Using the Fib-4 Score to Monitor Morbidity and Mortality Risk in Chronic Hepatitis C Patients

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Abstract

Introduction: In the recent past, many patients with chronic Hepatitis C infections [HCV] delayed treatment until symptoms emerged due to significant, direct and indirect costs associated with older treatments. Physicians may have acquiesced to delays in therapy as clinical research data on new treatment options began to emerge in the literature. However, delaying therapy must be coupled with valid methods for monitoring the patient's disease progression over time to insure that mortality and morbidity risks do not become untenable. This study examined if FIB-4 values can be used to monitor the risk of liver-related events and mortality in HCV patients.

Methods: A cohort of patients was selected from the Veterans Health Affairs (VHA) Hepatitis C Clinical Case Registry (Hep C CCR) of confirmed HCV patients. The primary outcomes were time to death and time to a composite for first liver-related clinical events. Cox proportional hazards models were estimated using time to a patient's FIB-4 exceeding 1.45 or 3.25 as the risk factor of interest. Cox models were performed to examine the risk for patients using age, gender, genotype, race, ethnicity, BMI, prior hospitalizations and HIV and hepatitis B co-infection.

Results: 187,860 patients met study requirements. Patients whose FIB-4 level exceeded 3.25 were at significantly higher risk of death [Hazard Ratio (HR) = 3.56 (3.47-3.65)] and an adverse liver-related clinical event [HR = 4.01 (3.92-4.10)]. Exceeding FIB-4 > 1.45 was also associated with a significant but smaller increased risk of death [HR = 2.27 (2.21-2.33)] and the composite event [HR = 2.23 ([2.18-2.28)].

Conclusion: FIB-4 is a significant predictor of risk, even at the lower threshold (1.45).

Keywords: Hepatitis C; Morbidity and Mortality; Cox proportional hazards models; FIB-4

Introduction

Hepatitis C Virus (HCV) is associated with significant global public health and economic burden, affecting approximately 130-170 million people worldwide and an estimated 3.2 to 7 million people in the United States [1-4]. HCV patients are at a risk of developing progressive liver disease and related complications such as cirrhosis, liver failure, liver transplantation, Hepatocellular Carcinoma (HCC), and death [1,2,5-12]. Many patients with chronic HCV infections may fail to develop symptoms over their lifetime that would require medical treatment. The rate of progression to cirrhosis is estimated to be about 5-20% in chronic patients at 20 years of infection [13].

Standard therapy prior to 2011 [Pegylated interferon plus Ribavirin] was commonly met with patient reluctance to initiate therapy. For example, our previous analysis of VA patients with a detectable viral load at baseline found that less than 25% of patients were ever treated and only 4% of patients with a detectable viral load ever achieved an undetectable viral load [14]. As new therapies began to emerge, patients and their physicians faced a decision whether or not to initiate interferon-based therapy or wait for better treatment options [15]. These treatment options are now available but at very high cost per course of therapy. This welcomed change in clinical options has created a demand for information on how best to focus limited resources on HCV patients at highest risk for adverse clinical events, especially in managed care plans and government programs in the U.S. and Europe.

The purpose of this study is to evaluate the feasibility of using a single clinical marker to monitor the progression of HCV as measured by the risk of future adverse events and death. Specifically, we investigate the use of the FIB-4 score, a non-invasive biomarker of fibrosis, as a predictor of future risk of liver related events and death. The FIB-4 score is used to estimate liver fibrosis stages, with a FIB-4 index > 3.25 having been found to have a positive predictive value of 82.1% to confirm the existence of significant fibrosis in a HCV infected cohort, while a FIB-4 index < 1.45 found to have a negative predictive value of 94.7% [16]. Recent research has further explored the use of FIB-4 as well as gender as predictors of HCV disease progression [17,18].

To better accomplish this goal, we expanded our earlier sample of VA/HCV patients with a detectable viral load at baseline to include patients with or without a baseline viral load but with sufficient data to calculate at least one FIB-4 score over time. Using this larger VA cohort, we tested the hypothesis that FIB-4 index values of greater than 1.45 and 3.25 are associated with increased risk of liver-related complications and death.

Multivariate statistical models will be estimated to better clarify the utility of FIB-4 as clinical marker for HCV progression. These models will generate estimates of the effects of numerous other risk factors. Previous research has documented the impact of age, male gender, alcohol consumption, HIV co-infection and a fatty liver on the likelihood of disease progression [19]. BMI and Hispanic ethnicity have been found to be associated with disease progression [20], while African Americans may have a lower rate of disease progression relative to white patients [20-22]. Results from our earlier analysis of 128,769 VA patients with detectable viral loads at baseline found that black patients were at lower risk for the composite late-stage liver event [HR = 0.72 (0.71-0.72)] and death [HR = 0.65 (0.62-0.67)] than white patients. But more importantly, this study documented that achieving viral suppression reduced risk of the composite clinical endpoint by 27% [HR = 0.73 (0.66-0.82)] and the risk of death by 45% [HR = 0.55 (0.47-0.64)] [14].

The impact of viral genotype on the risk of future liver-related events and death is much less clear. Preliminary data suggested patients with genotype 1 may be at higher risk of disease progression [23]. However, follow up studies did not confirm these observations [5,24]. More recent studies have found that, genotype 3 carries an increased risk of worse clinical outcome [25-27]. Our previous study using VA patients found that patients with genotype 2 were at significantly lower risk, and patients with genotype 3 were at higher risk for all study outcomes relative to genotype 1 (p < 0.01 for all estimates)[14].

Other studies have looked at the impact of laboratory tests on disease progression and death including albumin, AST/ALT ratio, and platelets [28-30]. The results of our recently published analysis of the VA data identified 5 laboratory tests associated with increased risk [31]. The estimated hazard ratios for the composite of liver-related complications/death were 1.35/1.84 for the AST/ALT ratio > 1; 2.35/5.01 for albumin < 3 g/dl; 1.58/1.15 for GGT > 195 IU/L; 3.85/1.55 for platelet count < 100 k/mm^2 and 4.48/2.39 for alpha fetoprotein > 144 ng/mL. But more importantly, this analysis determined that patients who delayed starting drug therapy until after any one of the above lab tests became abnormal significantly reduced the effectiveness of drug therapy in reducing the risk of adverse clinical events and death.

Methods

Data

The data used in this study were taken from the Veterans Affairs [VA] Clinical Case Registry (CCR) for HCV infected patients. This retrospective cohort data was de-identified before being made available to the research team. Moreover, the research team members responsible for conducting the analyses using the de-identified data [Matsuda, Tonnu-Mihara] were required to conduct all analyses on site at the VA in Long Beach.

HCV patients included in the CCR were initially identified using routine computer-based scans of the Electronic Medical Record (EMR) data for the presence of an HCV-related ICD-9 diagnosis code [see Appendix 1] or a positive HCV exposure assessment using the Hepatitis C Antibody Test, the Hepatitis C Recombinant Immunoblot Assay [RIBA] or the Qualitative Hepatitis C RNA Test. A local CCR coordinator was provided a list of all newly identified HCV patients. The local CCR coordinator removed a patient from the CCR manually if they determine that the patient had been included in the HCV/CCR erroneously. Upon this confirmation, all historical data from the patient's EMR were pulled and added to the CCR. The VA EMR system was fully implemented in 1999 and the data period for this study covers the entire time period over which EMR data were available from all VA regions from 1999 to 2010 [32].

An intermediate patient-level analytic database was created consisting of summary variables for each month before and after the patient's HCV confirmation date [index date], defined as earliest date of detectable HCV viral load or genotype. The following summary data were created:

1. Patient demographic data (age in months at baseline, gender, race, ethnicity): Race and ethnicity data were based on patient self-report as recorded in the VA EMR system and were included in the analysis based on the previous research documenting race and ethnicity as risk factors for liver-related clinical events.

2. The patient's diagnostic profile was created consisting of monthly dichotomous variables reflecting the diagnoses recorded each month.

3. Monthly dichotomous variables were created for hospital admissions for any diagnosis and liver related diagnoses.

4. Prescription drug data were used to create monthly dichotomous variables indicating when patients received HCV-related treatment [peg-interferon alfa [2a or 2b], interferon alfa [2a or 2b] and interferon alfacon-1]. The use of ribavirin as monotherapy was not considered to be a drug therapy for HCV.

5. Monthly values for most common laboratory tests, including viral load [VL] and viral genotype were created. These laboratory data were used to calculate an FIB-4 score in those months in which sufficient data were available. Missing values were assigned when no tests were recorded during the month. These FIB-4 values were then used to calculate the patient's time to exceeding the FIB-4 levels under study [1.45, 3.25] as the patient's FIB-4 level changed over time. The specification of the patient's FIB-4 level as a time dependent variable allows us to test the temporal relationship between changes in FIB-4 and patient outcomes. For example, in the analysis using the critical FIB-4 value of 3.25, the estimated effect

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of the FIB-4 variable measures the impact on patient risk of those patient having exceeded an FIB-4 > 3.25. but only if this level is exceeded before the event.

6. The objective of treatment is to suppress the patients HCV viral load to undetectable levels. Another important factor of interest of this research was to document the impact of viral load suppression, while taking into account the temporal relationship between achieving an undetectable viral load and event dates. To achieve this, we specified undetectable viral load as a time dependent variable. This specification represents a practical improvement in the real world data analysis relative to Sustained Viral Response [SVR], the gold standard for measuring treatment response in clinical trials. Whether or not the patient has achieved an undetectable viral load will be updated in the Cox model whenever a more recent measurement is available regardless of the interval between tests. This time-dependent specification can help better capture the long-term sustainability of viral suppression beyond 6 months.

Sample Selection Criteria

Study patients were screened for baseline data for at least 6 months prior to their index date and sufficient data to calculate one or more FIB-4 score at some point in longitudinal data. These data were then used to measure time-to-events and estimate the impact of achieving two alternative FIB-4 levels: 1.45 and 3.25. Time to an undetectable viral load was calculated and included in the analysis of event risk.

Patient Outcomes

HCV infected patients are at risk for progressive liver disease and related complications such as cirrhosis, liver failure, Hepatocellular Carcinoma (HCC) and death.[1,2,5-7]Therefore, the patient outcomes specified for this analysis were all-cause mortality and liver-related morbidity [a composite of newly diagnosed cirrhosis(compensated or decompensated), HCC, or a liver-related hospitalization]. The time to the composite event was set at the earliest event date for any of the composite events. Monthly dichotomous variables were created for the outcomes of the study based on recorded diagnostic codes [e.g., diagnosis of cirrhosis, etc.] and selected CPT-4 codes included in data from hospital admissions and outpatient services. Hospitalizations were defined being liver-related if the primary diagnosis for the hospitalization was found in Appendix_1. Cirrhosis and HCC events were compiled by searching the inpatient, outpatient and problem lists for ICD-9 codes 571.5, 571.2, 571.6 and 155,155.1, 155.2, respectively. Decompensated cirrhosis was defined as a diagnosis of cirrhosis combined with a diagnosis of hepatic coma [70.44, 71.71, 348.3, 348.31, 572.2], portal hypertension [572.3], hepatorenal syndrome [572.4], jaundice [782.4], ascites [789.59], or esophageal varices [456, 456.1, 456.2, 456.21] or a FIB-4 score > 3.25. The FIB-4 score was also segmented into three categories which were previously found to correctly classify nearly 73% of liver biopsies in a HCV infected cohort: < 1.45, 1.45 to 3.25 and > 3.25 [16].

Statistical Methods

The time-to-event variables for death and the composite event [morbidity] were analyzed using time dependent Cox proportional hazards models to test the correlation between potential predictors and study endpoints. Achieving FIB-4 > 1.45 and FIB-4 > 3.25 were included in separate analyses as time-dependent independent variables. The models control for genotype, race, ethnicity, age, gender, BMI and other factors such as diagnosis of diabetes, co-infections with HIV or HBV at baseline and any hospital admission in the 6 months prior to the patient's index date. Time to an undetected Viral Load (VL) was also included as an independent variable.

We also conducted sensitivity analyses of the validity of the FIB-4 as a risk factor for predicting adverse events and death in HCV patient by replacing the FIB-4 with the AST to Platelet Ratio Index (APRI), a serological marker that has satisfactory sensitivity and specificity together with a high predictive value of fibrosis. The correlation of APRI with significant fibrosis and cirrhosis has been evaluated in various studies and patient cohorts [33-36]. The advantages of both the FIB-4 and APRI are that they utilize readily available laboratory though the APRI has not been validated in terms of following patients.

Results

Descriptive Statistics

A total of 233,424 patients met study requirements for 6 months of data before their index date. Eighty-one percent [81%] of these patients met the criteria for a minimum of one FIB-4 measurement at some point on their longitudinal data file and comprised the study sample [N = 187,860]. Table 1 presents the descriptive statistics for the study sample and compares these patients to patients excluded due to missing FIB-4 data. Overall, 19.7% of patients in the analytic sample received treatment at any time following HCV diagnosis and treatment rates were significantly higher in the cohort with FIB-4 scores [21%] than for patients with no FIB-4 data [14%]. The VA/HCV patients were predominantly male of either white or black race [51% and 28%, respectively] with nearly 18% of patients with unknown race. The mean age was 53 years [SD = 8] and nearly 50% of patients were documented as genotype 1 [38% missing data]. Just fewer than 15% of the FIB-4 cohort had no baseline FIB-4 score. Of patients with a baseline score, only 18% had an FIB-4 score > 3.25 (not shown in Table 1), which is correlated with a Metavir fibrosis stage of F3-F4 [16] or an Ishak fibrosis stage of F4-F6 [37]. Finally, just over 3% of 233,424 patients had an undetectable viral load at baseline and 19% of patients had not reported viral load at baseline (not shown on Table 1).

Predictors of All-Cause Mortality

The estimated hazard ratios for the risk factors for all-cause mortality are displayed in Table 2. The models using FIB-4 > 1.45 and FIB-4 > 3.25 are displayed side-by-side to facilitate comparing results.

A patient's FIB-4 is a significant predictor of the risk of death. Patients whose FIB-4 value exceeds 1.45 at some point in their

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Table 1: Descriptive Statistics of the Patient Population.

Demographic characteristics	With FIB-4 data N = 187,860		No FIB-4 data N = 45,564		
	N	%	N	%	P - value
Age [Mean ± SD]	52.32 ± 7.84		53.88 ± 8.31		< 0.0001
Male (n, %)	182014	96.89	44093	96.77	0.2003
Ethnicity	N	%	N	%	
Hispanic	11241	5.98	2176	4.78	
Non-Hispanic	150086	79.89	35564	78.05	< 0.0001
Multi-ethnic	1037	0.55	55	0.12	
Unknown	25496	13.57	7769	17.05	
Race	N	%	N	%	
White	95486	50.83	23794	52.22	
Black	54424	28.97	11252	24.69	
Mixed	3519	1.87	445	0.98	< 0.0001
Other	2302	1.23	690	1.51	
Unknown	32129	17.1	9383	20.59	
Diabetes prior	31269	16.64	7840	17.21	0.004
Hospitalization prior	36925	19.66	6335	13.90	< 0.0001
Viral load at baseline	N	%	N	%	
Missing [no baseline readings]	38193	20.33	5240	11.50	
Detectable	144108	76.71	38240	83.93	< 0.0001
Undetectable	5559	2.96	2084	4.57	
Ever treated	39651	21.11	6345	13.93	< 0.0001
Genotype	N	%	N	%	< 0.0001
Missing	66663	35.49	22374	49.10	
1	96365	51.30	18251	40.06	
2	13966	7.43	2875	6.31	< 0.0001
3	9307	4.95	1811	3.97	
other	1559	0.83	253	0.56	
Baseline FIB-4*	N	%	N	%	
Missing	27572	14.68	45564	100	
< 1.45	74702	39.76	0	0	
1.45-3.25	57274	30.49	0	0	
>3.25	28312	15.07	0	0	

*Formula used to calculate this FIB-4 value [14]:

$$\text{FIB-4} = \frac{\text{age(years)* AST(IU / L)}}{\text{platelets}(10^9 / \text{L})* \sqrt{\text{ALT(IU / L)}}}$$

Table 2: Impact of Risk Factors on the Risk of Death.

	FIB-4 > 1.45	FIB-4 > 3.25
	N = 187,860	
Number of Events [%]	29,316 [15.6%]	
FIB-4 > Critical value	2.27*** [2.21-2.33]	3.56*** [3.47-3.65]
Achieved undetectable VL	0.71*** [0.67-0.75]	0.78*** [0.72-0.83]
Gender [Male]	1.63*** [1.49-1.79]	1.65*** [1.50-1.81]
Age [vs. < 45]		
45-65	1.49*** [1.43-1.55]	1.54*** [1.47-1.60]
> 65	2.53*** [2.40-2.67]	2.64*** [2.50-2.79]
Race [vs White]		
Black	0.71*** [0.69-0.73]	0.79*** [0.77-0.82]
Mixed	0.73*** [0.67-0.81]	0.77*** [0.70-0.84]
Other	0.83** [0.74-0.93]	0.83** [0.74-0.94]
Unknown	0.88*** [0.85-0.92]	0.91*** [0.87-0.95]
Ethnicity [vs non-Hispanic]		
Hispanic	0.97 [0.92-1.02]	0.91* [0.87-0.96]
Mixed	0.65*** [0.53-0.78]	0.61*** [0.50-0.74]
Other/Unknown	2.18*** [2.09-2.27]	2.07*** [1.99-2.15]
Prior Admission [6 months]	1.63*** [1.59-1.68]	1.63*** [1.59-1.68]
HCV Genotype [vs 1]		
2	0.92** [0.87-0.92]	0.95* [0.90-1.00]
3	1.08** [1.02-1.14]	1.02 [0.97-1.08]
Missing	1.51*** [1.47-1.55]	1.50*** [1.46-1.54]
other	0.91 [0.78-1.05]	0.90 [0.78-1.04]
Body Mass Index		
< 25	1.27*** [1.24-1.31]	1.28*** [1.24-1.31]
> 30	1.03 [1.00-1.06]	1.02 [1.00-1.05]
Missing	1.16*** [1.08-1.24]	1.11*** [1.04-1.19]
Diagnosis at baseline		
Diabetes	1.68*** [1.64-1.73]	1.66*** [1.61-1.70]
HIV	1.41*** [1.20-1.66]	1.41*** [1.20-1.66]
HBV	1.07 [0.99-1.16]	1.05 [0.97-1.13]

*p < 0.05; **p < 0.01; ***p < 0.0001. Estimates adjusted for the risk factors in the table for which individual results are presented and for the patient's baseline diagnostic profile.

Table 3: Impact of Risk Factors on Morbidity [Composite Event].

Patient Characteristics	FIB-4 > 1.45	FIB-4 > 3.25
	N = 180,789	
Number of Events [%]	52,863 [29.2%]	
FIB-4 > Critical Value	2.23*** [2.18-2.28]	4.01*** [3.92-4.10]
Achieved undetectable VL	0.68*** [0.64-0.72]	0.71*** [0.67-0.76]
Gender [Male]	1.10** [1.04-1.18]	1.13** [1.06-1.20]
Age [vs. < 45]		
45-65	0.86*** [0.83-0.89]	0.90*** [0.88-0.93]
> 65	0.58*** [0.55-0.62]	0.59*** [0.55-0.63]
Race [vs White]		
Black	0.77*** [0.75-0.79]	0.83*** [0.81-0.85]
Mixed	1.11*** [1.04-1.19]	1.16*** [1.08-1.24]
Other	0.84** [0.76-0.92]	0.84** [0.76-0.92]
Unknown	0.61*** [0.58-0.64]	0.63*** [0.60-0.66]
Ethnicity [vs non-Hispanic]		
Hispanic	1.26*** [1.21-1.31]	1.20*** [1.16-1.26]
Mixed	1.42*** [1.26-1.58]	1.38*** [1.24-1.55]
Other/Unknown	0.97 [0.92-1.01]	0.94** [0.89-0.98]
Prior Admission [6 mo.]	1.56*** [1.52-1.60]	1.53*** [1.50-1.57]
HCV Genotype [vs 1]		
2	0.85*** [0.82-0.88]	0.87*** [0.83-0.90]
3	1.07** [1.03-1.12]	1.02 [0.97-1.06]
Missing	0.62**** [0.60-0.63]	0.61**** [0.59-0.62]
other	0.93 [0.84-1.04]	0.92 [0.83-1.02]
Body Mass Index		
< 25	0.93*** [0.91-0.95]	0.92*** [0.90-0.94]
> 30	1.05** [1.02-1.07]	1.05** [1.02-1.07]
Missing	0.43*** [0.39-0.48]	0.42*** [0.38-0.46]
Diagnosis at baseline		
Diabetes	1.18*** [1.15-1.21]	1.16*** [1.13-1.19]
HIV	0.89 [0.76-1.04]	0.89 [0.76-1.04]
HBV	0.96 [0.89-1.04]	0.95 [0.88-1.02]

*p < 0.05; **p < 0.01; ***p < 0.0001. Estimates adjusted for the risk factors in the table for which individual results are presented and for the patient's baseline diagnostic profile.

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post-index period, experience an increased risk of death by 127% [HR = 2.27 (2.21 – 2.33)]. Mortality risk increases significantly to + 2.56% if the patient's FIB-4 exceeds 3.25 at any time in the patient's post-index period [HR = 3.56,(3.47-3.65)]. Equally important, the impacts of other risk factors on mortality risk are independent of FIB-4. Patients who achieved an undetectable viral load significantly reduced their risk of death by between 22% and 29% relative to patients with a detectable viral load over their entire post-index period. Mortality risk increased monotonically with age, while minority and Hispanic patients exhibit lower risk. Genotype 2 patients are at lower risk of death than patients infected with HCV genotype 1. Genotype 3 patients may be at higher risk of death than genotype 1 patients but the evidence is marginally significant. Patients with lower than normal and higher than normal BMI are at higher risk of death. Patients with diabetes, HIV and HBV at baseline are also at higher risk of death.

Predictors of Morbidity

The estimates for the risk of a patient experiencing the composite clinical event are presented in Table 3. The risk of experiencing an adverse clinical event more than doubles if FIB-4 exceeds 1.45 [HR= 2.23,(2.18-2.28)]. If the patient's FIB-4 exceeds 3.25 at some point over time, the risk of the composite event increases four-fold [HR= 4.01 (3.92-4.10)]. As with the risk of death, the morbidity risk effects of other risk factors are independent of the patient's FIB-4 level. In particular, achieving an undetectable viral load, reduced mortality risk by 29% to 32%. Male gender increased mortality risk by 10-13%. Age at diagnosis monotonically decreased mortality risk, possibly due to the effect of a delayed diagnosis, or possible missing comorbidities due to secondary insurance coverage to VA coverage. Black HCV patients are at lower risk for all clinical events while Hispanic patients are at higher risk for clinical events. Genotype 2 patients were at 13-15% lower risk for experiencing the composite clinical event while genotype 3 patients were at 2-7% higher risk relative to genotype 1 patients, though significance was mixed. Increased BMI monotonically increased mortality risk. Prior hospital admissions at baseline and a baseline diagnosis of diabetes were consistent predictors of increased morbidity risk while baseline diagnoses of concomitant infection with HIV or HBV had no impact on risk in HCV patients.

Sensitivity Analyses

The results from the sensitivity analyses substituting APRI cutoff points for the FIB-4 values used in the main analysis are presented in Table 4. The results for the components of the composite event have been added to this table for both the FIB-4 and APRI risk factors. The results for the APRI are unstable. Patients who exceed APRI > 0.70 are at lower risk than patients who have not exceeded this value prior to any of the events studied and the results are statistically significant except for the composite event. This result is not driven by the inclusion of patients who have an undetectable viral load at baseline [< 3% of study patients, Table 1]. Conversely, patients who exceed APRI > 1.0 are at higher risk than patients who do not exceed this cut point. Moreover, the estimated hazard ratios are much larger for FIB-4 indicating that it is a superior predictor for future risk than the APRI.

Discussion

This study used data from a large cohort of real-world HCV patients at various stages of disease progression to investigate if FIB-4 can be used to monitor changes in patient risk for liver-related events and death. Our results confirm that the risk of liver-related events and death increased significantly with elevated FIB-4, even at FIB-4 as low as 1.45. Healthcare systems need to prioritize immediate access to the new HCV treatment and the FIB-4 index may be an additional viable tool to assess liver disease risk profile and treatment prioritization. While other biomarker methods of assessing liver fibrosis are available to fill the need for monitoring asymptomatic patients, we used the FIB-4 as the data for this calculation was widely available in the VA data. The FIB-4 has been shown to be superior to APRI, another well-known biomarker method [38-40], but may be not as accurate as transient elastography (Fibroscan) methods, though evidence is mixed [38, 40-41]. However, Fibroscan has its limitations as it does require elastimetry equipment that would be more costly and not as readily available as the FIB-4 calculation, and has been shown to have a high rate of failure in obese patients [38].

These results are relevant to the rational use of the newest therapies emerging onto the market with very high cure rates

EVENT Number of Events	FIB-4 > 1.45	FIB-4 > 3.25	APRI > 0.70	APRI > 1.00
Death N = 29,316 [15.6%]	2.27*** [2.21-2.33]	3.56*** [3.47-3.65]	0.87*** [0.83-0.90]	2.62*** [2.56-2.68]
Composite Event N = 52,863 [29.2%]	2.23*** [2.18-2.28]	4.01*** [3.92-4.10]	0.97 [0.94-1.00]	3.06*** [2.99-3.12]
Cirrhosis N = 25,791 [14.3%]	7.42*** [7.10-7.75]	10.14*** [9.84-10.44]	0.90*** [0.86-0.94]	7.84*** [7.60-8.09]
Decompensate Cirrhosis N = 12,313 [6.6%]	23.74*** [21.48-26.25]	18.54*** [17.69-19.43]	0.75*** [0.70-0.80]	12.89*** [12.27-13.55]
HCC N = 6,837 [3.7%]	9.02*** [8.23-9.88]	8.85*** [8.38-9.34]	0.86** [0.80-0.94]	7.59*** [7.17-5.04]
Liver-related Hospitalization N = 43,960 [23.4%]	1.91*** [1.86-1.95]	3.24*** [3.17-3.32]	0.93*** [0.90-0.96]	2.53*** [2.48-2.59]

Table 4: Sensitivity Analysis Comparing the Predictive Properties of FIB4 and ARPI.

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and priced very high for each patient. For example, the average wholesale charges for currently approved direct acting agents for the treatment of chronic hepatitis C genotype 1 can range from $60,000 to over $300,000 depending on the treatment regimen [42,43]. It is not surprising that health insurance companies, government programs and HMOs face a significant increase in demand for HCV treatment from two sources. First, more HCV patients are clinically eligible for treatment due to the improved SVR rates and more benign side effects profile for new therapies. But more important, significant pent-up demand exists for treatment from patients who could not tolerate older treatment regimens and patients who have delayed initiating treatment awaiting the approval of more effective and more tolerable treatment alternatives. Health insurance companies and capitation Health Maintenance Organizations [HMOs] in the U.S and government agencies in Europe are reluctant to immediately approve treatment for all patients infected with HCV, instead opting for a watchful waiting treatment strategy to avoid the staggering costs of treating all patients quickly. Some insurance companies and government programs are adopting, for the first time ever, criteria for approving therapies, and requiring a minimal liver biopsy threshold of stage 2 or 3 fibrosis. This is in line with the recent recommendation by the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America to give priority to patients at high risk for severe liver-related and extrahepatic manifestations of HCV infection [44].

Limitations

This study only considers the risk of developing significant liver-related events such as progressing to a diagnosis of cirrhosis or being hospitalized for a liver related event. Even access to EMR data cannot measure the risk of less well-defined HCV related 'events' such as chronic fatigue that can impose significant quality of life costs on HCV patients. More research is needed to tease out the relationship between viral load suppression and FIB-4 levels on these HCV-related costs.

There are several important technical limitations in our study. First the VA study population differs significantly from the U.S population, consisting mostly of non-Asian men. Therefore, results for the risk associated with gender and the catch-all category of 'other race' should be viewed with caution. Nevertheless, most of the US patients with HCV are male [3-4], and the VA is the largest provider of care to chronically HCV-infected patients in the United States [45].

We do not measure Sustained Viral Response [SVR], which has been shown to reduce risk of mortality and disease progression [26,28,46]. SVR requires that an undetectable viral load be maintained for six months following the termination of treatment, a requirement that is difficult to document even in an EMR environment. Instead, we used time-dependent specification of undetectable VL variable, which is a more practical measure of viral suppression in this real world data analysis, and is a proxy for treatment in the majority of the cases.

This study does not estimate or control for the effects of

treatment on clinical endpoints and death. This was done for two reasons. First, viral suppression without treatment is exceeding rare. Second, the parameters with which to determine if a patient completed an adequate course of therapy vary by genotype and other factors, such as allowable duration or breaks in the treatment. While developing counts of continuous days of therapy have been used by this research team in the past [47], we elected to use viral load suppression as our measure of treatment success. The effect of treatment and viral suppression before and after a patient has crossed these FIB-4 thresholds is also unknown and should be investigated further.

Finally, our study does not capture medical care outside the VA system, such as the Medicare program, which may cloud the relationship between viral load suppression and event risk. The potential for missing Medicare data lead us to enter age as a categorical variable and the "protective" effects of age > 65 for hospitalization likely reflects the availability of Medicare coverage for this age group and is consistent with our mixed results on the effect of age on the risk of events.

Conclusion

Health insurance companies, managed care organizations and government health care programs are struggling to develop a rational treatment protocol that manages the new, very expensive and very effective treatments for HCV while taking advantage of these cost-effective treatment alternatives. Plans are looking for a method of optimizing access over time, treating the highest risk patients first while monitoring untreated patients for emerging risk. In order to win support of physicians, any treatment protocol designed to rationalize the use of these products must be evidence based. Our results demonstrate a patient's FIB-4 level may be a viable tool in this quest to provide care more efficiently.

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Declarations

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Appendix 1: List of Study Related Diagnosis and Procedure Codes.
Hepatitis C Diagnostic Codes and Laboratory Tests
The ICD-9 codes that are used to identify pending hepatitis C patients are: V02.62, 070.41,070.44, 070.51, 070.54, 070.70, and 070.71.
The LOINC codes for the lab tests that are used to identify pending hepatitis C patients are: Hepatitis C Antibody Test 11259, 13955-0, 16128-1, 16129-9, 16936-7, 22327-1, 33462-3, 34162-8, 39008-8, 40762-2, 5198-7, 5199-5 Hepatitis C RIBA Test 24011-9 Qualitative Hepatitis C RNA Test 11259-9, 5010-4, 5011-2, 5012-0, 6422-0
Liver-related Diagnosis for Hospital Admissions Acute or unspecified hepatitis C with hepatic coma
Chronic hepatitis C with hepatic coma
Other specified viral hepatitis with hepatic coma
Other specified viral hepatitis without mention of hepatic coma code range
Unspecified viral hepatitis with hepatic coma
Unspecified viral hepatitis C code range
Unspecified viral hepatitis without mention of hepatic coma
Toxoplasma hepatitis
Malignant neoplasm of liver, primary
Malignant neoplasm of intrahepatic bile ducts
Malignant neoplasm of liver, not specified as primary or secondary

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Esophageal varices with bleeding
Spontaneous bacterial peritonitis
Alcoholic fatty liver
Acute alcoholic hepatitis
Alcoholic cirrhosis of liver
Alcoholic liver damage, unspecified
Chronic hepatitis, unspecified
Chronic persistent hepatitis
Chronic active hepatitis
Cirrhosis of liver without mention of alcohol
Biliary cirrhosis (chronic nonsuppurative destructive cholangitis)
Other chronic non-alcoholic liver disease
Unspecified chronic liver disease without mention of alcohol
Portal pyemia
Hepatic coma
Portal hypertension
Hepatorenal syndrome
Other sequelae of chronic liver disease
Hepatitis in viral diseases classified elsewhere
Hepatitis in other infectious diseases classified elsewhere.
Hepatitis, unspecified (trauma and toxic reactions)
Other specified disorders of liver
Unspecified disorder of liver
Jaundice
Hepatomegaly
Ascites
Hepatitis C carrier, unspecified
Liver transplant status

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