Predictive modeling of fibrosis scores for patients diagnosed with chronic hepatitis C in a state Medicaid program

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Background

- Many payers, particularly state Medicaid programs with a large burden of chronic hepatitis C (HCV) patients, limit access to direct-acting antivirals (DAAs) to patients with marked fibrosis, citing high regimen costs as a necessity to prioritize patients for treatment.[1,2,3]
- Liver fibrosis has been used as a marker for prioritizing patients, giving highest priority to patients with METAVIR fibrosis scores of F3 or F4. A higher score indicates higher disease severity.[3]
- Analysis tools using claims data to estimate fibrosis scores and utilization of health care resources in a specific population would be valuable to payers that are considering lessening coverage requirements based on fibrosis score thresholds.

References:
1. Centers for Disease Control and Prevention. Hepatitis C information for healthcare professionals. Available online at: www.cdc.gov/hepatitis/hcv/hcvfaq.htm. Last revised: 04/30/2018. Last accessed: 03/18/2019.
2. Francisco A. HCSP fact sheet: A brief history of hepatitis C. Available online at: http://hcvadvocate.org/hepatitis/factsheets_pdf/Brief_History_HCV.pdf. Last revised: 02/2017. Last accessed 03/18/2019.
3. Canary LA, Klevens RM, Holmberg SD. Limited access to new hepatitis C virus treatment under state Medicaid programs. *Ann Intern Med* 2015;163:226-8.

Objective

- To develop and assess a method for determining the METAVIR fibrosis score for patients diagnosed with HCV utilizing a health plan's administrative paid claims data.

Methods

- Historical, cross-sectional cohort from a Medicaid payer perspective
- Two data sources were used: 1) prior authorization (PA) requests from the patient management system, and 2) Medicaid paid claims data
- Inclusion criteria: adult Oklahoma Health Care Authority (OHCA) (Medicaid) members (18-64 years) diagnosed with chronic HCV and who had a PA submission (i.e., both approved and unapproved requests) for treatment with one of the newer DAAs during the study period of 07/01/2014-10/31/2017; up to 1 year pre-index period was utilized with ≥6 months continuous eligibility
- Exclusion criteria included members with dual-Medicare eligibility; history of or complications from a liver transplantation; and members with no hospital, medical, or pharmacy claims during their study period
- The primary outcome was METAVIR fibrosis score, an ordinal measure, with categories consisting of F0, F1, F2, F3, and F4
- Proportional-odds ordered logit model was specified using robust statistical inference via Huber-White standard errors (heteroscedasticity consistent) for all cases and non-cirrhotic cases; a sensitivity analysis with a forward-stepwise logit regression was conducted, implementing p=0.10 for variable removal and p=0.05 for variable addition
- Support Vector Machines (SVM), a machine learning algorithm for classification and regression analyses, was specified with a multiclass (i.e., class-against-class method), full model, radial basis function kernel; tuning was conducted via modifications of margin of error parameters and gamma scaling factors in the nonlinear kernel as a scaling factor for linear components, with findings calculated as a percentage that were support vectors

Results

Table 1. Multivariable Regression Analyses for Outcome of METAVIR Fibrosis Score among Medicaid Beneficiaries with Hepatitis C

	All Cases (n = 850)		Non-Cirrhotic Cases Only (n = 669)	
	Full Model[A] Odds Ratio (95% CI)	Stepwise Model[B] Odds Ratio (95% CI)	Full Model[A] Odds Ratio (95% CI)	Stepwise Model[B] Odds Ratio (95% CI)
Demographics				
Age	1.046*** (1.027,1.064)	1.046*** (1.029,1.061)	1.048*** (1.029,1.067)	1.049*** (1.033,1.066)
Male Sex	1.822*** (1.328,2.500)	1.754*** (1.316,2.337)	1.851*** (1.338,2.559)	1.822*** (1.361,2.440)
Race (referent: White)				
African American	0.785 (0.473,1.304)		0.786 (0.468,1.322)	
Asian or Pacific Islander	0.923 (0.415,2.053)		0.840 (0.372,1.896)	
American Indian/Alaskan Native	0.920 (0.484,1.748)		0.988 (0.521,1.874)	
Other	0.786 (0.404,1.529)		0.866 (0.439,1.705)	
Year (referent: 2014)				
2015	0.988 (0.397,2.458)		0.986 (0.394,2.465)	
2016	1.271 (0.510,3.167)		1.202 (0.481,3.005)	
2017	0.714 (0.278,1.836)	0.601** (0.445,0.813)	0.668 (0.259,1.723)	0.580*** (0.427,0.788)
Hepatitis Clinical Characteristics				
DAA Treatment Length	1.193*** (1.126,1.265)	1.183*** (1.117,1.254)	1.178*** (1.110,1.250)	1.163*** (1.098,1.232)
Genotype (other than 1)	1.674** (1.162,2.411)	1.620** (1.139,2.304)	1.529* (1.050,2.227)	1.467* (1.023,2.105)
Cirrhosis	21.233*** (10.597,42.545)	21.521*** (11.444,40.471)		
Hepatocellular Carcinoma	5.452* (1.252,23.734)	4.835* (1.103,21.193)		
Ascites	2.094 (0.848,5.171)	2.265* (1.006,5.101)	1.975 (0.721,5.405)	
Hepatic Encephalopathy	0.718 (0.100,5.151)			
Portal Hypertension	2.401 (0.801,7.195)		2.616 (0.656,10.430)	
Esophageal Varices	7.546** (1.204,47.302)	9.927* (1.488,66.238)		
Other Sequelae of Chronic Liver Disease	2.100 (0.393,47.302)		0.510 (0.203,1.285)	
Non-alcoholic Fatty Liver Disease or Non-alcoholic Steatohepatitis	2.920 (0.647,1.493)		0.970 (0.631,1.490)	
Extrahepatic Manifestations				
Cerebrovascular Disease	0.508 (0.242,1.065)	0.457** (0.264,0.792)	0.539 (0.246,1.179)	0.448** (0.252,0.795)
Type 2 Diabetes Mellitus	1.691** (1.215,2.355)	1.596** (1.163,2.189)	1.608** (1.145,2.257)	1.504* (1.086,2.082)
Nephritis, Nephrotic Syndrome, or Nephrosis	0.620 (0.301,1.278)		0.621 (0.282,1.368)	
Depression	1.122 (0.798,1.575)		1.038 (0.731,1.473)	
GERD	1.424* (1.030,1.971)		1.429* (1.027,1.989)	
Alcohol Use Disorder	0.854 (0.496,1.471)		0.826 (0.465,1.466)	
Opioid Use Disorder	0.854 (0.549,1.329)		0.918 (0.586,1.439)	
Other Solid Tumor	0.735 (0.287,1.884)	0.402* (0.170,0.951)	0.491 (0.172,1.407)	0.111*** (0.146,0.304)
/cut1	−1.189 (−3.062,0.685)	−1.290 (−2.901,0.320)	−1.319 (−3.209,0.570)	−1.417 (−3.040,0.204)
/cut2	2.473 (1.026,3.921)	2.353 (1.316,3.390)	2.347 (0.881,3.813)	2.229 (1.180,3.279)
/cut3	4.909 (3.415,6.402)	4.728 (3.628,5.827)	4.795 (3.251,6.310)	4.616 (3.500,5.731)
/cut4	6.266 (4.737,7.796)	6.050 (4.914,7.187)	6.100 (4.550,7.651)	5.883 (4.733,7.034)
Overall Pseudo R^2 (ordered logit regressions)	24.00%	22.71%	9.50%	8.00%
Machine Learning/Computational Intelligence Predictive Model[C]				
Percentage that are Support Vectors (tuned)	47.7%		75.3%	
Percentage that are Support Vectors (untuned)	≥93.2%		≥79.8%	

[A] Proportional-odds ordered logit regression with robust standard error calculation (i.e., Huber-White heteroskedasticity consistent)
[B] Forward stepwise logit regression, p=0.10 for removal and p=0.05 for addition, robust standard error calculation (i.e., Huber-White heteroskedasticity consistent)
[C] Support Vector Machine (SVM) specified with multiclass (i.e., class-against-class method), full models, radial basis function kernel; tuning via modifications of margin of error parameters and gamma scaling factors in the nonlinear kernel as a scaling factor for linear components.
* p<0.05; ** p<0.01; *** p<0.001

Results

- A total of 1,096 Medicaid members were eligible for the study
- Average age 48.8±10.6 years, 43.3% were male, 68.8% were genotype-1
- Notable univariable associations with increasing METAVIR score and clinical comorbidities included: increased percentage of GERD, diabetes, CHF, and Deyo-Charlson scores (p<0.05); most clinical associations were consistent among non-cirrhotic cases, though noting insignificant associations with METAVIR scores and ascites (p=0.185)
- The multivariable analysis across all cases indicated significantly higher associations (p<0.05) with higher METAVIR scores and several factors including male sex (OR=1.82), age (OR=1.05), genotype other than 1 (OR=1.67), DAA treatment length (OR=1.19), diabetes (OR=1.69), hepatocellular carcinoma (OR=5.45), cirrhosis (OR=21.23), varices (OR=7.55), and GERD (OR=1.42)

Limitations

- METAVIR scoring was based on MD-reported PA submissions using various techniques (e.g., biopsy, non-invasive scoring methods)
- Liver-related comorbidities and extrahepatic manifestations of Hepatitis C may be associated with varying standards of care and clinician perception
- Administrative claims data are for billing purposes and may contain errors
- Caution should be exerted concerning generalizability to other health care settings and patient populations

Conclusions

- This investigation observed numerous multivariable clinical associations with METAVIR fibrosis scores in Medicaid members, with machine learning suggesting moderate to strong predictive capabilities when tuned.
- Information extracted from administrative claims data may be suitable for categorizing chronic HCV patients by METAVIR classification, without availability of actual laboratory results.
- Disease severity prediction via a claims-based proxy may assist policymakers with appropriate resource allocation and benefit design

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