Abdominal Imaging and HCC Risk

Shelley Facente and Steph Holm

March 4, 2020

1. Background

A. Brief Introduction

Hepatocellular carcinoma (HCC), a type of liver cancer, is the second most common cause of liver-related death throughout the world (Bosetti et al 2014). HCC is a major complication of infection with hepatitis C (HCV) virus, occuring in 1%-4% of people with liver cirrhosis each year (Omland et al 2010). HCV becomes chronic infection for about 80% of adults, and if left untreated can cause increasing cirrhosis over a period of 20-30 years of often asymptomatic disease, until damage is severe and major complications are irreversable (El-Serag 2012). Certain HCV viral genotypes (particularly genotype 3) are associated with higher risk of HCC, as is continued smoking (Chuang et al 2010) and alcohol use (Donato et al 2002), as well as concurrent diabetes or obesity (Huang et al 2017, Calle et al 2003).

Since 2014, direct-acting antiviral (DAA) therapy has dramatically improved prognosis for people living with HCV; 8-12 weeks of well-tolerated oral therapy leads to cure in more than 90% of patients (Burstow et al 2017), halting cirrhosis progression and apparently reducing the elevated risk of HCC (Axley et al 2017). Patients whose HCV has already caused some cirrhosis continue to be at some increased risk of HCC even post-cure, and given the high mortality risk it is recommended that people with HCV infection receive systematic monitoring with liver ultrasound (EASL 2015). However, despite having evidence of visits with a primary care physician or hepatologist, some UCSF patients chronically infected with HCV do not have evidence of abdominal imaging at least once per year. In this study we aimed to estimate 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.

B. Description of our Dataset

We are using a dataset of chronic hepatitis C patients receiving care in the UCSF system since 2009. There are 1905 patients, who were adults seen in the UCSF system by the end of 2015 and have been seen in a variety of primary care clinics and the hepatology (liver) clinic between 2015 and 2019. These data come from a query of Apex, the UCSF-specific build of the electronic medical record system Epic.

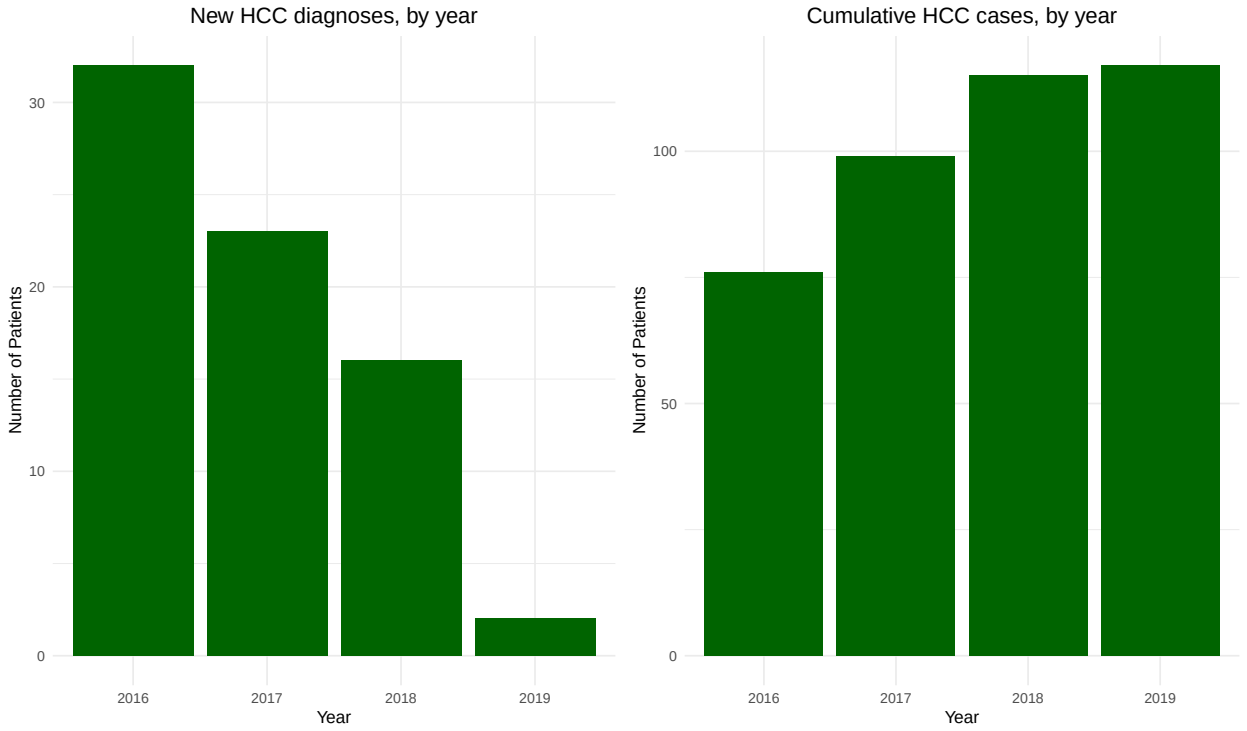
We restricted our dataset to adult UCSF patients diagnosed with HCV who, prior to the start of follow up (ie. as of 12/31/14) were not known to have indications of cirrhosis or HCC. (n = 1628) For those who had been in the system prior to 2015, historical data back to 2011 was used to calculate their FIB-4 score at the beinning of follow up (ie. by the end of 2014). For those who did not yet have those data, the FIB-4 score in 2014 was imputed using multiple imputation (m=5).

C. Our Observed Data

Number of Visits (annually)

The number of visits per patient ranges from 0 to 44 in any given year, with a median of 1 visit per year overall. The figure below presents number of visits per patient in each year, truncated at 25 visits.

149 people (9.2%) developed the outcome of interest (were diagnosed with HCC during the course of the study). The figure below shows the number of people diagnosed with HCC in each year, and cumulatively, throughout the study period (**note** that 2019 is an incomplete year of data.)



FIB-4 Score (annually)

FIB-4 scores are calculated with inputs of age, platelet count, AST, and ALT. 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.

FIB-4 scores in this dataset range of 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. 487 FIB-4 scores are >3.25 throughout all years of follow-up on all patients, indicating likely cirrhosis and increased risk of HCC at those timepoints. There are 80 instances where a patient's FIB-4 score was calculated to be greater than 9.

Other demographics

- **Sex**. This is a dichotomous variable, with two categories (male, female), as UCSF has not been capturing other gender categories within Epic.
- **Race**. This is a categorical variable, which recategorized into White, Black/African American, Latinx, and Other for ease of analysis given the bias introduced into causal analyses by practical positivity violations.
- **SES**. We used insurance type (Medi-Cal, or not Medi-Cal) as a marker of SES status, which is again a dichotomous variable.

The table below displays the demographic breakdown of the sample.

Demographic	Category	n	%
Sex	Male	897	55.1%
	Female	731	44.9%
Race/ethnicity	Black/African American	262	16.1%
	Latinx	217	13.3%
	White	818	50.2%
	Other	331	20.3%
	Unknown	NA	NA%
SES (Payor type)	Medi-Cal	288	17.7%
	Not Medi-Cal	1340	82.3%
TOTAL		1628	100%

D. Structural Model

We defined our **exposure** as the total number of abdominal imaging results reported within the UCSF system for each chronic HCV patient, annually from 2015 through 2018. We then dichotomized this variable (0 images, or 1+ images) due to the current computational limitations of longitudinal targeted machine learning estimation (LTMLE).

We defined our **outcome** as diagnosis of HCC, by the final year (2019).

We included 6 **covariates** in our model: race, sex, and SES as defined above, as well as:

- Total number of primary care or hepatology visits in the UCSF system, annually from 2015 - 2019.
- FIB-4 score (a validated measure used for prediction of cirrhosis (Khan et al 2017), which uses age, platelet count and liver transaminases),
- Years since FIB-4 score was last measured

This is a survival analysis, with a Structural Causal Model $O = \{W, L(t), Y(t), A(t)\}$ where:

- W is the baseline covariates (race, sex and SES)
- L(t) is the set of 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)

$U = (U_{L(t)}, U_{A(t)}, U_{C(t)}, U_{Y(t)},), t = 1, 2, 3, 4, 5 \sim P_U$

Structural Equations, $\mathcal{M}^{\mathcal{F}}$, for t from 1 to 5, were:

$$
\begin{aligned}
W &= f_W(U_W) \\
L(1) &= f_{L(1)}(U_{L(1)}) \\
A(1) &= f_{A(1)}(W, L(1), U_{A(1)}) \\
L(t) &= f_{L(t)}(\bar{L}(t-1), \bar{A}(t-1), U_{L(t)}) \\
A(t) &= f_{A(t)}(W, \bar{L}(t), \bar{A}(t-1), U_{A(t)}) \\
Y(t) &= f_{Y(t)}(W, \bar{L}(t-1), \bar{A}(t-1), Y(t-1), U_{Y(t)}) \\
Y(K) &= f_{Y(K)}(W, \bar{L}(K-1), \bar{A}(K-1), Y(K-1), U_{Y(K)})
\end{aligned}
$$

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

E. Estimation of our Target Causal Parameter

The target causal parameter is $\psi^F(\mathcal{P}_{U,X}) = E_{U,X}(Y_{\bar{a}=1(5)} - Y_{\bar{a}=0(5)})$, the average treatment effect on HCC diagnosis in year 5 assuming that all patients had abdominal imaging every year for the 4 prior years ($Y_{\bar{a}=1}$), compared to HCC outcomes in year 5 if all patients did NOT have abdominal imaging at any time point during the preceding four years ($Y_{\bar{a}=0}$).

We have 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. 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 below).

	G-Comp	IPTW	TMLE
Bias	-0.002316	0.288015	-0.00239
Variance	0.0000002	0.019492	0.00097
MSE	0.0000056	0.102445	0.00098

The bias seen in the IPTW estimator is likely a result of practical positivity violations in our observed data.

F. Findings

Ultimately, implementing *ltmle* with *Super Learner* on our observed data produced the following estimates for the risk difference 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, when controlling for the number of hepatology or primary care visits, FIB-4 score, sex, race, and SES was:

G-Comp (95% CI)	**IPTW** (95% CI)	**TMLE** (95% CI)
1.102 (-0.913, 3.116)	1.149 (-0.872, 3.169)	1.124 (-0.887, 3.136)

Using any of our estimators, 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. While a 1.1% decrease in HCC risk over 5 years sounds clinically non-significant at first glance, **this represents 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 5 years. Given that abdominal imaging is a non-invasive and relatively inexpensive intervention, this underscores 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.