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Hereditary hemochromatosis as an independent risk factor for liver cancer: A matched case-control study of the National Inpatient Sample Database

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Cox regression analysis of 30 untreated patients revealed that only a high-grade DN was significantly associated with an increased risk of the progression to HCC (P<0.05), as was neither arterial phase enhancement nor size of nodule. Additional immunohistochemical staining of 26 untreated RN or DN specimens identified no significant histologic predictor for HCC development. **Conclusion:** Our findings suggest that more careful and active surveillance for HCC is needed in cirrhotic patients with high-grade DNs in the liver, for which LAT could be considered likely with a preemptive intent. Future studies should focus on the development of biopredictives for malignant transformation of hepatic nodules.

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1058
HEPATOCELLULAR CARCINOMA IN NON-ALCOHOLIC STEATOHEPATITIS AND CRYPTOGENIC CIRRHOSIS OVER A 15-YEAR PERIOD

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Background: Non-alcoholic steatohepatitis (NASH) has been recognized as the main cause of cirrhosis in patients previously categorized under the term “cryptogenic cirrhosis” (CC). The data regarding similarities and disparities between hepatocellular carcinoma (HCC) patients with either NASH cirrhosis or CC remains limited. We aimed to study the characteristics and trend of biopsy-proven NASH cirrhosis and CC in patients with HCC. **Methods:** We identified all adult patients with HCC and concomitant diagnosis of NASH-related cirrhosis or cryptogenic cirrhosis who received care at two quaternary liver transplant centers in the United States, between January 2000 and December 2015. Presence of liver cirrhosis was determined based on radiologic and histologic evidence. CC was determined in patients who had no identifiable cause of cirrhosis after extensive clinical, serological and pathological evaluations. Patient with excessive alcohol consumption were excluded. HCC was diagnosed by either pathological diagnosis or radiological diagnosis of Liver Imaging Reporting and Data System (LI-RADS) 5 criteria. Descriptive statistics were presented by mean and standard deviation or median and percentiles for continuous variables and frequencies for categorical variables. Statistical difference between the groups were analyzed using the chi-square test, fisher exact test, student t-test or Mann-Whiney U- test as appropriate. **Results:** A total of 328 HCC patients were included in the study, 195 patients with biopsy-proven NASH cirrhosis and 133 patients with CC, of which 35 patients had liver biopsy and 98 patients without liver biopsy. Patients with CC were older [(69.9 ± 10.2 vs. 66.9 ± 8.4 years; (p=0.004)]. The prevalence of metabolic risk factors, hypertension (71% vs. 69%), diabetes mellitus (67% vs. 59%), and dyslipidemia (47% vs. 41%) in patients with NASH cirrhosis and CC were similar (all P=NS), however, obesity was more prevalent in NASH cirrhosis patients than in CC patients [63% vs. 44% (p=0.001)]. Those with CC had higher median tumor size [5.9 (IQR 3.1, 9.3) vs. 3.5 (IQR 2.6, 5) cm], more extrahepatic metastasis [18.1% vs. 8.2%; (p<0.01)], and were less likely to be within Milan criteria [31.6% vs. 49.7%; (p<0.01)] than patients with NASH cirrhosis. Over the past 15-year period, we found a trend of increasing proportion of patients who would have been classified as cryptogenic cirrhosis being diagnosed with NASH cirrhosis (0% in 2000, 16.7% in 2005, 27% in 2010, and 56.3% in 2015). **Conclusion:** The prevalence of hypertension, diabetes mellitus, and dyslipidemia in NASH cirrhosis and CC patients with HCC were similar. CC patients were more likely to have more advanced HCC at diagnosis. Finally, there is an increasing trend in NASH cirrhosis and a decreasing trend in cryptogenic cirrhosis in patients with no identifiable cause of liver disease.

Figure 1. The prevalence of metabolic risk factors in NASH group, CC group and a subgroup of CC patients with available biopsy data

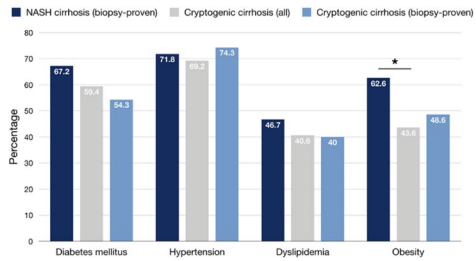
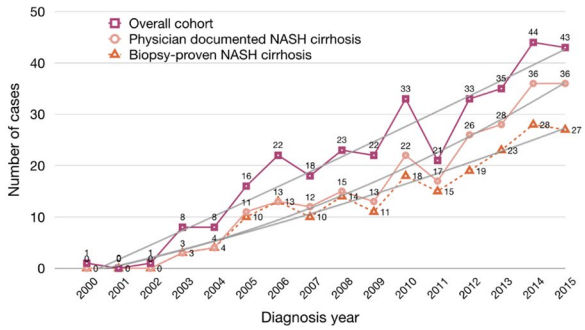


Figure 2. Percentage of biopsy-proven NASH cirrhosis and physician documented NASH cirrhosis in the cohort of HCC in NASH cirrhosis and cryptogenic cirrhosis by diagnosis period



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1059
HEREDITARY HEMOCHROMATOSIS AS AN INDEPENDENT RISK FACTOR FOR LIVER CANCER: A MATCHED CASE-CONTROL STUDY OF THE NATIONAL INPATIENT SAMPLE DATABASE

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Background: Hereditary hemochromatosis (HH) is a genetic metabolic disorder that increases alimentary iron absorption resulting in the iron overload that can be carcinogenic. In this study, we investigated the carcinogenic potential of HH resulting in liver cancer not only through development of cirrhosis but also in relation to hepatic iron deposition.

Methods: We conducted a retrospective matched case-control analysis study from National Inpatient Sample (NIS) database between 2016 and 2018. International Classification of Diseases, Tenth Revision (ICD-10) was used to identify patients with a primary or secondary diagnosis of liver cancer (ICD-10 codes C22.0, C22.2, C22.3, C22.4, C22.7, and C22.8). We selected a matched group of patients without liver cancer with the 1:1 fixed ratio nearest neighbor (greedy) propensity score method using the patient's age, sex, and race. Patients with liver cancer were established as cases, and patients without liver cancer were established as the control group. We also identified established risk factors of liver cancer using ICD-10 codes, including cirrhosis, viral hepatitis, HH (excluding cirrhosis), type 2 diabetes, alcohol, obesity, Tobacco, Non-alcoholic fatty liver disease (NAFLD), and transfusion of blood and blood products. Univariate and multivariate regression analyses were conducted to identify significant correlates of liver cancer. Statistically analysis is performed in RStudio 1.4. P-values < 0.05 demonstrated statistical significance. **Results:** 34582 patients with liver cancer were identified. Multivariate analyses demonstrated that cirrhosis (aOR, 46.666; 95% CI, 42.659 – 51.050), viral hepatitis (aOR, 13.601; 95% CI, 12.603 – 14.679), hereditary hemochromatosis excluding cirrhosis (aOR, 18.216; 95% CI, 5.348 – 62.045), type 2 diabetes (aOR, 1.613; 95% CI, 1.541 – 1.689), tobacco use (aOR, 1.131; 95% CI, 1.082 – 1.182), NAFLD (aOR, 5.544; 95% CI, 4.709 – 6.528), blood transfusion (aOR, 2.532; 95% CI, 2.334 – 2.746), are independent risk factor of liver cancer. **Conclusion:** Patients with HH can be at an increased risk for liver cancer independent of cirrhosis status. This may be related to carcinogenic properties of iron deposition related to the disease. More studies are required in controlled settings to further consolidate these findings.

Table 1: Risk Factor Analysis with and without Liver Cancer, NIS 2016 to 2018

Variables	Liver Cancer 1:1 Ratio Age, Sex, and Race Matched		*P* value
	No (N= 34582) 50%	Yes (N= 34582) 50%	
Cirrhosis	731 (2.11%)	20759 (60.03%)	<0.001
Viral Hepatitis	936 (2.71%)	15279 (44.18%)	<0.001
Heredity Hemochromatosis	3 (0.01%)	25 (0.07%)	<0.001
Type 2 Diabetes	8261 (23.89%)	12383 (35.81 %)	<0.001
Alcohol consumption	2265 (6.55%)	8449 (24.43%)	<0.001
Tobacco Use	11025 (31.88%)	15805 (45.70%)	<0.001
NAFLD	233 (0.67%)	1572 (4.55%)	<0.001
Blood Transfusion	1382 (4.00%)	4225 (12.22%)	<0.001

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The following people have nothing to disclose: Maryam Haider, Ali F Alsbihi, Zaid Imam, Adnan Malik, Sana Iqbal, Mahum Nadeem, Ahmed J Chaudhary

1060

IMbrave150: EXPLORATORY EFFICACY AND SAFETY OF ATEZOLIZUMAB (ATEZO) + BEVACIZUMAB (BEV) VS SORAFENIB (SOR) IN PATIENTS WITH HEPATOCELLULAR CARCINOMA (HCC) WITH NON-VIRAL ETIOLOGY IN A GLOBAL PHASE III STUDY

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Background: Atezo + bev has been approved in >70 countries to treat systemic treatment–naive unresectable HCC, based on results from the IMbrave150 study (NCT03434379; Finn RS *NEJM* 2020). Here, we report data from an exploratory analysis of patients with non-viral HCC etiology using updated IMbrave150 data (median follow-up: 15.6 mo; Finn RS ASCO GI 2021). **Methods:** IMbrave150 enrolled patients with systemic treatment–naive unresectable HCC and ≥1 measurable untreated lesion (RECIST 1.1), Child-Pugh class A liver function and Eastern Cooperative Oncology Group performance score 0 or 1, including those with non-viral etiology. Patients were randomized 2:1 to atezo 1200 mg + bev 15 mg/kg IV every 3 weeks or sor 400 mg PO twice daily until unacceptable toxicity or loss of clinical benefit per investigator. **Results:** Of the 501 enrolled patients, 153 (31%) had non-viral etiology (100 received atezo + bev and 53 received sor). Patients with non-viral etiology had baseline characteristics that were consistent with those of the intention-to-treat (ITT) population. In the non-viral population, median body mass index was 26.7 kg/m^2 and 27.8 kg/m^2 in the atezo + bev arm and the sor arm, respectively, and alpha-fetoprotein ≥400 ng/mL was observed in 29 (29%) and 20 patients (38%), respectively. Among patients with non-viral HCC, 35 (35%), 38 (38%), and 27 patients (27%) in the atezo + bev arm and 23 (43%), 16 (30%), and 14 patients (26%) in the sor arm had a documented history of alcohol use, no alcohol use, and unknown alcohol use status, respectively. In the non-viral population, while overall survival (OS) was similar between the atezo + bev and sor arms, progression-free survival (PFS) and overall response rate (ORR) per IRF-assessed RECIST 1.1 were improved with atezo + bev vs sor (Table). Grade 3/4 and Grade 5 treatment-related adverse events occurred in 34 (35%) and 4 patients (4%) in the atezo + bev arm (n=98) and 23 (44%) and 0 patients in the sor arm (n=52), respectively. **Conclusion:** The relative benefit of atezo + bev vs sor was maintained for PFS and ORR in patients with non-viral etiology. Although OS in the non-viral population was similar in both arms due to an unusually high median OS with sor, OS in patients receiving atezo + bev was similar in the non-viral and ITT populations. Overall, atezo + bev showed meaningful efficacy and a tolerable safety profile in patients with non-viral etiology, supporting the use of atezo + bev in this patient population.