The Changing Face of Hepatocellular Carcinoma: Forecasting Prevalence of Nonalcoholic Steatohepatitis and Hepatitis C Cirrhosis

Osmanuddin Ahmed^{*}, Lisa Liu^{*}, Antony Gayed^{*}, Amanjit Baadh^{*}, Mikin Patel[†], Jordan Tasse^{*}, Ulku Turba^{*}, Bulent Arslan^{*}

^{*}Rush University Medical Center, 1653 W Congress Parkway, Chicago, IL 60612, USA and [†]University of Chicago Medical Center, 584 S Maryland Avenue, Chicago, IL 60637, USA

Background/objectives: The purpose of this research is to analyze the past and forecast the future prevalence of Hepatitis C Virus (HCV) and Nonalcoholic Steatohepatitis (NASH) and their respective contribution to Hepatocellular Carcinoma (HCC) incidence in the setting of novel anti-viral agents and rising obesity rates in the United States. **Methods:** Existing data of HCV and NASH prevalence in the United States utilizing the National Health and Nutrition Examination Survey (NHANES) and Organ Procurement and Transplantation Network (OPTN) was collected and analyzed to project future prevalence trends. **Results:** Prevalence of NASH and HCV are expected to increase and decline respectively over the next two decades with alcoholic cirrhosis expected to stay relatively unchanged. The estimated prevalence of NASH equaled and overtook the projected prevalence of HCV in 2007 at approximately 3 million persons. Estimates of NASH's contribution to HCC overtook HCV-HCC in 2015 at an approximately 25 million persons. Projection models suggest HCV prevalence declining to 1 million active cases by 2025, while NASH potentially increases to 17–42 million depending on a linear or exponential trendline. Projections of NASH-HCC similarly outpace HCV-HCC by 2025 with 45 million or 106 million (linear, exponential) versus 18 million persons respectively. **Conclusions:** The future prevalence of HCV and NASH are expected to become further divergent with NASH emerging as the major contributor of cirrhosis and HCC in the United States. (J CLIN EXP HEPATOL 2019;9:50–55)

In the United States, deaths attributable to Hepatocellular Carcinoma (HCC) are increasing faster than any other cancer. Since the early 1980s, liver and intrahepatic bile duct cancer has increased from less than 3 cases per 100,000 to nearly 8 per 100,000 in 2010.¹ Development of HCC is strongly correlated with cirrhosis as 80% of HCC cases occur in patients with a cirrhotic liver.² For this reason, the primary causative agents of cirrhosis are among the major risk factors for HCC. Currently, the four leading causes of chronic liver disease necessitating transplant in the US are Hepatitis C Virus (HCV), alcoholic liver disease, Nonalcoholic Steatohepatitis (NASH), and HCV/alcoholic liver disease accounting for 35.2%, 18.3%, 15.8%, and 9.7% of patients registered for liver transplants from 2004 to 2013.³

While HCV rates have been declining recently due to novel advancements in the treatment of HCV through curative antiviral therapy, NASH cirrhosis has greatly increased in correlation with increasing obesity in America.⁴ Based on the National Health and Nutrition Examination Survey (NHANES), obesity prevalence has continuously increased from 13% in 1980 to 36% in 2014. However, a paucity of literature exists regarding the expected NASH incidence or prevalence trends for the upcoming decades, though it is estimated that despite higher mortality on the waitlist, NASH will surpass HCV as the leading etiology behind liver transplantation by 2020.³ Understanding the changing demographic of HCC patients in the United States is critical to improving screening, diagnosis, and treatment of HCC. The purpose of this current study is to analyze the past prevalence of HCV, NASH, and alcoholic cirrhosis in the US, and forecast future trends to further understand the evolving face of hepatocellular carcinoma.

Keywords: epidemiology, interventional oncology, liver, obesity

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Address for correspondence: Lisa Liu, 1725 W. Harrison St., Suite 450, Chicago, IL 60612, USA. Tel.: +1 818 620 8915.

E-mail: lisa_b_liu@rush.edu

Abbreviations: HCC: Hepatocellular Carcinoma; HCV: Hepatitis C Virus; NASH: Nonalcoholic Steatohepatitis; NHANES: National Health and Nutrition Examination Survey; OPTN: Organ Procurement and Transplantation Network

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METHODS

Publicly available estimates of NASH prevalence in 1994, 2004, and 2008 based on probability sampling from the NHANES database were utilized. New NASH-diagnosis

liver transplant registrations from 1995-2016 were also obtained from the Organ Procurement and Transplantation Network (OPTN). Using the overlapping 2004 and 2008 data, the proportions of NASH patients progressing to cirrhosis were calculated. NASH prevalence was then calculated for all years except the NHANES sampling years by using the mean proportion as a coefficient. With this calculation, NASH prevalence was interpolated into the intervening years between NHANES sample sets. A linear and an exponential regression models were created using the interpolated and actual prevalence over time. These models were used to forecast potential future trends in NASH prevalence.

Publicly available estimates of HCV prevalence in 1994, 2002, and 2010 based on probability sampling from the NHANES database were utilized. HCV-diagnosis liver transplant registrations from 1995 to 2016 were used from OPTN. Using the overlapping 2002 and 2010 data, and utilizing 1994 NHANES data as a proxy estimate for 1995, the proportions of HCV patients progressing to cirrhosis were calculated. HCV prevalence was then calculated for all years except the NHANES sampling years by using the mean proportion as a coefficient. With this calculation, HCV prevalence was interpolated into the intervening years between HCV sample sets. A model was created using the interpolated and actual prevalence over time. To build this model, a quadratic regression was applied to fit the prevalence data to a curve. This model was used to forecast future HCV prevalence. As an accuracy control, our prevalence model was compared against the base case HCV prevalence model developed by Kabiri et al. accounting for or based on NHANES data, CDC data, developed an HCV prevalence model based on NHANES, CDC, and clinical study data.⁵

To estimate the differential progression of NASH cirrhosis and HCV cirrhosis to HCC, progression was calculated based on rates from a direct comparison of one-year cumulative progression. In this report, the one-year

Table 1 Predicted NASH and HCV Prevalence in the US (in Millions).

Year	HCV	NASH (linear model)	NASH (exponential model)
2005	3.22	1.37	2.41
2010	3.17	5.51	4.93
2015	2.79	9.66	10.10
2020	2.09	13.80	20.68
2025	1.06	17.95	42.34

cumulative progression rates were 2.6% for NASH-HCC and 4.0% for HCV-HCC.⁶

RESULTS

Predicted NASH and HCV prevalence in the United States from 2005 to 2025 are presented in Table 1 and Figure 1. HCV prevalence is predicted to steadily decline from 3.22 million in 2005 to 1.06 million in 2025. Whereas NASH prevalence is predicted to increase rapidly from 1.37 million in 2005 to 17.95 million in 2025 based on the conservative linear model versus 2.41 million in 2005 to 42.34 million with the exponential model. According to the estimation and prediction models generated for NASH and HCV prevalence in the US, in both linear growth and exponential growth scenarios for NASH, NASH exceeded HCV in prevalence in or around 2007 (Figure 1). By 2025, our predictions suggest that even assuming the more conservative linear growth model, NASH prevalence will outnumber HCV prevalence in the US by a factor of almost 18 times (Table 1).

Predictions of progressions of NASH and HCV to HCC in the United States from 2005 to 2025 are presented in Table 2 and Figure 2. HCV-HCC cases are predicted to climb and reach a peak around 2015 at approximately

Figure 1 Predicted NASH and HCV progression to HCC in the United States (2004–2025).

Figure 2 Predicted NASH and HCV prevalence in the United States (2004–2025).

Table 2 Predicted NASH and HCV Progression to HCC in the US.

Year	HCV	NASH (linear model)	NASH (exponential model)
2005	21,613	4972	6025
2010	27,462	14,922	12,335
2015	28,737	24,872	25,253
2020	25,438	34,821	51,700
2025	17,565	44,771	105,842

29,000 cases before declining to less than 18,000 cases by 2025. Like NASH prevalence, NASH-HCC is predicted to increase rapidly from about 5000 to 6000 cases in 2005 to 45,000 in 2025 utilizing the linear model and as high as 106,000 according to the exponential model. NASH-related HCC cases are estimated to have surpassed HCV-HCC cases in the US in or around 2015 for both linear NASH growth and exponential NASH growth models (Figure 2). The linear model of growth for NASH and NASH-HCC suggests that NASH-HCC cases will outnumber HCV-HCC by a factor of almost 3 times by 2025 (Table 2).

DISCUSSION

In order to more comprehensively study attribution of HCV and NASH to the development of HCC, both transplant data and the natural history of the diseases were taken into account. Liver transplant data was utilized as a reliable proxy for HCC prevalence over time to capture the reported etiologies of cirrhosis, the main limitation being that data was dependent on the accuracy of reported etiologies, which particularly for NASH was underreported as awareness of the

disease has only grown recently in the past decade. To compensate, only transplant data from 1994 onward was utilized.

The natural history of HCV has been well-documented in literature. According to the CDC, 5–20% of untreated HCV infections develop into HCV-cirrhosis. A review of 111 studies of the natural history of HCV infection reported that over a duration of 20 years, 16% of patients developed cirrhosis.⁷ In patients with HCV cirrhosis, the yearly incidence of HCC is reported to be between 1 and 3%, with approximately 15% developing HCC within 10 years.^{8,9} Conversely, the natural history of NASH has been less studied, though interest in NASH has grown significantly within the past 10 years. Among patients with NASH, a review of 7 studies found that 35% develop progressive fibrosis. Based on the fibrosis progression rate in this review, at 14 stages/year, progression to stage 4 (cirrhosis) takes approximately 29 years.¹⁰ In a review study of patients with NASH cirrhosis, the risk of HCC ranges from 2.4% over seven years to 12.8% over three years. The risk of HCC in NASH cirrhosis cohorts was lower than in HCV cirrhosis cohorts in this review, and in a report of 195 patients, in which the one year incidence of HCC in NASH cirrhosis was 2.6% compared to 4.0% with HCV cirrhosis.^{6,11} A higher proportion of patients with NASH develop cirrhosis, but of those who develop cirrhosis the probability of developing HCC is higher in patients with HCV. Predicted annual incidence of NASH-related HCC may also be underestimated due to a growing observation of HCC incidence related to non-cirrhotic NASH. In contrast, HCV progression to HCC rarely occurs in non-cirrhotic patients. Despite the lack of existing data off of which to work, the general trends of our prediction models are consistent with the documented trends of liver transplant etiology, as well as 2010 insurance data indicating nonalcoholic fatty liver disease/NASH as the leading etiology associated with HCC.¹²

In the United States, while the incidence of HCC continues to rise based on new transplant registrations, the etiological trends behind the development of cirrhosis and HCC have been undergoing a profound change. Based on OPTN data as of December 30, 2016, the proportion of all transplant registrations for alcoholic cirrhosis varied between 12 and 16% from 1995 to 2013, and saw an annual stepwise increase to 21% from 2014 to 2016. Registrations for HCV cirrhosis hovered above 26% from 1999 to 2012 before steadily decreasing yearly to 16% in 2016. Meanwhile NASH cirrhosis registration increased exponentially from 0.1% in 2002 to 15.2% in 2016. Our models suggest that the prevalence of NASH surpassed HCV by 2006 and that NASH-related HCC incidence surpassed HCV-related HCC incidence by 2015. In prediction of future NASH prevalence, both linear and exponential growth models were developed; even in the more conservative estimates of linear growth, our models suggest that by 2025 NASH prevalence will be almost 18 times greater than HCV, contributing to approximately 3 times as many cases of HCC than HCV.

Understanding the projected trends of HCC etiology in the United States provides insights for development of future approaches to the screening, diagnosis, and treatment of HCC. As NASH outpaces HCV as the leading HCC etiology, differences in the pathology, natural history, and treatment options between the two are important to consider. The pathology behind the progression of NASH to NASH-HCC remains unclear. Histologically, NASH shares characteristics with alcoholic liver disease, primarily proinflammatory fat accumulation in parenchymal cells. Key players in NASH progression to HCC are suggested to include genetic modifications, proinflammatory high fat and/or high fructose diets, and oxidative and endoplasmic cellular stresses.¹³ Advanced fibrosis increases the risk of progression to HCC, but NASH-HCC in the absence of cirrhosis has been increasingly recognized as a phenomenon.¹⁴ Meanwhile, the relationship between HCV and HCC has been extensively studied. In HCV progression to HCC, the presence of the HCV core protein may induce HCC without the prerequisite load of genetic errors normally required for cancer development, skipping or accelerating some of the classic steps of cancer induction. HCC development is typically dependent on liver fibrosis by way of chronic hepatitis and cirrhosis.¹⁵

As compared to HBV-related HCC, HCV-related HCC tumors are more frequently found as single tumors that are smaller and encapsulated. Imaging diagnosis is made with ultrasound, CT, MR, and selective angiography sometimes in concert with CT which can be instrumental in identifying very small HCC tumors. Definitive diagnosis is made with biopsy when certain diagnosis cannot be made with imaging.¹⁵ With the advent of curative therapy for HCV, the risk of HCC is expected to be greatly reduced given that the majority of HCC occurs in patients infected

with HCV or HBV.¹⁶ Curative therapies are liver resection, liver transplantation and radiofrequency ablation. Treatments that are considered palliative include stereotactic body radiotherapy, transarterial embolization, Transarterial Chemoembolization (TACE), radioembolization and chemotherapy.¹⁷ Compared to HCV-HCC, HCC in the setting of NASH typically presents at time of diagnosis as relatively more advanced cases, often found at terminal stage or BCLC stage D. Likely, this trend is the result of insufficient surveillance of HCC occurrence in NASH patients at risk, partially because, as previously mentioned, relatively little has been understood about the natural history of NASH progression to HCC. NASH-HCC patients have also been identified as a group less likely to receive treatment for their HCC, despite studies which suggest favorable response of NASH-HCC tumors to curative therapies. Though data is limited, current literature suggests that NASH-HCC responds similarly to these treatments as does HCC in other settings such as HCV.¹⁴

A large cohort study in Germany between 2000 and 2010 compared the treatments and survival of NASH-HCC compared to non-NASH HCC. The most important finding was that patients with NASH-HCC have superior liver function compared to other patients with HCC. In this cohort, the most common treatment was TACE in both NASH (42.2%) and other HCC (46.8%). No patients with NASH-HCC received transplants as their primary treatment, but 4.4% received transplants after bridging with TACE whereas 17.8% received transplants after bridging in the non-NASH HCC group. Primary treatment with sorafenib was significantly more frequent in NASH-HCC. These treatment differences may have been secondary to larger and more multifocal tumors with more metastasis in the NASH-HCC group. Because liver function is relatively well preserved in NASH-HCC, cirrhosis detection may occur later as compared to non-NASH HCC. In this cohort study, overall survival was statistically longer in the Non-NASH group, 15.5 months vs 11.28 months in the NASH group.¹⁸ Overall survival in the German study was not consistent with results of earlier studies, and this effect might be attributable to delayed detection, different treatments, and the comorbidities including age in the NASH group.^{19,20}

Our study was subject to limitations. Published literature and publicly available data related to NASH prevalence remains scarce, in part due to only recently rising recognition of NASH in the clinic. NASH-related cases are expected to have been consistently underreported or misreported as cryptogenic, especially in earlier years. We did not utilize OPTN data prior to 1995 in order to compensate for the most drastically underdiagnosed numbers, but it is impossible to know how reliable the reported numbers of NASH were after 1994, or how underreported NASH diagnoses are currently. NASH prevalence was then

estimated from OPTN based on interpolation of available overlapping NHANES data, limited to three data points: 1994, 2002, and 2010. As OPTN data prior to 1995 was not used, 1994 HCV NHANES data was matched as a proxy to the 1995 OPTN data as part of the calculation for the interpolation coefficient. Published literature and public data related to NASH-HCC progression is similarly scarce, as NASH as a contributor to HCC development is only recently becoming more understood. Therefore, our ability to compare our models to existing predictions in literature was limited. Despite the lack of existing data from which to work, the general trends of our prediction models are consistent with the documented trends of liver transplant etiology as well as with 2010 insurance data indicating nonalcoholic fatty liver disease/NASH as the leading etiology associated with HCC.^{12,21} Projection as a method is inherently subject to limitations, as it does not take into account the changing environment which may affect the trend in an unpredictable manner. Our models should be understood as a base scenario, where it is assumed that the environmental and genetic factors driving nonalcoholic fatty liver disease/NASH development continue their current trends. Therefore, the possibility exists that our models underestimate the response of the medical community in addressing the rising nonalcoholic fatty liver disease/NASH epidemic. As NASH becomes the dominant player in HCC development in the US, further research into understanding the mechanisms of NASH and maximizing screening protocol and therapy results is paramount to the treatment of HCC.

CONCLUSION

HCC incidence in the United States continues to rise even as overall cancer incidence drops. A major contributor to the observed increase in HCC despite a decrease in HCV prevalence is the drastic increase in obesity rates and subsequently NASH in America, with a conservative prediction of NASH contributing to 3 times as many cases of HCC than HCV by 2025. Screening and treatment of HCC in the United States should take into account the shifting trends in the make-up of the patient population.

CONFLICTS OF INTEREST

The authors have none to declare.

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