Identifying cirrhosis, decompensated cirrhosis and hepatocellular carcinoma in health administrative data: A validation study

Lauren Lapointe-Shaw1,2,3*, Firass Georgie4, David Carlone5, Orlando Cerocchi6, Hannah Chung3, Yvonne Dewit7, Jordan J. Feld1,6, Laura Holder3, Jeffrey C. Kwong3,7,8,9,10, Beate Sander2,3,6,8,11, Jennifer A. Flemming7,12

1 Department of Medicine, University of Toronto, Toronto, Canada, 2 Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada, 3 Institute for Clinical Evaluative Sciences, Toronto, Canada, 4 McGill University Medical School, Montreal, Canada, 5 Queen's University School of Medicine, Kingston, Canada, 6 University Health Network, Toronto, Canada, 7 Institute for Clinical Evaluative Sciences, Kingston, Canada, 8 Public Health Ontario, Toronto, Canada, 9 Dalla Lana School of Public Health, Toronto, Canada, 10 Department of Family and Community Medicine, University of Toronto, Toronto, Canada, 11 Toronto Health Economics and Technology Assessment Collaborative, Toronto, Canada, 12 Department of Medicine and Department of Public Health Sciences, Queen's University, Kingston, Canada

* lauren.lapointe.shaw@mail.utoronto.ca

Abstract

Background
To evaluate screening and treatment strategies, large-scale real-world data on liver disease-related outcomes are needed. We sought to validate health administrative data for identification of cirrhosis, decompensated cirrhosis and hepatocellular carcinoma among patients with known liver disease.

Methods
Primary patient data were abstracted from patients of the Toronto Center for Liver Disease with viral hepatitis (2006–2014), and all patients with liver disease from the Kingston Health Sciences Centre Hepatology Clinic (2013). We linked clinical information to health administrative data and tested a range of coding algorithms against the clinical reference standard.

Results
A total of 6,714 patients had primary chart data abstracted. A single physician visit code for cirrhosis was sensitive (98–99%), and a single hospital diagnostic code for cirrhosis was specific (91–96%). The most sensitive algorithm for decompensated cirrhosis was one cirrhosis code with any of: a hospital diagnostic code, death code, or procedure code for decompensation (range 88–99% across groups). The most specific was one cirrhosis code and one hospital diagnostic code (range 89–98% across groups). Two physician visit codes or a single hospital diagnostic code, death code, or procedure code combined with a code for cirrhosis were sensitive and specific for hepatocellular carcinoma (sensitivity 94–96%, specificity 93–98%).
any underlying individuals is low. While data sharing agreements and privacy legislation for the province of Ontario prohibit ICES from making the data set publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS.

Funding: This work was supported by a grant from the Physician Services Incorporated (PSI) Foundation (#14-13) and by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). LLS is supported by a CIHR Fellowship Award. JAF is supported by a Southeastern Ontario New Clinician Scientist Award. JCK is supported by a CIHR New Investigator Award and a University of Toronto Department of Family & Community Medicine Investigator Award. The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI) and by Cancer Care Ontario (CCO). However, the analyses, conclusions, opinions, and statement expressed herein are those of the authors, and not necessarily those of CIHI or CCO. No endorsement by ICES, MOHLTC, CIHI, or CCO is intended or should be inferred. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: Jennifer A. Flemming declares investigator-driven research support received from Gilead Sciences Canada, as well as speaker fees from Gilead Sciences, AbbVie, and Lupin Pharmaceuticals. Jordan J. Feld reports consulting fees and research support from Abbvie, Gilead Sciences, Janssen Pharmaceuticals and Merck. The commercial affiliations of the authors JAF and JJF had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript and only provided financial support in the form of author’s salaries. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

Conclusion
These sensitive and specific algorithms can be used to define patient cohorts or detect clinical outcomes using health administrative data. Our results will facilitate research into the adequacy of screening and treatment for patients with chronic viral hepatitis or other liver diseases.

Introduction
In 2016, 1.26 million people worldwide died of cirrhosis and chronic liver diseases, and their complications.[1] Hepatocellular carcinoma (HCC) mortality rates are rising faster than those from any other malignancy.[2] Globally, viral hepatitis secondary to hepatitis B and C virus infection underlies 55% of cirrhosis-related deaths and 61% of deaths from HCC.[1] Yet, many patients with liver disease remain undiagnosed, largely because they remain asymptomatic until a late stage.[3, 4] Of late, much progress has been made in the prevention and treatment of viral hepatitis. Many jurisdictions have advanced the timing of immunization against hepatitis B virus (HBV) from early adolescence to infancy.[5, 6] Further, new treatments for chronic hepatitis C virus (HCV) infection have enabled large numbers of patients to achieve sustained virologic response, a marker of long-term clinical cure.[7–10] Finally, our understanding of the epidemic of non-alcoholic fatty liver disease (NAFLD) in North America is just beginning and the natural history of this disease is still not completely defined.

To evaluate the epidemiology and the long-term clinical effectiveness of treatments and screening programs for chronic liver diseases, it is essential to accurately detect clinical outcomes such as cirrhosis, decompensated cirrhosis, and HCC. Although a registry of patients could be used to measure long-term treatment effects, it is ill-suited to study the overall burden or healthcare utilization related to liver disease since liver-related outcomes can take decades to occur. Longitudinal, systematically collected information from large cohorts of patients with chronic liver disease is needed.

Routinely collected health administrative data enable efficient research on real-world outcomes of patients with liver disease, while offering objective evidence of past healthcare utilization. Although several studies have validated data algorithms for identifying cirrhosis, decompensated cirrhosis, and HCC, these have been limited to International Classification of Diseases 9th revision (ICD-9) codes in the healthcare system of the United States.[11–17] In Canada, all hospitalization data have been coded using the ICD-10 system since 2002 and as of as of October 2015, all hospital discharge information in the United States have also been coded using the ICD-10 system.[18, 19] While administrative data codes have been used in outcomes research[20, 21], there are no existing validation studies for liver-related outcomes in Canadian patients and no validation studies using ICD-10 codes in the United States.

The primary objective of this study was to measure the validity of combined ICD-9 and ICD-10 health administrative data codes for detecting cirrhosis, decompensated cirrhosis, and HCC in patients with known chronic liver disease. This will facilitate the study of the long-term effects of antiviral treatment or policy changes relating to this patient population. Furthermore, as the epidemiology of chronic liver diseases such as NAFLD and alcohol-related disease have a different natural history than viral hepatitis, we also aimed to assess their broader validity in a group of patients with liver diseases of all causes.
Methods

Setting

The validation cohorts consisted of patients from two different university-affiliated tertiary care hepatology clinics in Ontario, Canada: The Toronto Centre for Liver Disease (TCLD) at the University Health Network (UHN) located in Toronto and the Liver Disease Clinic at the Kingston Health Sciences Centre (KHSC) located in Kingston. Both clinics are staffed by subspecialty trained academic hepatologists and receive patient referrals for patients with acute or chronic liver diseases. At both sites, clinicians employ a standardized computerized form for clinical data entry. Patient status, including test results and treatments, are updated at every encounter. UHN and KHSC clinical records include information on patient demographics, most responsible diagnosis, laboratory data, imaging data, endoscopic reports, pathology data, non-invasive fibrosis assessment tests and results, and any hepatic decompensation events.

Administrative databases

The Institute for Clinical Evaluative Sciences holds health administrative data for all Ontario residents with provincial health insurance. Data on demographics, physician visits, emergency department visits, hospital admissions and procedures are linked using an encrypted patient identifier.[22] The Ontario Health Insurance Program (OHIP) database contains all billing claims made by physicians.[23] The Canadian Institute for Health Information’s Discharge Abstract Database contains information for all admissions to acute care hospitals in Ontario[24], and the National Ambulatory Care Reporting System database contains information on emergency department and day surgery visits.[22] The Office of the Registrar General Death Database contains the cause of death for all deaths in the province.[25] The Ontario Cancer Registry includes detailed clinical information on malignancies such as anatomical site and tumour histology.[26]

Study population

We identified patients for inclusion in the chronic HBV and HCV cohorts using a two-step process. First, any patient followed at the TCLD with an HBV or HCV treatment status, positive HBV or HCV serology, positive HBV DNA, or positive HCV RNA, with a clinic visit between April 2006 and March 2014 were selected for further review. We then reviewed the charts to confirm chronic HBV or HCV status rather than resolved prior infection (patients with the latter were not included in the study cohorts). Patients who had evidence of ongoing infection with HBV or HCV at any time from their first clinic visit to March 31st 2014 were included in the study. The cohort of patients from KHSC comprised consecutive patients seen at the KHSC Liver Clinic from May through August 2013. Patients in the KHSC cohort had liver disease of viral and non-viral etiology. Across all groups, any patient that could not be linked to administrative data holdings was excluded from the study.

Reference standard: Clinical outcomes

Outcomes evaluated in this study included cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma. Two trained medical graduates (FG at TCLD and DC at KHSC) reviewed the charts to identify clinical outcomes.

Decompensated cirrhosis was identified based on the presence of any of the following in the clinical record: ascites, bleeding varices, encephalopathy, use of spironolactone without alternative indication, or explicit mention of decompensated cirrhosis. Cirrhosis was identified based on any of the decompensated cirrhosis criteria, or explicit mention of cirrhosis, non-
bleeding varices, or use of nadolol without alternative indication. In addition, cirrhotic appearance on ultrasound, a liver biopsy result of F4 fibrosis, or a non-invasive test result consistent with F4 fibrosis were also considered diagnostic of cirrhosis. Hepatocellular carcinoma was identified based on explicit mention anywhere in the clinical note. Uncertain cases were reviewed and classified by a hepatologist (JJF at UHN or JAF at KHSC).

A 5% random sample of charts was re-abstracted by a general internist at TCLD (LLS) and a hepatologist at KHSC (JAF). Agreement beyond chance on the outcome ascertainment by both abstracters was measured using Cohen’s kappa.

**Administrative data outcomes**

The primary outcomes of cirrhosis, decompensated cirrhosis and HCC were defined using relevant physician visit, emergency department visit, hospital diagnosis, procedure, death and pathology codes (Table 1). A secondary outcome of 2-year all-cause mortality following last clinic visit was reported as an overall measure of patient severity of illness.

| Table 1. Administrative data codes used to identify cirrhosis, decompensated cirrhosis and hepatocellular carcinoma. OHIP = Ontario Health Insurance Plan, ICD-9 = International Classification of Diseases, 9th Revision, ICD-10 = = International Classification of Diseases, 10th Revision, CCP = Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures, CCI = Canadian Classification of Health Interventions. |
|---|
| **Cirrhosis** |
| Physician Visit Code | OHIP: 571 |
| Hospital Diagnostic Codes | ICD-9 : 456.1, 571.2, 571.5 |
| | ICD-10: 185.9, 198.2, K70.3,K71.7, K74.6 |

| Chronic Liver Disease |
|---|
| Hospital Diagnostic Codes | ICD-9: 070.2X, 070.3X, 070.4X, 070.5X, 070.6, 070.9, 571.0, 571.1, 571.4X, 571.8, 573.1, 573.3 |
| | ICD-10: K70.0, K70.2, K73.X, K754, K758, K75.9, K76.0, B18.0, B18.1, B18.2, B18.8, B18.9 |

| Complications of Cirrhosis |
|---|
| Diagnostic and Procedure Codes | ICD-9: 155.0, 572.2, 572.3, 572.4, 456.0, 456.2, 782.4, 789.5, V427 |
| | ICD-10 : C22.0,C22.9, 81703,81803, 815.0, I86.4, I98.20, I98.3, K721, K729, K76.6, K76.7, R17, R18, T86.400, T86.401, Z76804, Z944 |
| | CCP: 1006, 6691,62.40, 62.41, 62.49 |
| | CCI: 1.NA.13.BA-FA, 1.NA.13.BA-X7, 1.NA.13.BA-BD, 1.KQ.76GP-NR, 1.OT.52. HA,1.OA.59^^, 1.OA.85^^ |
| | OHIP: 155, J057, J069, Z591, S294, S295, S265, S266 |

| Decompensated Cirrhosis |
|---|
| Hospital Diagnostic Codes | ICD-9: 456.0, 456.2, 572.2, 572.3, 572.4, 782.4, 789.5 |
| | ICD-10 : 185.0, I86.4, I98.20, I98.3, K721, K729, K76.6, K76.7, R17, R18 |
| Procedure Codes | CCI: 1.NA.13.BA-FA, 1.NA.13.BA-X7, 1.NA.13.BA-BD, 1.KQ.76GP-NR, 1.OT.52.HA |
| | CCP: 1006, 6691 |
| | OHIP: J057, Z591 |

| Death Codes | ICD-9: 5715, 5712, 5722, 5723, 5724, 5728, 4560 |
| | ICD-10: K721, K729, K703, K704, K717, K74, K746, K766, K767, I85X, I864, I982X, I983 |

| Hepatocellular Carcinoma |
|---|
| Physician Visit Code | 155 |
| Hospital Diagnostic Codes | ICD-9 : 155.0 |
| | ICD-10 : C22.0, C22.9, 81703, 81803 |
| Procedure Codes | OHIP: J069 |
| | CCI: 1.OA.59^^ |

| Death Codes | ICD-9: 1550 |
| | ICD-10: 81703, 81803 |

| Ontario Cancer Registry Codes | Morphology: 81703, 81723, 81733, 81743, 81753, 81803 |
| | Topography: C220 |

https://doi.org/10.1371/journal.pone.0201120.t001
We built a series of diagnostic algorithms for each outcome ranging from simple (e.g. a single physician visit code) to more complex. This was done to identify the most parsimonious algorithms that were also highly sensitive and/or specific. We aimed to utilize all available health administrative data, and include both hospital-based and outpatient physician visits in our algorithms. Data sources were searched for relevant codes ten years prior to two years following the date of last clinical assessment (up to March 31\textsuperscript{st}, 2014 for TCLD and August 31\textsuperscript{st}, 2013 for KHSC).

Cirrhosis algorithms ranged from cirrhosis codes only to combinations with codes for chronic liver disease or any complication (decompensation events, HCC or liver transplant). Algorithms were combined in such a way as to make them more sensitive (“or” combinations) or specific (“and” combinations). As physician visit codes were noted to be less specific, we aimed to increase specificity by combining two or more such codes with hospitalization codes. Decompensation algorithms included hospital diagnostic and death codes for portal hypertension, hepatorenal syndrome, jaundice, hepatic coma, hepatic failure, bleeding esophageal varices, gastric varices (bleeding not specified), and ascites. There were no physician visit codes available for decompensation events. We included procedure codes for endoscopy or insertion of Sengstaken tube for upper gastrointestinal bleeding, transjugular intrahepatic portosystemic shunt, and paracentesis. Since several of these procedures could occur for reasons other than decompensated cirrhosis (such as bleeding from an ulcer, or ascites secondary to an extra-hepatic malignancy), we tested combinations of procedure codes with a cirrhosis code from a physician visit.

Hepatocellular carcinoma algorithms ranged from simple (a single physician visit code) to more complex. We tested several combinations in order to optimise both sensitivity and specificity. We combined physician visit codes, hospital diagnostic codes, and cause of death codes. Further, we included procedure codes for radiofrequency ablation. Since this procedure can also be used to ablate tumours outside the liver (e.g., renal tumours), we combined ablation codes with an outpatient code for cirrhosis. Finally, we tested our results with and without anatomical and pathology codes from the Ontario Cancer Registry.

Analysis

Characteristics of patients in each validation cohort (HBV and HCV patients from TCLD, patients from KHSC) and 2-year mortality were described using univariate statistics. We tested the performance of administrative data algorithms for cirrhosis, decompensated cirrhosis, and HCC against the clinical reference standard. Each algorithm was evaluated for sensitivity, specificity, and overall accuracy. Performance measures were reported with their 95% confidence intervals. We did not report positive and negative predictive values as these parameters are highly dependent on prevalence in the reference population, making them poorly generalizable.

Measurement of algorithm performance was performed using SAS software, version 9.4 (SAS Institute Inc., Carey, NC). This project was approved by the Research Ethics Boards of UHN and KHSC.

Results

From April 2006 to March 2014, there were 3,502 patients with chronic HBV and 2,956 patients with chronic HCV seen at TCLD, of which 3,381 (97%) with HBV and 2,891 (98%) with HCV could be linked to administrative data. From May to August 2013, there were 444 patients seen at the KHSC Liver Clinic, of which 442 (99.5%) could be linked to administrative data. The most common causes of liver disease in KHSC patients were: HCV in 199 (45%),
NAFLD in 49 (11%), alcohol-related liver disease in 37 (8%), autoimmune liver disease in 36 (8%) and HBV infection in 34 (8%).

The characteristics of TCLD patients with HBV or HCV and all KHSC patients are presented in Table 2. The patients in the validation cohorts were, on average, middle-aged (median age 48–57 years), more likely to be male (57–60%), frequently low-income (26–28%), and mostly urban (74–99%). Many TCLD patients were either still consuming alcohol or had done so regularly in the past (37% of HBV patients, 64% of HCV patients). Few patients had been hospitalized in the previous year (1–16%), however many KHSC patients had visited the emergency department (44%). Most patients had not undergone a liver biopsy, but had been assessed clinically, including using non-invasive fibrosis testing (44–75%).

Of TCLD patients with HBV infection, 669 (19%) had cirrhosis, 99 (3%) had decompensated cirrhosis and 133 (4%) had hepatocellular carcinoma at any time during follow-up. Of the patients with HCV, 1,175 (40%), 335 (11%) and 167 (6%) had a clinical diagnosis of cirrhosis, decompensated cirrhosis, and HCC, respectively. For KHSC patients, this was 233 (53%), 93 (21%) and 25 (6%) for cirrhosis, decompensated cirrhosis, and HCC, respectively. By two years following their last clinic visit, 4% (n = 140) of TCLD patients with HBV, 8% (n = 243) of TCLD patients with HCV and 12% (n = 53) of KHSC patients had died.

At re-abstraction of charts belonging to HBV patients (n = 176) from TCLD, Cohen’s Kappa was 0.94 for cirrhosis, 1 for decompensated cirrhosis and 1 for hepatocellular carcinoma. For HCV patients (n = 148), Cohen’s kappa was 0.99 for cirrhosis, 0.92 for decompensated cirrhosis, and 1 for hepatocellular carcinoma. For KHSC patients (n = 20), there was complete agreement (kappa = 1) for the presence of cirrhosis, decompensated cirrhosis and hepatocellular carcinoma.

Table 2. Characteristics of patients in the three validation cohorts, at the time of last clinical follow-up. HBV = Hepatitis B Virus infection, HCV = Hepatitis C virus infection, TCLD = Toronto Centre for Liver Disease, KHSC = Kingston Health Sciences Centre, NA = not available.

|                        | HBV Patients, TCLD (n = 3,381) | HCV Patients, TCLD (n = 2,891) | KHSC Patients (n = 442) |
|------------------------|---------------------------------|---------------------------------|-------------------------|
| Age in years, median (IQR) | 48 (37–57)                      | 55 (47–61)                      | 57 (49–62)              |
| Sex Female, n (%)      | 1,447 (43)                      | 1,154 (40)                      | 180 (41)                |
| Income quintile, n(%)  | 916 (27)                        | 742 (26)                        | 123 (28)                |
| 1- Lowest              | 767 (23)                        | 557 (19)                        | 90 (20)                 |
| 2                      | 625 (19)                        | 513 (18)                        | 82 (19)                 |
| 3                      | 573 (17)                        | 539 (19)                        | 79 (18)                 |
| 4                      | 476 (14)                        | 517 (18)                        | 62 (14)                 |
| 5- Highest             |                                 |                                 |                         |
| Rural, n (%)           | 19 (1)                          | 138 (5)                         | 115 (26)                |
| Alcohol consumption, n (%) |                   |                                 |                         |
| Currently drinking     | 847 (25)                        | 853 (30)                        | N/A                     |
| Never Used             | 2,115 (63)                      | 1,004 (35)                      |                         |
| Stopped drinking       | 402 (12)                        | 993 (34)                        |                         |
| Urgent hospitalization in year prior, n(%) | 43 (1)                          | 108 (4)                         | 71 (16)                 |
| ER visit in year prior, n(%) | 248 (7)                          | 502 (17)                        | 194 (44)                |
| Fibrosis Assessment, n (%) | 2,372 (70)                      | 1,261 (44)                      | 328 (74)                |
| Non-invasive score or clinical | 1,009 (30)                      | 1,630 (57)                      | 114 (26)                |
| Liver biopsy           |                                 |                                 |                         |
| Fibrosis Stage, n (%)  |                                 |                                 |                         |
| F0                     |                                 |                                 | 62 (14)                 |
| F1                     |                                 |                                 | 43 (10)                 |
| F2                     |                                 |                                 | 68 (15)                 |
| F3                     |                                 |                                 | 36 (8)                  |
| F4                     |                                 |                                 | 233 (53)                |

https://doi.org/10.1371/journal.pone.0201120.t002
Algorithms for cirrhosis

A single physician visit code for cirrhosis was highly sensitive (98% for HBV, 99% for HCV and KHSC group, Table 3), while a single hospital diagnostic code for cirrhosis was specific (96% for HBV, 91% for HCV, 92% for KHSC group). Greatest specificity was achieved using a combination of a chronic liver disease code, a complication code and either 2+ physician visit codes or a single hospital diagnostic code (algorithm 13: 98% in HBV, 95% in HCV, 97% for KHSC cohort). A single hospital diagnosis code had the greatest overall accuracy in all three groups (HBV 88%, 95% CI 87–90%, HCV 84%, 95% CI 83–85%, KHSC 87%, 95% CI 84–90%).

Algorithms for decompensated cirrhosis

The algorithm with the greatest sensitivity (88% in HBV, 92% in HCV, 99% in KHSC group), was one physician visit code for cirrhosis and any of the following: one hospital diagnostic code occurs on at least one date; 2+ = code occurs on at least two separate dates.

| Algorithm | HBV Patients, TCLD (n = 669) | Sens (95%CI), % | Spec (95%CI), % |
|-----------|-------------------------------|----------------|----------------|
| 1         | 1+ Hospital Diagnosis CIRRHOSIS | 57 (53–60)     | 96 (96–97)     |
| 2         | 1+ Hospital Diagnosis CIRRHOSIS or 1+ COMPLICATION | 67 (63–70) | 90 (89–92)     |
| 3         | 1+ Physician Visit CIRRHOSIS | 98 (96–99) | 78 (76–80) |
| 4         | 1+ Physician Visit or 1+ Hospital Diagnosis CIRRHOSIS | 98 (97–99) | 77 (75–78) |
| 5         | 1+ Physician Visit or 1+ Hospital Diagnosis CIRRHOSIS and 1+ CLD | 73 (70–77) | 88 (87–89) |
| 6         | 1+ Physician Visit or 1+ Hospital Diagnosis CIRRHOSIS or 1+ COMPLICATION | 98 (97–99) | 74 (72–0.75) |
| 7         | 1+ Physician Visit or 1+ Hospital Diagnosis CIRRHOSIS and 1+ COMPLICATION | 46 (43–50) | 97 (96–97) |
| 8         | 1+ Physician Visit or 1+ Hospital Diagnosis CIRRHOSIS and 1+ COMPLICATION and 1+ CLD | 40 (37–44) | 98 (97–98) |
| 9         | 2+ Physician Visit or 1+ Hospital Diagnosis CIRRHOSIS | 94 (92–95) | 85 (83–86) |
| 10        | 2+ Physician Visit or 1+ Hospital Diagnosis CIRRHOSIS and 1+ CLD | 72 (68–75) | 91 (90–92) |
| 11        | 2+ Physician Visit or 1+ Hospital Diagnosis CIRRHOSIS or 1+ COMPLICATION | 94 (92–96) | 81 (79–82) |
| 12        | 2+ Physician Visit or 1+ Hospital Diagnosis CIRRHOSIS and 1+ COMPLICATION | 46 (42–50) | 97 (97–98) |
| 13        | 2+ Physician Visit or 1+ Hospital Diagnosis CIRRHOSIS and 1+ COMPLICATION and 1+ CLD | 40 (36–44) | 98 (98–99) |

https://doi.org/10.1371/journal.pone.0201120.t003
For the HBV and HCV groups, this algorithm also had the highest overall accuracy (95%, CI 94–96% in HBV group; 88%, CI 87–90% in HCV group). The most specific algorithm was one physician visit code for cirrhosis and one hospital diagnostic code for decompensation (95% in HBV, 88% in HCV, 79% in the KHSC group); this was also the algorithm with the greatest overall accuracy in the KHSC group (83%, 95% CI 80–87%). After excluding a single hospital diagnostic code which accounted for many false positives (ICD-10 code for portal hypertension K766), the specificity of this algorithm was further improved to 98% in HBV, 95% in HCV, and 89% in KHSC groups.

Algorithms for hepatocellular carcinoma

The most sensitive algorithm for HCC was any of: two or more physician visit codes, a hospital diagnostic code, a death code or a procedure code (Table 4). For the HBV and HCV groups, this algorithm also had the highest overall accuracy (95%, CI 94–96% in HBV group; 88%, CI 87–90% in HCV group). The most specific algorithm was one physician visit code for cirrhosis and one hospital diagnostic code for decompensation (95% in HBV, 88% in HCV, 79% in the KHSC group); this was also the algorithm with the greatest overall accuracy in the KHSC group (83%, 95% CI 80–87%). After excluding a single hospital diagnostic code which accounted for many false positives (ICD-10 code for portal hypertension K766), the specificity of this algorithm was further improved to 98% in HBV, 95% in HCV, and 89% in KHSC groups.

Discussion

We identified sensitive and specific algorithms for the identification of cirrhosis, decompensated cirrhosis and HCC in patients with HBV or HCV infection, and confirmed these findings in patients with known liver disease of other causes. While identifying an algorithm that combines optimal sensitivity and specificity is desired, this is not always possible, and thus...
different criteria can be used depending on the study purpose. If the goal is to identify a cohort of individuals with a condition, highly specific criteria are preferable as this maximizes the likelihood that included individuals indeed have the target condition. In contrast, when the condition is the outcome variable in a study, a more sensitive definition can be used to prevent underestimation.

In our study, the tradeoff between sensitivity and specificity was most notable for cirrhosis. In particular, outpatient physician claims for cirrhosis were very sensitive but not specific. We believe this is because, until recently, physicians in Ontario could receive additional payment for a visit with a diagnosis of cirrhosis. On this basis, physicians may have been more likely to correctly list this diagnosis on their billing claim, or even to “up-code” patients with borderline clinical features consistent with cirrhosis. Although algorithms for cirrhosis and decompensated cirrhosis demonstrated inverse relationships between sensitivity and specificity, we were able to identify an algorithm for HCC that was both highly sensitive and specific.

Hospitalization diagnostic data are entered by trained chart abstractors and may be more reliable than outpatient physician billing claims. Hospitalization codes were more specific than physician visit codes for the target conditions in our study. The only exception was the in-

### Table 5. Administrative data algorithms used to identify patients with hepatocellular carcinoma.

Number of patients in each group with hepatocellular carcinoma (reference outcome) indicated (n) at top of column. HBV = Hepatitis B Virus infection, HCV = Hepatitis C virus infection, TCLD = Toronto Centre for Liver Disease, KHSC = Kingston Health Sciences Centre, CLD = Chronic Liver Disease, Sens = sensitivity, Spec = specificity, CI = confidence interval. 1+ = code occurs on at least one date; 2+ = code occurs on at least two separate dates.

| Algorithm | HBV patients, TCLD (n = 133) | HCV patients, TCLD (n = 167) | KHSC patients (n = 25) |
|-----------|-----------------------------|-----------------------------|-----------------------|
|           | Sens (95%CI), %              | Sens (95%CI), %              | Sens (95%CI), %        |
|           | Spec (95%CI), %              | Spec (95%CI), %              | Spec (95%CI), %        |
| 1         | 1+ Physician Visit           | 83 (76–89)                  | 84 (79–90)            |
|           |                             | 95 (94–96)                  | 85 (84–86)            |
| 2         | 2+ Physician Visit           | 74 (66–81)                  | 75 (69–82)            |
|           |                             | 99 (99–99)                  | 96 (96–97)            |
| 3         | 1+ Hospital Diagnosis or 1+ Death Code | 80 (62–78)                  | 78 (72–85)            |
|           |                             | 100 (99–100)                | 99 (99–99)            |
| 4         | Diagnosis in Ontario Cancer Registry | 81 (75–88)                  | 82 (76–88)            |
|           |                             | 99 (99–100)                | 99 (99–99)            |
| 5         | Diagnosis in Ontario Cancer Registry or 1+ Hospital Diagnosis or 1+ Death Code | 87 (82–93)                  | 92 (87–96)            |
|           |                             | 99 (99–100)                | 99 (98–99)            |
| 6         | 1 Physician Visit CIRRHOSIS and 1+ Procedure | 46 (37–54)                  | 58 (51–66)            |
|           |                             | 100 (99–100)                | 100 (99–100)          |
| 7         | 1+ Hospital Diagnosis or 1+ death code or 1+ Physician Visit | 88 (82–94)                  | 90 (85–94)            |
|           |                             | 95 (94–96)                  | 85 (83–86)            |
| 8         | 1+ Hospital Diagnosis or 1+ Death Code or 2+ Physician Visits | 82 (75–89)                  | 86 (81–92)            |
|           |                             | 99 (98–99)                  | 96 (95–97)            |
| 9         | 1+ Hospital Diagnosis or 1+ Death Code or 2+ Physician Visits or (1+ Physician Visit CIRRHOSIS and 1+ Procedure) | 96 (92–99)                  | 97 (94–100)            |
|           |                             | 98 (98–99)                  | 96 (95–96)            |
| 10        | 1+ Hospital Diagnosis or 1+ Death Code or 2+ Physician Visit or 1+ Physician Visit CIRRHOSIS and 1+ Procedure or Diagnosis in Ontario Cancer Registry | 97 (94–1.00)                  | 97 (94–100)            |
|           |                             | 98 (98–99)                  | 96 (95–96)            |
|           |                             |                             | 96 (88–100)           |
|           |                             |                             | 93 (91–96)            |

https://doi.org/10.1371/journal.pone.0201120.t005
hospital diagnostic code for portal hypertension, which falsely identified several patients as having decompensated cirrhosis. Non-cirrhotic portal hypertension is covered by this diagnostic code, as is portal hypertensive gastropathy, a condition diagnosed based on non-specific endoscopic findings, raising the possibility that it might be over-diagnosed. These conditions may explain this diagnostic code’s lack of specificity.

Overall, algorithms to identify complications in HBV-infected patients tended to be less sensitive but more specific than the same algorithms, when used in the HCV or KHSC groups. The difference was largest for algorithms identifying decompensated cirrhosis. We suspect that this can be explained by lower rates of hospital-based care for HBV-infected patients, who had fewer previous hospitalizations and emergency department visits than the other two groups. Substance use and mental health issues may contribute to greater healthcare usage by patients with HCV infection.[29] The range in results obtained in our study underscores the importance of testing administrative algorithms in several different patient populations. Although sensitivity, specificity and accuracy varied across patient groups, the most sensitive, specific and accurate algorithms in each group remained the same or very similar.

Previous studies have validated administrative data algorithms for cirrhosis, decompensation and HCC in U.S. populations. As we have done, others have also included codes for decompensation events as part of their administrative data definition of cirrhosis, or have combined HCC codes with cirrhosis codes to improve algorithm performance.[11, 12] In one validation study of cirrhosis definitions, sensitivity using multiple codes was achieved at the expense of low specificity, similar to what we observed.[15] While prior studies were limited to ICD-9 codes, ours is the first study to test the performance of ICD-10 codes for the detection of liver disease outcomes. U.S. hospital data have been coded using ICD-10 since 2015.[19] The algorithms and codes we provide can now be used to identify liver disease outcomes using Canadian, U.S. and European health administrative data, as well as any data coded in the widely-used ICD-9 or ICD-10 systems.

Strengths of our study are the inclusion of inpatient and outpatient data, as well as procedures, cause of death and pathology results, all tested against a physician-confirmed reference standard. Further, we included a large number of individuals in three patient cohorts from two institutions, with different etiologies of liver disease. The consistency of the relative ranking of algorithms across patient groups suggests that the most sensitive or specific algorithms can be applied broadly to all patients with known liver disease. Finally, our study results are comprehensive as they can be used to identify all three important clinical outcomes in patients with chronic liver disease.

Our study has several limitations. First, the existence of a premium payment for physician visits in Ontario may indicate that cirrhosis billing codes were claimed more often in our study setting than they would be elsewhere. Without a premium code, one might expect that a single physician visit code for cirrhosis would have greater specificity and lower sensitivity than measured in our study. Second, the study of hepatology clinic patients has advantages and disadvantages. One advantage is that specialist physicians with expertise in evaluating patients for liver outcomes can be expected to have greater diagnostic accuracy than generalist physicians. However, patients seen in a specialist clinic are likely to have more severe disease, which can lead to spectrum bias.[30] We would expect this to be most relevant for cirrhosis, where there is a clear spectrum of disease ranging from asymptomatic to severely symptomatic, decompensated cirrhosis.

If patients in a hepatology clinic are sicker than the general population, we would expect our measured sensitivity to be higher, and specificity to be lower, than they would be in the general population. Our results are valid for patients like those seen in a hepatology clinic: that is, patients with diagnosed liver diseases. Therefore, studies validating health administrative
data codes against patient data abstracted from community hospitals, primary care clinics, or the general population would be an important contribution to the literature. In the general population, our specific algorithms can be used to define cohorts, however they may not be sensitive enough to identify all cases, and as such may underestimate outcome rates. An additional caveat is that some decompensation codes (e.g. ascites) can occur without liver disease. In order to avoid misclassification when applied to the general population, these codes should be combined with liver disease or cirrhosis codes.

**Conclusions**

Liver diseases such as chronic HBV and HCV infection are a major cause of mortality worldwide. Administrative data can be used to identify large groups of patients with complications of chronic liver disease. We have reported the operating characteristics of algorithms for cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma, using ICD-9 and ICD-10 health administrative data. We have identified sensitive and specific algorithms for each of these clinical conditions, which can be used to define patient cohorts or detect clinical outcomes. Our results will facilitate research into the adequacy of screening and treatment outcomes for patients with chronic HBV, HCV, or other liver diseases. Future research should test the performance of health administrative data codes in the general population.

**Acknowledgments**

This work was supported by a grant from the Physician Services Incorporated (PSI) Foundation and by the Institute for Clinical Evaluative Sciences (ICES), which is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care (MOHLTC). The study sponsors did not participate in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review or approval of the manuscript; or the decision to submit the manuscript for publication.

LLS is supported by a CIHR Fellowship Award. JAF is supported by a Southeastern Ontario New Clinician Scientist Award. JCK is supported by a CIHR New Investigator Award and a University of Toronto Department of Family & Community Medicine Investigator Award.

The opinions, results, and conclusions reported in this paper are those of the authors and are independent from the funding sources. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI) and by Cancer Care Ontario (CCO). However, the analyses, conclusions, opinions, and statement expressed herein are those of the authors, and not necessarily those of CIHI or CCO. No endorsement by ICES, MOHLTC, CIHI, or CCO is intended or should be inferred.

**Author Contributions**

**Conceptualization:** Lauren Lapointe-Shaw, Jordan J. Feld, Jennifer A. Flemming.

**Data curation:** Lauren Lapointe-Shaw, Firass Georgie, David Carlone, Orlando Cerocchi, Hannah Chung, Yvonne Dewit, Laura Holder, Jennifer A. Flemming.

**Formal analysis:** Lauren Lapointe-Shaw, Firass Georgie, Hannah Chung, Yvonne Dewit, Laura Holder, Jennifer A. Flemming.

**Funding acquisition:** Lauren Lapointe-Shaw, Jordan J. Feld, Jennifer A. Flemming.

**Investigation:** Lauren Lapointe-Shaw, Firass Georgie, David Carlone, Orlando Cerocchi, Hannah Chung, Yvonne Dewit, Laura Holder, Jennifer A. Flemming.
Methodology: Lauren Lapointe-Shaw, Jordan J. Feld, Jeffrey C. Kwong, Beate Sander, Jennifer A. Flemming.

Project administration: Lauren Lapointe-Shaw.

Resources: Lauren Lapointe-Shaw, Jeffrey C. Kwong, Jennifer A. Flemming.

Supervision: Jennifer A. Flemming.

Validation: Firass Georgie.

Writing – original draft: Lauren Lapointe-Shaw.

Writing – review & editing: Lauren Lapointe-Shaw, Firass Georgie, David Carlone, Orlando Cerocchi, Hannah Chung, Yvonne Dewit, Jordan J. Feld, Laura Holder, Jeffrey C. Kwong, Beate Sander, Jennifer A. Flemming.

References

1. Naghavi M, Abajobir AA, Abbafati C, Abbas KM, Abd-Allah F, Abersa SF, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 390(10100):1151–210. https://doi.org/10.1016/S0140-6736(17)32152-9 PMID: 28919116

2. Ryerson AB, Eheman CR, Altekruse SF, Ward JW, Jemal A, Sherman RL, et al. Annual Report to the Nation on the Status of Cancer, 1975–2012, featuring the increasing incidence of liver cancer. Cancer. 2016; 122(9):1312–37. Epub 2016/03/10. https://doi.org/10.1002/cncr.29936 PMID: 26959385; PubMed Central PMCID: PMCPMC4840031.

3. Rotermann M, Langlois K, Andonov A, Trubnikov M. Seroprevalence of hepatitis B and C virus infections: Results from the 2007 to 2009 and 2009 to 2011 Canadian Health Measures Survey. 2013.

4. Denniston MM, Kleven RM, McQuillan GM, Jiles RB. Awareness of infection, knowledge of hepatitis C, and medical follow-up among individuals testing positive for hepatitis C: National Health and Nutrition Examination Survey 2001–2008. Hepatology. 2012; 55(6):1652–61. Epub 2012/01/04. https://doi.org/10.1002/hep.25556 PMID: 22213025; PubMed Central PMCID: PMCPMC4586034.

5. Centers for Disease Control and Prevention. Implementation of Newborn Hepatitis B Vaccination—Worldwide, 2006. Morbidity and Mortality Weekly Report. 2008; 57(46):1249–52. PMID: 19023261

6. Centers for Disease Control and Prevention. Newborn Hepatitis B Vaccination Coverage Among Children Born January 2003—June 2005—United States. Morbidity and Mortality Weekly Report. 2008; 57(30):825–8. PMID: 1868021

7. Veldt BJ, Heathcote EJ, Wedemeyer H, Reichen J, Hofmann WP, Zeuzem S, et al. Sustained virologic response and clinical outcomes in patients with chronic hepatitis C and advanced fibrosis. Ann Intern Med. 2007; 147(10):677–84. Epub 2007/11/21. PMID: 18025443.

8. Swain MG, Lai MY, Shiffman ML, Cooksley WG, Zeuzem S, Dieterich DT, et al. A sustained virologic response is durable in patients with chronic hepatitis C treated with peginterferon alfa-2a and ribavirin. Gastroenterology. 2010; 139(5):1593–601. Epub 2010/07/20. https://doi.org/10.1053/j.gastro.2010.07.009 PMID: 20637202.

9. Asselah T, Marcellin P, Schinazi RF. Treatment of hepatitis C virus infection with direct-acting antiviral agents: 100% cure? Liver international: official journal of the International Association for the Study of the Liver. 2018; 38 Suppl 1:7–13. Epub 2018/02/11. https://doi.org/10.1111/liv.13673 PMID: 29427484.

10. Maylin S, Martinot-Peignoux M, Moucair R, Boyer N, Ripault MP, Cazals-Hatem D, et al. Eradication of hepatitis C virus in patients successfully treated for chronic hepatitis C. Gastroenterology. 2008; 135(3):821–9. Epub 2008/07/03. https://doi.org/10.1053/j.gastro.2008.05.044 PMID: 18593587.

11. Goldberg D, Lewis J, Halpern S, Weiner M, Lo Re V 3rd. Validation of three coding algorithms to identify patients with end-stage liver disease in an administrative database. Pharmacoepidemiol Drug Saf. 2012; 21(7):765–9. Epub 2012/06/08. https://doi.org/10.1002/pds.3200 PMID: 22674685; PubMed Central PMCID: PMCPmc4267226.

12. Goldberg DS, Lewis JD, Halpern SD, Weiner MG, Lo Re V 3rd. Validation of a coding algorithm to identify patients with hepatocellular carcinoma in an administrative database. Pharmacoepidemiol Drug Saf. 2013; 22(1):103–7. Epub 2012/11/06. https://doi.org/10.1002/pds.3367 PMID: 23124932; PubMed Central PMCID: PMCPmc3540172.
13. Kramer JR, Davila JA, Miller ED, Richardson P, Giordano TP, El-Serag HB. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. Aliment Pharmacol Ther. 2008; 27(3):274–82. https://doi.org/10.1111/j.1365-2036.2007.03572.x PMID: 17996017.

14. Lo Re V 3rd, Lim JK, Goetz MB, Tate J, Bathulapalli H, Klein MB, et al. Validity of diagnostic codes and liver-related laboratory abnormalities to identify hepatic decompensation events in the Veterans Aging Cohort Study. Pharmacoeconomics Drug Saf. 2011; 20(7):689–99. Epub 2011/06/01. https://doi.org/10.1002/pdc.2148 PMID: 21626605; PubMed Central PMCID: PMC331229.

15. Nehra MS, Ma Y, Clark C, Amarasingham R, Rockey DC, Singh AG. Use of administrative claims data for identifying patients with cirrhosis. J Clin Gastroenterol. 2013; 47(5):e50–4. Epub 2012/10/24. https://doi.org/10.1097/MCG.0b013e318268bd2f PMID: 23090041; PubMed Central PMCID: PMC3556340.

16. Niu B, Forde KA, Goldberg DS. Coding algorithms for identifying patients with cirrhosis and hepatitis B or C virus using administrative data. Pharmacoeconomics Drug Saf. 2015; 24(1):107–11. Epub 2014/10/23. https://doi.org/10.1002/pdc.3721 PMID: 25335773; PubMed Central PMCID: PMC4293241.

17. Sada Y, Hou J, Richardson P, El-Serag H, Davila J. Validation of Case Finding Algorithms for Hepatocellular Cancer From Administrative Data and Electronic Health Records Using Natural Language Processing. Med Care. 2016; 54(2):e9–14. https://doi.org/10.1097/MLR.0b013e3182a30373 PMID: 23929405; PubMed Central PMCID: PMCPM612083 [Available on 02/01/17].

18. Canadian Institute for Health Information. Discharge Abstract Database Metadata 2017 [cited 2017 November 30]. Available from: https://www.cihi.ca/en/discharge-abstract-database-metadata.

19. Centers for Disease Control and Prevention. International Classification of Diseases, (ICD-10-CM/PCS) Transition—Background 2015 [cited 2018 January 26]. Available from: https://www.cdc.gov/nchs/icd/icd10cm_pcs_background.htm.

20. Thein HH, Campitelli MA, Yeung LT, Zaheen A, Yoshida EM, Earle CC. Improved Survival in Patients with Viral Hepatitis-Induced Hepatocellular Carcinoma Undergoing Recommended Abdominal Ultrasound Surveillance in Ontario: A Population-Based Retrospective Cohort Study. PLoS One. 2015; 10(9):e0138907. Epub 2015/09/24. https://doi.org/10.1371/journal.pone.0138907 PMID: 26398404; PubMed Central PMCID: PMC4580446.

21. Tonelli M, Wiebe N, Fortin M, Guthrie B, Hemmelgarn BR, James MT, et al. Methods for identifying 30 chronic conditions: application to administrative data. BMC Med Inform Decis Mak. 2015; 15:31. Epub 2015/04/18. https://doi.org/10.1186/s12911-015-0155-5 PMID: 25886580; PubMed Central PMCID: PMCPMC4415341.

22. Institute for Clinical Evaluative Sciences. Improving Healthcare Data in Ontario. Toronto: 2005.

23. Shah BR, Hux JE, Laupacis A, Zinman B, Cauch-Dudek K, Booth GL. Administrative data algorithms can describe ambulatory physician utilization. Health Serv Res. 2007; 42(4):1783–96. Epub 2007/07/06. https://doi.org/10.1111/j.1475-6773.2006.00681.x PMID: 17610448; PubMed Central PMCID: PMCPM455277.

24. Juurlink DN, Preyra C, Croxford R, Chong A, Austin PC, Tu JV, et al. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto, Ontario: Institute for Clinical Evaluative Sciences, 2006.

25. Iron K, Zagorski BM, Sykora K, Manuel DG. Living and Dying in Ontario: An Opportunity for Improved Health Information. Toronto: Institute for Clinical Evaluative Sciences, 2008.

26. Hall S, Schulze K, Groome P, Mackillop W, Holowaty E. Using cancer registry data for survival studies: the example of the Ontario Cancer Registry. J Clin Epidemiol. 2006; 59(1):67–76. Epub 2005/12/20. https://doi.org/10.1016/j.jclinepi.2005.05.001 PMID: 16360563.

27. Ministry of Health and Long Term Care. Schedule of Benefits. Toronto, Ontario: Province of Ontario; 2013.

28. Physician Services Committee. Chronic Disease Assessment Premium: Code E078 http://www.ontla.on.ca/library/repository/ser/274754/2007v5no02.pdf. Legislative Assembly of Ontario; 2007 [cited 2018 June 19].

29. Rifai MA, Gleason OC, Sabouni D. Psychiatric Care of the Patient With Hepatitis C: A Review of the Literature. Prim Care Companion J Clin Psychiatry. 2010; 12(6):PCC.09r008777. https://doi.org/10.4088/PCC.09r008777w PubMed PMID: PMC3067894. PMID: 21493439

30. Montori VM, Wyer P, Newman TB, Keitz S, Guyatt G. Tips for learners of evidence-based medicine: 5. The effect of spectrum of disease on the performance of diagnostic tests. CMAJ. 2005; 173(4):385–90. Epub 2005/08/17. https://doi.org/10.1503/cmaj.1051666 PMID: 16103515; PubMed Central PMCID: PMCPMC1188226.