—	—	19,838 (45)	41,406 (21)	< 0.001	0.51
Obesity	—	—	15,386 (35)	21,394 (11)	< 0.001	0.58
Malnutrition	—	—	1729 (3.9)	9329 (4.9)	< 0.001	0.04
History of Cancer	—	—	15,053 (34)	48,864 (25)	< 0.001	0.58
Ischemic heart disease	—	—	8454 (19)	26,473 (13)	< 0.001	0.15
Heart failure	—	—	5274 (12)	20,940 (11)	< 0.001	0.04
Cerebrovascular disease	—	—	3657 (8)	13,797 (7)	< 0.001	0.06
Chronic kidney disease	—	—	6008 (14)	23,020 (12)	< 0.001	0.05

NASH indicate nonalcoholic steatohepatitis.

com/JCG/B70). The statistical significance was set at a 2-sided *P*-value of less than 0.05. All the statistical analyses were performed using the TriNetX platform.

RESULTS

We identified 290,840 patients with cirrhosis from 62 health care organizations, and 45,063 (15.5%) had NASH cirrhosis. About 50,000 patients had more than one etiology of cirrhosis or unclear etiology of cirrhosis. Patients with NASH were older (61 y vs. 59 y), White (78% vs. 64%), and women (58% vs. 38%). Patients with NASH cirrhosis more frequently had a diagnosis of diabetes mellitus (45% vs. 21%), obesity (35% vs. 11%), ischemic heart disease (19% vs. 13%), history of cancer (34% vs. 25%), and CKD (14% vs. 12%) compared with non-NASH cirrhosis (Table 1).

We present results before and after propensity score matching. We found improved 3-year overall survival in NASH cirrhosis compared with non-NASH cirrhosis (78% vs. 73%) before propensity score matching [HR 0.80, 95% CI 0.80 (0.78–0.82)]. In age-matched, gender-matched and comorbidity-matched cohorts, the 3-year probability of survival was 78% in patients with NASH cirrhosis compared with 74% in non-NASH cirrhosis (HR 0.79, 95% CI 0.77–0.82) (Table 2). Figure 2 illustrates the Kaplan-Meier survival graph before and after propensity score matching. The details on Kaplan-Meier survival analysis are presented as supplement files, Supplemental Digital Content 4, http://links.lww.com/JCG/B70. The rate of hepatic decompensation was comparable in both the cohorts before (33%) and after matching (33.6% vs. 32.6%, $P = 0.06$). HCC was diagnosed less commonly in patients with NASH cirrhosis [6.7% vs. 10.6%, RR 0.63 95% CI [0.61-0.66)] compared with patients with non-NASH cirrhosis. Liver transplantation was performed in 6.1% of patients with NASH cirrhosis compared with 5.4% of patients with non-NASH cirrhosis [RR 1.13 (1.08–1.18)] during the follow-up period (Table 2).

DISCUSSION

NASH is the second leading indication for liver transplantation in patients with or without HCC and the most common indication for liver transplantation in women and elderly patients.[11,12] In our study, NASH cirrhosis accounted for ~20% of all patients with cirrhosis, and NASH cirrhosis was more common in women (58%). These figures are consistent with data from recent studies.[12,13] While gastrointestinal hemorrhage from variceal bleeding, infection, hepatocellular carcinoma, hepatic encephalopathy, and renal failure are the leading causes of death in non-NASH cirrhosis, most patients with NASH die from CVD and nonhepatic malignancies. Nonetheless, there has been a steady decline in cardiovascular and stroke-related mortality over the past 2 decades in the United States. The heterogeneity of factors contributing to the pathophysiology of NASH has significantly impeded the development of diagnostic tests and therapeutics.[14] Consequently, there has been limited progress in our ability to treat NASH or prevent the development of NASH in patients with NAFLD. It is intuitive to think that the lack of effective treatment options for NASH and improved survival from CVD and cancers will increase the prevalence of NASH and exacerbate the burden of NASH cirrhosis as these patients live longer.

Our findings show better 3-year overall survival in patients with NASH cirrhosis compared with patients with cirrhosis due to other etiologies (HR 0.78). This is an interesting finding, as patients with NAFLD/NASH are older and have more comorbidities. However, the 2 cohorts were matched for age, gender, and comorbidities. Studies have demonstrated a slower progression of NASH-related liver fibrosis than HCV-related liver fibrosis.[12,15] A large single-center study found that patients with NASH cirrhosis with low Model for End-Stage Liver Disease (MELD) scores were less likely to progress compared with HCV-related cirrhosis.[16] In a study on disease-specific waitlist outcomes in liver transplantation, Nagai et al showed that the 90-day and 1-year mortality was higher in

TABLE 2. Major Clinical Outcomes in Patients With NASH and non-NASH Cirrhosis Before and After Propensity Score Matching

	Before propensity score matching			After propensity score matching		
Outcomes*	**NASH cirrhosis, %**	**Non- NASH cirrhosis, %**	**HR or RR [95% CI]**	**NASH cirrhosis, %**	**Non- NASH cirrhosis, %**	**HR or RR [95% CI]**
3-year survival†	77.4	72.9	0.80 [0.78–0.82]‡	78.3	73.8	0.79 [0.77–0.82]‡
Hepatic decompensation§	33.3	32.8	1.01 [1.00–1.03]	33.6	32.6	1.02 [0.996–1.053]
Hepatocellular carcinoma	6.7	10.6	0.63 [0.61–0.66]	6.9	9.1	0.76 [0.72–0.79]
Liver transplantation	6.1	5.4	1.13 [1.08–1.18]	6.6	5.3	1.27 [1.22–1.32]

*All outcomes on 3-year follow-up, before and after propensity score matching.
†Based on the Kaplan-Meier analysis.
‡HR.
§Defined as the development of ascites, variceal GI bleeding, hepatic encephalopathy, hepatorenal syndrome, or hepatopulmonary syndrome.
CI indicates confidence interval; GI, gastrointestinal; HR, hazard ratio; NAFLD, nonalcoholic fatty liver disease; RR, risk ratio.

MELD-Na–adjusted NASH cirrhosis patients compared with those with other etiologies for cirrhosis.[17] Another study on patients awaiting liver transplantation found higher mortality in NASH cirrhosis compared with non-NASH cirrhosis at 90 days (HR 1.15) and 1 year (HR 1.25).[13] This was mostly due to a lower probability of

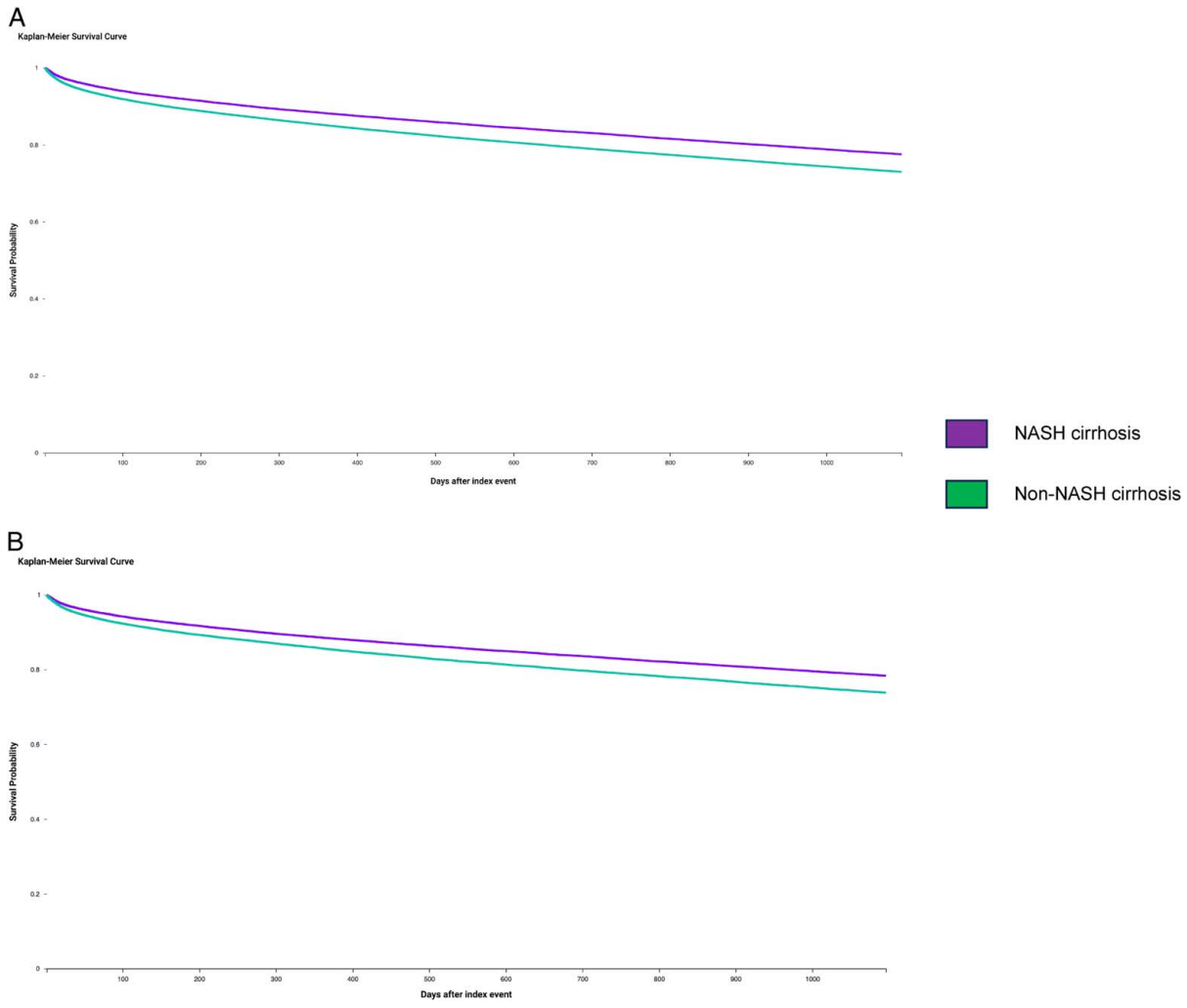

FIGURE 2. (A) K-M survival curve for 3-year overall survival in NASH versus non-NASH cirrhosis before propensity score matching. (B) K-M survival curve after propensity score matching. K-M indicates Kaplan-Meier; NASH, nonalcoholic steatohepatitis.

receiving a liver transplant due to lower MELD scores. However, both studies were on patients with decompensated cirrhosis with high MELD-sodium scores. The above evidence probably indicated that patients with NASH cirrhosis are more likely to spend longer in a compensated stage with lower MELD scores, providing opportunities for novel therapies as well as liver transplantation. On the flip side, a longer waitlist for patients with NASH cirrhosis has been shown to result in worsened outcomes.[13]

We found that patients with NASH cirrhosis are less likely to progress to HCC compared with non-NASH cirrhosis (11% vs. 13% during 3 years of follow-up). This is consistent with previous data.[16] However, NAFLD/NASH is the fastest-growing cause of HCC in Europe and the United States.[18] An observation is likely due to an overwhelming rise in the prevalence of NASH. Patients with NASH who develop HCC are more likely to be older, have other comorbidities, and are obese. Our findings are consistent with prior reports that patients with NASH-related cirrhosis were more likely to have comorbid conditions than patients with non-NASH cirrhosis. This purports a unique challenge in screening, diagnosing, and managing HCC in this population.[18] HCC arising in NASH is also different from that seen in other etiologies for cirrhosis, like viral hepatitis. Up to 50% of NASH-related HCC can develop without cirrhosis, but most noncirrhotic patients are not included in HCC screening programs.[19,20] An Italian multicenter observational prospective study on 756 patients with HCC showed that cirrhosis was present only in 46.2% of NASH-related HCC.[21] Other reasons that can impede early detection of HCC in this population include the presence of abdominal obesity, which can affect the accuracy of commonly used screening tools like ultrasound elastography and health care priorities given other coexisting cardiovascular diseases.[22] Furthermore, only about 15% of patients with HCC and NAFLD/NASH are diagnosed at Barcelona Clinic for Liver Cancer (BCLC) stages 0 or A, which would enable a curative approach.[23]

Our data also shows that NASH cirrhosis patients underwent liver transplantation more frequently. NAFLD is currently the fastest-growing indication for liver transplantation in the United States and Europe.[24] However, as noted above, patients with NASH cirrhosis can have a longer waitlist before liver transplantation due to lower MELD scores.[13] Given the coexistent metabolic dysfunction and obesity, patients with NAFLD are more prone to develop peri-operative complications, and in the long-term, they have a higher incidence of malignancies and cardiovascular events than patients transplanted for other reasons.[25,26] Surgery can also be more complex, with data showing increased operative time, risk of intra-operative complications like a hepatic artery, inferior vena cava injury, uncontrolled bleeding, and higher rate of operative revision in obese patients.[27]

Our study findings are constrained by notable limitations. The retrospective design has an inherent risk of selection bias. The database utilizes electronic health records for research purposes; however, detailed clinical information of individual patients is unavailable due to a lack of access to patient-level data, limiting our ability to assess the degree of fibrosis or MELD scores of individual patients. We reported the overall mortality of patients with cirrhosis; however, liver disease-specific mortality cannot be estimated due to the use of electronic health record-based data. Furthermore, we defined decompensated cirrhosis as cirrhosis with one of the decompensation events. While combining the diagnosis of cirrhosis and the development of one of the decompensations gives us a reliable idea of decompensated cirrhosis, it may not be perfect given the use of a database and lack of individual data. Another limitation of an electronic health record-based database is the potential loss of patients if they transfer their care from one health network to another.

This is a large study from 62 health care organizations, which increases the generalizability of our findings. Moreover, our study comprises a recent cohort of patients (within the last 5-6 y), which reflects the current trend in the management and outcome of patients with cirrhosis. Multiple potential confounders can skew the direction of our clinical outcomes; thus, probable confounders were controlled using propensity score matching. We matched the study and comparison groups for age, gender, and comorbidities, including cardiac comorbidities (ischemic heart disease and heart failure) and cerebrovascular diseases, which are the leading causes of mortality other than cancer among subjects with cirrhosis.

CONCLUSION

Patients with NASH-related cirrhosis probably have better overall 3-year survival and a slower rate of decompensation than patients with other etiologies of cirrhosis. This is an interesting finding, as patients with NASH are older and have more comorbidities. Improved survival can be partly explained by slower disease progression, our finding of a higher probability of liver transplantation, and general improvements in cardiovascular outcomes. Our findings highlight the fact that patients with NASH cirrhosis have a better opportunity to get through liver transplantation with good supportive care and potentially have a long-term survival. Furthermore, the slower progression of the disease can potentially provide a window for novel therapies and clinical trials in addition to the prospect of receiving a liver transplant. Our findings highlight the need for further research and coordinated efforts in the early diagnosis and effective management of NASH.

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