Higher Levels of Fibrosis in a Cohort of Veterans with Chronic Viral Hepatitis are Associated with Extrahepatic Cancers

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Background and aims: **An estimated 2.4 million Americans, including more than 150,000 veterans, are chronically infected with hepatitis C virus (HCV). HCV is estimated to cause roughly 25% of all hepatocellular carcinoma. Although its mechanism is unknown, developing evidence suggests that chronic HCV infection is also associated with the development of extrahepatic cancers (EHCs). This paper aims to assess the relationship of hepatic fibrosis and chronic HCV with the risk of developing EHC.** ***Methods:*** **We conducted a single-center retrospective chart review of 1541 patients linked to the hepatitis clinic at the Veterans Affairs (VA) Maryland Health Care System who underwent transient elastography for evaluation and management of liver disease from 2014 to 2018. Liver fibrosis was measured using ultrasound and transient elastography. Extrahepatic cancer and site was identified by a retrospective chart review.** ***Results:*** **In adjusted analysis of EHCs, advanced age (OR: 1.97, 95% CI: 1.30–3.04), and higher measured stiffness (OR 2.19, 95% CI: 1.32–3.64) were associated with an increased likelihood of developing EHC, controlling for HBV infection, HCV exposure, heavy alcohol use, and body mass index.** ***Conclusions:*** **We observed a significant association between increasing age and increasing levels of liver fibrosis with increased risk of EHC, notably prostate, head and neck squamous cell, lung, and hematologic cancers. (J Clin Exp Hepatol 2021;11:195–200)**

An estimated 2.4 million Americans, including more than 150,000 veterans, are chronically infected with hepatitis C virus (HCV).[1] Those who do not clear the virus go on to develop a chronic infection with a widely varying course, influenced by host, viral, and environmental factors.[2] Despite improved treatments for HCV, ongoing and apparent large increases in the incidence of reported acute hepatitis C have been recently highlighted by the CDC 2019 National Progress report.[1]

Hence, rates of cirrhosis and HCC are expected to rise for at least ten more years.[2] Unfortunately, HCV is estimated to cause roughly 25% of all hepatocellular carcinoma (HCC).[3] The role of HCV and the development of advanced fibrosis in extrahepatic malignancies remain unclear, but developing evidence suggests it may play a role in a subset of EHCs.[4]

Prior studies have demonstrated an association between chronic HCV infection and breast, thyroid, prostate, and renal cancer.[4] Rather than a direct effect of the virus, it is thought that the development of these cancers is from sequelae of longstanding immune activation.[5] Prior groups have hypothesized that through the chronic activation of B-cells, chronic HCV is also likely associated with B-cell lymphoid malignancies such as non-Hodgkin's lymphoma.[5] Interestingly, eradication of chronic HCV infection with antiviral therapy seems to induce remission of lymphoma in some cases.[6]

While the natural history of chronic HCV infection is highly variable among patients, monitoring the degree of fibrosis is a reliable marker to determine progression of disease. Fibrosis levels are routinely used in determining optimal treatment of HCV, predicting risk of liver-related mortality in cirrhosis, and determining the need for liver transplantation.[7] To our knowledge, the role of fibrosis as a marker of EHC risk has not been previously evaluated. We analyzed data from a cohort of patients with advanced liver disease, due to chronic HCV infection, HBV, and/or nonalcoholic steatohepatitis (NASH), assessed by transient elastography, to understand the relationship between fibrosis level and intrahepatic cancer and EHC rates.

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Abbreviations: CAP: Controlled attenuation parameter; EHC: Extrahepatic cancer; HBV: Hepatitis B Virus; HCC: Hepatocellular carcinoma; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; NASH: Nonalcoholic steatohepatitis; VA: Veterans Affairs; VAMHCS: Veterans Affairs Maryland Health Care System
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METHODS

We conducted a single-center retrospective chart review of patients linked to our hepatitis clinic at the Veterans Affairs (VA) Maryland Health Care System (VAMHCS) who underwent transient elastography for evaluation and management of liver disease from 2014 to 2018. Charts were reviewed for the following characteristics: age, gender, hypertension, diabetes mellitus, lifetime tobacco use, heavy alcohol use, body mass index, race, ethnicity, liver stiffness, controlled attenuation parameter (CAP) score, imaging evidence of hepatocellular carcinoma, a diagnosis of EHC, and mortality. This investigation was reviewed by the joint University of Maryland Medical Center and VAMHCS Institutional Review Board as part of a quality improvement project and was determined to be nonhuman subjects research.

Hypertension was defined as systolic blood pressure greater than or equal to 140, diastolic blood pressure greater than or equal to 90, or the use of antihypertensive medication. Diabetes mellitus was defined as hemoglobin A1c greater than or equal to 6.5 or the use of insulin or antidiabetic medications. Harmful drinking was defined as consumption of greater than 21 drinks per week in men and greater than 14 drinks per week in women by self-report. Race was classified into Caucasian, African American, and other. Ethnicity was grouped into Hispanic or non-Hispanic. Patients were determined to be alive or dead by documentation in the computerized patient records system.

Liver stiffness was measured in kilopascals (kPa) and derived from transient elastography reports. The CAP score was also derived from elastography reports after March 2017 (when the software for the CAP measurement was implemented at our VA). Fibrosis stage was categorized by previously validated scales dependent on etiology of liver disease.[8] For patients with HCV, fibrosis stage 0–1 was defined as less than 7.0 kPa, stage 2 was defined as between 7.0 and 9.5 kPa, stage 3 was defined as between 9.5 and 12.0 kPa, and stage 4 was defined as greater than or equal to 12.0 kPa.

All statistical analyses were conducted using SAS version 9.4 for Windows (SAS Institute Inc, Cary, NC). Chi-square and Fisher's exact tests were used for bivariate analyses. Multivariable logistic regression was performed to evaluate relationships between EHCs on various demographic and clinical characteristics. Covariates that were thought to influence the primary end point were identified a priori and included age, HIV infection, HBV infection, HCV infection, age, and heavy alcohol use. In the analysis, p-values < 0.05 were considered statistically significant, while controlling for multiple comparisons.

RESULTS

A total of 1541 patients had transient elastography measured by our hepatitis clinic during the period of 2014–2018. The mean age for the sample was 60.6 ± 8.7 years. The mean body mass index was 28.3 ± 5.6 kg/m^2. The majority of our sample were men (n = 1479, 96%) with just 62 women (4%). The majority, 983 patients (71%), were African American, 384 were Caucasian (28%), and 21 were other races (1%). 11 patients had Hispanic ethnicity (1%). The vast majority of our patient population had a history of hypertension (n = 1309, 85%). About a third had evidence of diabetes (n = 508, 33%), and about one fourth had evidence of heavy alcohol use (n = 377, 25%) per self-report. The majority of our patients reported a history of smoking tobacco (n = 1185, 88%). 1318 patients (87%) had HCV infection, 76 patients had HIV infection (5%), and 60 patients had HBV infection (3%). Of the patients with HCV, 17 were co-infected with HBV, and 63 were co-infected with HIV. 706 patients had CAP scoring by transient elastography, with 290 (41%) having minimal steatosis, 97 (14%) having S1 or mild steatosis (>11% fat), 97 (14%) having S2 or moderate steatosis (>34% fat), and 222 (31%) having S3 or severe steatosis (>67% fat). Patients with history of HCV infection were further evaluated for HCV treatment, and patients with HBV infection were evaluated for viral suppression (Table 1).

Indications for transient elastography included HBV evaluation (n = 53, 3%), HCV evaluation (n = 1260, 82%), fatty liver assessment (n = 149, 10%), and other indications (n = 72, 5%) (Table 1). Among all indications using fibrosis cutoffs, 368 were F1 (24%), 220 were F2 (14%), 320 were F3 (21%), and 632 were F4 (41%). As expected, HCC rates increased with rising levels of fibrosis. Five cases of HCC (12.5%) were found in early fibrosis (F0–F2), 7 (17.5%) in F3 fibrosis, and 28 (70%) in F4 fibrosis, totaling 40 cases of HCC in our population. One hundred eleven patients had EHCs, 24 of which were found in F0–F2 fibrosis (21%). 29 EHCs were found in F3 fibrosis (26%), and the remaining 58 (52%) were found in patients with F4 fibrosis (Table 2). Of patients with EHCs, 8 (7%) had 2 concomitant primary cancers.

The types of EHCs identified in our population included hematologic, breast, gastrointestinal, head and neck, skin, lung, prostate, renal, thyroid, bladder, and ependymoma (Table 3). The most common EHCs included prostate (n = 43, 38.7%), lung (n = 18, 16.2%), head and neck (n = 14, 12.6%), GI (n = 8, 7.2%), and hematologic (n = 8, 7.2%). GI malignancies were comprised of colon, esophageal, gastrointestinal stromal tumor, pancreatic, and rectal cancers. Hematologic malignancies were comprised of leukemia, lymphoma, and multiple myeloma. Of the 111 EHCs in the cohort, 11 (9.9%) were from patients with fatty liver and no viral infections. Two had HBV mono-infection (1.8%), 86 had HCV mono-infection (77.4%), 7 (6.3%) had HIV/HCV co-infection, and 5 (4.5%) had HBV/HCV co-infection (Table 4).

In adjusted analysis of EHCs among the entire cohort linked to hepatitis clinic, advanced age (odds ratio (OR):

Table 1 Demographic and Clinical Characteristics of the Veteran Cohort Assessed with Transient Elastography by the Baltimore Hepatitis Clinic from 2014 to 2018.

Variable	Variables (mean ± SD)	Range
Age (years)	60.6 ± 8.7	(22, 88)
BMI	28.3 ± 5.6	
Liver stiffness (kPa)	14.0 ± 11.2	(2.9, 75)
CAP (dB/m)	260.4 ± 64.2	(100, 495)
Variables (n, %)		
Sex		
Male	1479 (96)	
Female	62 (4)	
Race		
Black	983 (71)	
White	384 (28)	
Other	21 (1)	
Ethnicity		
Hispanic	11 (1)	
Non-Hispanic	1382 (99)	
Hypertension		
Yes	1309 (85)	
No	229 (15)	
Diabetes		
Yes	508 (33)	
No	1030 (67)	
History of smoking		
Yes	1290 (85)	
No	232 (15)	
Heavy drinking		
Yes	377 (25)	
No	1147 (75)	
HIV infection		
Yes	76 (5)	
No	1316 (95)	
HBV infection		
Yes	60 (4)	
No	1423 (96)	
HCV exposure		
Yes	1318 (87)	
No	191 (13)	
Fibrosis stage		
F1	368 (24)	
F2	220 (14)	
F3	320 (21)	
F4	632 (41)	
CAP grade		
Minimal	290 (41)	
S1	97 (14)	
fS2	97 (14)	
S3	222 (31)	
Elastography indication		
HCV evaluation	1260 (82)	
HBV evaluation	53 (3)	
Fatty liver assessment	149 (10)	
Other	72 (5)	

(*Continued on next page*)

Table 1 (*Continued*)

BMI, body mass index; kPa, kilopascals; CAP, controlled attenuation parameter; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus.

2.04, 95% confidence interval (CI): 1.32, 3.09), higher measured stiffness on FibroScan (OR 2.66, 95% CI: 1.59, 4.46), and HBV infection (OR: 3.30, 95% CI: 1.30, 8.37) were associated with an increased likelihood of EHC after controlling for HCV exposure, type 2 diabetes mellitus (DM), tobacco use, and heavy alcohol use (Table 5).

DISCUSSION

It is well established that the risk of HCC increases with chronic HCV infection and that the risk of HCC rises with higher levels of liver fibrosis. More recently, data have emerged to suggest that HCV and HBV are associated with increased risk of several EHCs, including pancreatic adenocarcinoma, non-Hodgkin's lymphoma, and prostate cancer, although this is not reproduced uniformly across populations.[23–25] Our data demonstrates a potentially strong association between higher liver fibrosis levels and risk for EHCs, which has not been previously reported to our knowledge. In addition, it has previously been demonstrated that treatment of HCV with different

Table 2 HCC and Extrahepatic Cancers among Veterans Divided by Various Stages of Liver Fibrosis.

Stage	HCC (n, %)	Extrahepatic cancer (n, %)	p-value
F1	3 (7.5)	18 (16)	HCC: $P < 0.01$
F2	2 (5)	6 (5)	
F3	7 (17.5)	29 (26)	EHC: $P < 0.01$
F4	28 (70)	58 (52)	

Statistical significance was calculated using the Fisher's exact test. HCC, hepatocellular carcinoma.

Table 3 Types of Extrahepatic Cancers seen in Veterans Linked to Hepatitis Clinic.

Extrahepatic cancer type	n (%)
Hematologic	8 (7.2)
Breast	3 (2.7)
Gastrointestinal	8 (7.2)
Head and neck	14 (12.6)
Skin	3 (2.7)
Lung	18 (16.2)
Central nervous system	2 (1.8)
Prostate	43 (38.7)
Renal	5 (4.5)
Thyroid	1 (0.9)
Bladder	2 (1.8)
Penile	1 (0.9)
Unknown primary	2 (1.8)
Kaposi's sarcoma	1 (0.9)
Total	111

Gastrointestinal malignancies included colon, esophageal, GIST, pancreatic, and rectal cancer. Hematologic malignancies included leukemia, lymphoma, multiple myeloma.

Table 5 Odds Ratio Estimates of Predictors of Extrahepatic Cancer in the Hepatitis Clinic Cohort.

Variable	OR	95% CI
Age >65	2.04	(1.34, 3.09)
HBV infection	3.3	(1.30, 8.37)
HCV infection	1.48	(0.67, 3.24)
Heavy alcohol use	0.92	(0.55, 1.53)
Advanced fibrosis	2.66	(1.59, 4.46)
DM	1.14	(0.75, 1.74)

Adjusted analysis controlling for the age group, HBV, HCV, heavy alcohol use, hepatic fibrosis, and DM. HBV, hepatitis B virus; HCV, hepatitis C virus; DM, diabetes mellitus type 2.

regimens of direct acting antivirals can lead to a gradual regression of fibrosis and decreased inflammation, with no difference in risk for development of HCC.[16,28,29] In conjunction with our finding, this suggests achieving SVR may confer the additional benefit of reduction of the risk of EHC. However, the natural history of fibrosis regression after sustained virological response (SVR) and the associated decreased risk of hepatic and EHC outcomes have yet to be completely described, and our study was not powered to assess the association of sustained SVR with EHC.[17] As such, these data have strong implications on the importance of treating all liver disease at the earliest stage possible and implementing the appropriate supportive services that continue to link patients with fibrosis secondary to any etiology, to treatment and follow up that includes age-appropriate cancer screening.

Table 4 Extrahepatic Cancer Frequency by Chronic Viral Infections.

Viral Infection	Extrahepatic cancers	Total cases	Percent
No viral infections	11	173	6.4%
HIV mono-infection	0	8	0.0%
HBV mono-infection	2	38	5.3%
HBV/HIV	0	2	0.0
HCV mono-infection	86	1235	7.0%
HIV/HCV co-infection	7	66	11.1%
HBV/HCV co-infection	5	20	29.4%

HIV: human immunodeficiency virus, HBV: hepatitis B virus, HCV: hepatitis C virus.

In our cohort, the increased association between advanced fibrosis and risk of EHC was independent of infection with HCV, HBV, or HIV, heavy alcohol consumption, increased age, and DM. Significant alcohol and tobacco use are well-established risk factors for many cancers, including HCC. Heavy alcohol use (25%) and regular tobacco use (88%) were self-reported in a significant proportion of our cohort. In addition, a large minority (33%) of our cohort suffered from DM and were receiving active treatment with insulin and oral hypoglycemics. The presence of DM significantly increases the risk of developing HCC, independent of HCV and HBV infection.[26] Increased incidence of several malignancies other than HCC have also been attributed to DM and thought to be mediated through hyperglycemia and the metabolic syndrome, chronic inflammation caused by adipokines, and dysregulation of insulin and IGF-1.[27]

In our study, the most common sites of EHC included prostate, lung, head and neck, gastrointestinal, and hematologic. Recent data have shown that chronic HBV infection is associated with a two-fold increased risk of developing any cancer and increased risk of developing several EHCs.[21] Population-based studies have also shown that chronic HCV infection may be associated primary cancers of the pancreas, lung, kidney, non-Hodgkin's lymphoma, and multiple myeloma.[9,23,25] It is hypothesized that chronic HBV and HCV infection increases EHC risk by dysregulation of the immune system, direct effect of the virus on nonhepatic histiocytes, and promotion of dysplasia in biliary epithelial cells.[21] The pancreas and liver share a common endodermal origin, which has led to the hypothesis that HCV may be able to replicate in pancreatic cells and potentially increase the risk of pancreatic cancer. Our cohort only had one case of pancreatic adenocarcinoma, similar to findings by other groups which did not find chronic HCV infection to be associated with pancreatic cancer in their cohorts.[11,12,24] Although similar sites of EHC were observed in these cohorts, the degree of

fibrosis was not serially assessed, limiting our ability to attribute cancer risk to the same mechanism for which fibrosis serves as a biomarker. In addition, HBV co-infections accounted for advanced fibrosis in only 3% of our cohort; therefore, we do not think that HBV infection alone accounts for the increased risk of EHC seen in patients with advanced fibrosis.

Although other studies have shown negative associations between chronic HCV infection and prostate cancer, it was the most common EHC site observed in our cohort.[10] This is likely secondary to the demographics of our cohort, was predominantly male, and had an average age of 60.6 years. Our findings were also consistent with two case–control studies that previously demonstrated increased prevalence of anti-HCV Ab in patients with lung cancer compared with healthy controls.[13,14] Studies evaluating the association between chronic HCV infection, renal cell carcinoma, and extrahepatic GI cancers have yielded inconclusive results.[15] In our cohort, there remained a significant association between the elevated fibrosis score and EHC, after controlling for HCV and HBV infection. Several studies have shown associations between greater liver fibrosis and all-cause mortality in patients with non-alcoholic fatty liver disease (NAFLD) but did not assess cancer incidence or cancer related mortality.[18–20] Our analysis further support the importance of evaluating liver fibrosis and other age-appropriate cancer screening longitudinally and also suggests that liver fibrosis, independent of its underlying etiology, mediates increased risk of EHCs.

The mechanisms involved in the pathogenesis of liver fibrosis are complex and the subject of ongoing research. Activation of hematopoietic stem cells, dysregulation of endothelial cell architecture, upregulation of tissue inhibitors of matrix metalloproteinases (TIMPs), alterations in cell signaling mediated by changes in the extracellular matrix, and angiogenesis leading to an exaggerated wound healing response are implicated in the development of liver fibrosis. This pro-inflammatory environment of stem cell activation, TIMP-mediated cell cycle alteration, among other factors, may underlie the relationship between high-grade fibrosis and EHCs.[22] The autocrine and paracrine signaling network has been shown to be altered in fibrosis, but an altered endocrine signaling component would be more highly suggestive of this relationship.

Strengths of our study include a patient cohort linked to the VA infrastructure with an integrated electronic medical record and facilitated access to laboratory results, clinical imaging, and office visits, resulting in a relatively complete data set. We were able to collect relevant information regarding various comorbidities that could have strong implications on EHC development, such as HIV and HBV serologies, tobacco use, alcohol use, and diabetes. Routine screening for HCV in asymptomatic patients at the VA may have introduced lead time bias, as a large proportion of patients presented with F1 disease at time of diagnosis, higher than other cohorts in the literature. Additional limitations include the cohort's significant male predominance and smoking habits, similar to other veteran cohorts, which may limit the generalizability of our findings. A significant minority of patients had fibrosis secondary to a noninfectious etiology, which may limit our ability to extrapolate the association to include fibrosis mediated by other etiologies. Finally, this data set was limited to include patients who had undergone staging with transient elastography and excluded patients with liver disease decompensated by ascites.

In conclusion, we observed a significant association between increasing levels of liver fibrosis as measured by transient elastography and EHCs, notably prostate, head and neck squamous cell, lung, and hematologic cancers. Further research is needed to clarify and elucidate mechanisms that drive carcinogenesis in patients with advanced liver fibrosis.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Ameer Abutaleb: Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Jose Antonio Almario:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Project administration. **Saleh Alghsoon:** Investigation, Resources, Data curation, Writing - original draft. **Ji Ae Yoon:** Investigation, Resources, Data curation, Writing - original draft. **Kate Gheysens:** Investigation, Resources, Data curation, Writing - original draft. **Shyam Kottilil:** Conceptualization, Methodology, Writing - review & editing, Supervision. **Eleanor Wilson:** Conceptualization, Methodology, Formal analysis, Investigation, Writing - review & editing, Supervision, Project administration.

CONFLICTS OF INTEREST

The authors have none to declare.

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