**A causal analysis of the effect of routine abdominal imaging on risk of hepatocellular carcinoma for people living with chronic hepatitis C**

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**Abstract**

**Purpose:** Guidelines recommend semi-annual screening for hepatocellular carcinoma (HCC) among hepatitis C virus (HCV) patients with cirrhosis using abdominal ultrasound +/- alpha-fetoprotein, but patients without cirrhosis are not recommended for HCC screening. We aimed to estimate the benefit of abdominal imaging on HCC risk among non-cirrhotic patients, using causal inference methods.

**Methods:** This is a retrospective cohort of HCV patients in a tertiary healthcare system , restricting to adults with no cirrhosis and no HCC at study start in 2015 (n = 1628). Using SuperLearner with a G-computation estimator, we estimated the average treatment effect on HCC diagnosis in year 5 assuming all patients had annual abdominal imaging for the 4 prior years, compared to all patients not having imaging during that time.

**Results:** Our analyses indicate arisk difference of 1.102 (95%CI: -0.913–3.116). This indicates a 1.1% reduction in HCC risk over 5 years when all patients received abdominal imaging at least once annually for the 4 prior years, compared to no patients receiving imaging, after controlling for cirrhosis, number of primary care or hepatology visits, sex, race, and socio-economic status.

**Conclusions:** This is a clinically meaningful finding given that we excluded patients with evidence of cirrhosis at baseline and only followed patients for 5 years. The number needed to treat (NNT) is 91: for every 91 HCV patients who receive annual abdominal imaging despite no evidence of cirrhosis at baseline, 1 case of HCC can be prevented over only 5 years.

**Keywords:** Hepatitis C; HCV; Hepatocellular carcinoma; HCC; Abdominal imaging

**Introduction**

Hepatocellular carcinoma (HCC) is the fastest rising cause of cancer related deaths in the US in 1999-2013.(1) HCC is primarily caused by hepatitis C virus (HCV), affecting 2.4 million people in the US.(2) If HCV infection is left untreated, slowly progressive fibrosis of the liver leads to cirrhosis in approximately 20% of patients, and HCC occurs in 3-8% of people with HCV cirrhosis each year.(3) Since highly effective therapy for HCV infection became available in 2014 with the development of direct acting antivirals (DAAs), 12 weeks of antiviral treatment reduces HCC incidence by 71%.(4)

Surveillance for HCC has long been recommended for patients with HCV who have developed cirrhosis, using abdominal ultrasonography every six months, with or without the addition of serum alpha-fetoprotein [AFP] testing. Although DAA therapy is successful in achieving sustained virologic response (SVR) in more than 90% of patients,(5) the risk of HCC remains high enough after virologic cure that continued HCC screening is recommended for cirrhotic patients even after SVR.(6, 7) On the other hand, for patients with chronic HCV but without cirrhosis – even for those who have not had DAA therapy and have ongoing viremia – HCC screening has not been recommended. The proportion of patients with chronic HCV who are being successfully cured with DAA therapy is rising, yet there are concerns that the patients who remain untreated are those without access to specialty care, where most DAA therapy is provided.(8) These patients remain at higher risk for developing cirrhosis and HCC than those who have access to DAA therapy. In this DAA era, as the proportion of untreated HCV patients will continue to slowly decline, recommendations for HCC screening could be reconsidered for patients with ongoing viremia even without cirrhosis, who remain at high risk.

In the current study, we aimed to investigate the effect of HCC screening in non-cirrhotic HCV patients, by estimating the longitudinal association of abdominal imaging on HCC risk using causal inference methods. We hypothesized that patients with no cirrhosis at baseline would be less likely to develop HCC within 5 years when they had evidence of abdominal imaging at least once per year for 5 years, compared to patients who did not have annual abdominal imaging.

**Methods**

We built a dataset of all adult patients with chronic HCV at a large academic tertiary healthcare system who had received medical care between 2014-2017. To build this retrospective cohort for a larger study, R.F. and A.H. had queried the electronic medical record (EMR) for all patients with evidence of chronic HCV infection, defined by one or more of the following: 1) positive HCV ribonucleic acid test (RNA); 2) prescription for interferon and/or DAA; 3) ICD 9/10 code for chronic HCV (n=2823). They extracted all relevant demographic, clinical and visit history data available in the EMR for each patient over a 10-year period from 2009-2019, and completely de-identified it prior to beginning this analysis. For this analysis, we restricted our dataset to adult patients who were seen within this health system for at least one primary care clinic or hepatology clinic visit between 2015 and 2019 (N=1905). We determined the presence of cirrhosis using FIB-4 score, a widely accepted proxy for the presence of cirrhosis on liver biopsy.(9) Using the standard formula with inputs of age, platelet count, aspartate transaminase (AST) and alanine aminotransferase (ALT) levels, we computed the annual FIB-4 score for each patient, for each year between 2011-2015. FIB-4 scores of <1.45 are considered to be strongly suggestive of no liver fibrosis, and scores >3.25 are indicative of advanced fibrosis and/or cirrhosis.(10) To limit our study dataset to those HCV patients without cirrhosis at baseline, we excluded all patients who had a FIB-4 score >3.25 in the first year of the study (remaining n = 1628). For those with insufficient clinical data to calculate FIB-4 score directly in the first year of the study, historical data back to 2011 was used to calculate their FIB-4 score at the beginning of follow up (i.e., the most recent available measurement was used as baseline FIB-4 data). For those without historical data, the FIB-4 score in 2014 was imputed using multiple imputation (m=5).

As this was a statistical analysis involving no human subjects and a fully de-identified dataset, this study was considered exempt from IRB approval.

***Structural Model***

We defined our exposure as the total number of abdominal imaging results reported within the EMR for each chronic HCV patient, annually from 2015 through 2018. We then dichotomized this variable (0 images, or 1+ images) due to computational limitations of longitudinal targeted machine learning estimation (LTMLE). We defined our outcome as diagnosis of HCC, by the final year (2019); 149 people (9.2%) had developed the outcome of interest by end of 2019. We included 3 baseline covariates in our model: race (a categorical variable, recategorized into White, Black/African American, Latinx, and Other for ease of analysis given the bias introduced into causal analyses by practical positivity violations), sex (a dichotomous variable, with two categories (male, female), as other gender categories were not captured within the database), and socioeconomic status (SES), using insurance type—Medi-Cal, or not Medi-Cal—as a marker of SES (see Table 1).

We also included 3 longitudinal covariates in our model, assessed annually: Total number of primary care or hepatology visits recorded in the EMR, annually from 2015 – 2019; FIB-4 score; and years since FIB-4 score was last measured. FIB-4 scores in this dataset ranged from 0.181 to 45.96, with an IQR of 1.0378 (1.1003-2.1381), indicating the FIB-4 score of 45 is a substantial outlier. Throughout all years of follow-up on all patients, there were 487 FIB-4 scores >3.25 (among 203 unique patients), indicating likely cirrhosis and increased risk of HCC at those timepoints; there were 80 instances where a patient’s FIB-4 score was calculated to be greater than 9. Given that FIB-4 scores could not be measured every year for every patient during the years of follow-up, if test results were not available for a new FIB-4 calculation, the prior year’s FIB-4 score was carried forward; thus the number of years since FIB-4 was measured was also included as a longitudinal covariate in our model.

This is a survival analysis, with a Structural Causal Model where:

* *W* is the baseline covariates (race, sex and SES)
* *L(t)*  is the set of longitudinal covariates (number of primary care or hepatology visits, most recent FIB-4 score, years since last FIB-4) at time *t*
* *A(t)* is the exposure (presence of abdominal imaging)
* *Y(t)* is the outcome (an indicator of HCC diagnosis)

and .

Structural Equations, , for *t* from 1 to 5, were:

(1)

(2)

(3)

(4)

(5)

(6)

(7)

We included one key exclusion restriction: *Y(t)* is an indicator variable describing whether or not the patient had been diagnosed with HCC by time *t*; as such, once *Y* (*t*) = 1 it was deterministically set to 1 through *Y*(*K*).

**Estimation of our Target Causal Parameter**

The target causal parameter is the average treatment effect on HCC diagnosis in year 5

(8)

assuming that all patients had abdominal imaging every year for the 4 prior years (), compared to HCC outcomes in year 5 if all patients did *not* have abdominal imaging at any time point during the preceding four years ().

We estimated our target causal parameter using G-computation, Inverse Probability of Treatment Weighting (IPTW), and LTMLE estimators within the ltmleMSM function in the *ltmle* R package.(11) We implemented SuperLearner using generalized linear modeling (GLM), Bayesian GLM, generalized additive modeling (GAM), stepwise regression, stepwise regression with forward selection, adaptive regression splines, neural network analysis, a random forest algorithm, and mean of Y analyses to optimize our estimation.

When testing our estimators against a simulation of 100,000 patients roughly matching the variable distribution of our observed dataset, they performed with minimal bias and low overall mean squared error, with G-computation performing best overall (see Table 2).

**Results**

The number of primary care or hepatology visits in a single year per patient ranged from 0 to 44 in any given year, with a median of 1 visit per year overall. In years where they had at least one visit with a primary care physician or hepatologist, 86.4% of patients chronically infected with HCV had no evidence of abdominal imaging at least one of the years under study.

Ultimately, implementing ltmle with Super Learner and using the G-Computation estimator on our observed data led to an estimated risk difference of 1.102 (95% CI: -0.913 – 3.116) of developing HCC in year 5 when receiving abdominal imaging at least once per year for the 4 preceding years, compared to not receiving abdominal imaging during that time.Thus, we found that over the five years under study, patients with no cirrhosis at baseline were 1.1% less likely to develop HCC by year 5 when they had abdominal imaging each year for the 4 previous years, compared to patients who had no abdominal imaging, when controlling for liver cirrhosis, number of primary care or hepatology visits, sex, race, and SES.

**Discussion**

Our findings are clinically meaningful finding given that we excluded patients with evidence of cirrhosis at baseline and only followed patients for 5 years. Our approach focused on a target population with least likelihood of developing HCC (excluding all people with cirrhosis at baseline) and was least biased (using causal inference non-parametric methods with machine learning rather than parametric regression); if anything, we would expect the effect in a general population (including people with cirrhosis) to be even more substantial. Our findings represent a number needed to treat (NNT) of 91: for every 91 people who receive annual abdominal imaging despite no evidence of cirrhosis at baseline, 1 case of HCC could be prevented over only 5 years. Here’s why they’re meaningful.

LIMITATIONS: These include, at a minimum: bias due to coarsening of time, possible unmeasured confounding (such as X, Y, Z), measurement error (since a surrogate marker of cirrhosis was used), generalizability (this was a single health system in one state), among others. These should be mentioned and discussed.

Ultimately, given that abdominal imaging is a non-invasive and relatively inexpensive intervention, our findings underscore the potential impact of an intervention to educate primary care and hepatology providers about the importance of ensuring their chronically HCV-infected patients receive abdominal imaging at least once per year, regardless of liver cirrhosis.

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**Declaration of competing interest**

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**Figure 1. P-value function plot of the main effect.** The vertical line shows the null finding, and the area under the curve is the probability of the real value. The area under the curve to the left of null is dwarfed by the area under the curve to the right, making a positive (decreased) effect in HCC risk much more likely than a negative (increased) effect.