Reply to: "Pitfalls in measuring temporal trends for late diagnosis of viral hepatitis"

Considerations for studying trends in late diagnosis of hepatitis C virus and its liver complications

To the Editor:

By the year 2030, the Global Health Sector Strategy on viral hepatitis aims to reduce mortality by 65% and new infections by 90%. Reaching these goals will require diagnosing 90% of people living with HCV and treating 80% of those diagnosed. However, since HCV infection remains asymptomatic until late stage complications manifest, diagnosis rates are concerningly low in many countries. Screening programs are intended to diagnose individuals in the asymptomatic phase and reduce late stage HCV diagnosis when decompensated cirrhosis (DC) or hepatocellular carcinoma (HCC) has already occurred. Monitoring trends in late diagnosis of HCV and its liver complications is an important indicator to evaluate the success of screening efforts and progress towards the strategy's goals.

Limited research

There is a dearth of research measuring late diagnosis of HCV and its complications (DC/HCC) and a lack of standardized approaches/definitions (Table 1). While a consensus definition for late presentation to medical care for HBV/HCV was published in 2017,[1] it did not specifically address late diagnosis and lacked specific guidance for researchers seeking to measure this outcome (*e.g.* a time window for detection of liver complications).

A key aspect differentiating late diagnosis studies is the selection of either HCV-related liver complications (*e.g.* DC, HCC) (Approach 1) or HCV diagnosis (Approach 2) as the anchor point around which the outcome is assessed (Table 1). The limitations of the former and strengths of the latter were highlighted in a recent letter by Lapointe-Shaw *et al.*[2] These discussions are important for moving towards a more standardized approach to measuring late diagnosis.

Two different approaches

The study approach and interpretation of findings depend on the question being asked. In using DC/HCC as the anchor point and looking at the timing of HCV diagnosis in relation to this point – as done by our research team and others[3,4] – the question asked is: what proportion of DC/HCC disease progression could potentially have been avoided by earlier diagnosis of HCV? By definition, this approach excludes both 1) HCV diagnoses without record of a complication and 2) DC/HCC cases among HCV-undiagnosed individuals.

In our study, we found an overall decrease in this outcome from 1992 to 2011 in British Columbia (BC), suggesting that HCV screening efforts have improved.[3] Our analysis updated to 2015 is in Fig. 1A and shows a decrease in earlier years but a relatively stable proportion of late diagnoses in more recent years.

As pointed out by Lapointe-Shaw *et al.*, assessing trends over time using Approach 1 is biased by the longer length of follow-up (*i.e.* 'look-back' time to identify an HCV-positive test) for individuals diagnosed with DC/HCC in calendar years more distant from 1990, when HCV testing was introduced in BC. However, as we see in the Fig. 1A, there is stabilization in late diagnoses since 2009, suggesting that the shrinkage effect related to increased 'look-back' length may not be an issue in recent years. Further in-depth analyses are required to understand the impact of length of follow-up on estimates using this approach.

The alternative approach adopted by Lapointe-Shaw and others[2,5,6] uses HCV diagnosis as the anchor and identifies complications within a specified time window around this date. The question asked here is broader: what proportion of all HCV cases are diagnosed at a late stage? Uneven 'look-back' time is not an issue with this approach, as early diagnoses are defined by the absence of the outcome, rather than the presence as in Approach 1. However, Approach 2 may be problematic because not all individuals diagnosed with HCV are assessed for complications (discussed further below).

Lapointe-Shaw *et al.* compared these 2 approaches using Ontario data and noted differences in trends over time, which in itself is not necessarily surprising given the different – albeit related – questions being asked. Using our BC data source, we also note similar differences: an overall decreasing trend using Approach 1 which stabilized in 2009 (Fig. 1A) and increasing trend using Approach 2 (dark blue solid line in Fig. 1B).

Other considerations

There are some additional considerations for studying late diagnosis, particularly in administrative healthcare databases.

Decompensated cirrhosis and late stage liver disease

DC is one of the conditions used to define late stage liver disease in late diagnosis studies. In the late presentation consensus definition,[1] DC is defined as one or more of jaundice, hepatic encephalopathy, clinically detectable ascites or variceal bleeding. However, conditions used to define DC and late stage liver disease vary across studies published to date (Table S2), limiting comparability. Further, the inclusion of conditions that are often asymptomatic (*e.g.* portal vein hypertension, non-bleeding varices, compensated cirrhosis), as done in some studies, may bias trends over time (see 'Assessment for complications' section below).

Assessment for complications

Lack of assessment for complications after HCV diagnosis may lead to misclassification with Approach 2 (*i.e.*, some individuals classified as an early diagnosis may have had undiagnosed liver complications close to their HCV diagnosis date). Detection of asymptomatic or mildly symptomatic complications, such as HCC and some cirrhosis-related conditions, require an individual to be linked to care and screened/assessed appropriately. For example, guidelines generally recommend HCV-diagnosed individuals receive ultrasound screening pre-treatment and then at 6-month intervals for those with cirrhosis. Therefore, the increasing trend in Fig. 1B (dark blue solid line) could be partly due to improvements in linkage to care and/or screening for complications over time.

Keywords: Hepatitis C virus; Diagnosis; Decompensated cirrhosis; Hepatocellular carcinoma; Screening.

Table 1. Summary of select administrative health care studies measuring late diagnosis of HCV or its liver complications.

	Approach 1 (anchor = liver complication)		Approach 2 (anchor = HCV diagnosis)			
	Samji *et al.*[3] Alavi *et al.*[4] current paper	Lapointe-Shaw *et al.*[2]	Current paper	Chirikov *et al.*[6]	Moorman *et al.*[5]	Lapointe-Shaw *et al.*[2]
Anchor	DC, HCC	DC, HCC, liver transplant	HCV diagnosis	HCV diagnosis	HCV diagnosis	HCV diagnosis
Outcome	HCV diagnosis	HCV diagnosis	DC, HCC	CC, DC, HCC, liver transplant	DC, HCC, liver transplant	DC, HCC, liver transplant
Time window	2 years before to any time after	2 years before to six months after	Any time before to 2 years after	6 months before to 3 months after	Any time before to 1 year after	6 months before to 2 years after

CC, compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma. Time window = length of time around the anchor during which presence of the outcome indicates late diagnosis.

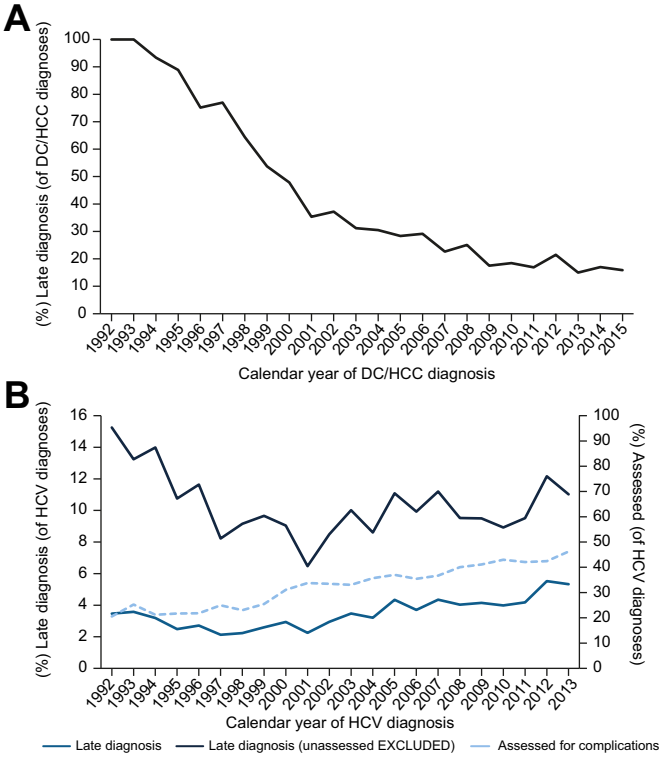

Fig. 1. A comparison of 2 approaches to measuring late diagnosis in British Columbia, Canada. (A) Prevalence of late diagnosis using Approach 1 (Late diagnosis = HCV diagnosis within 2 years before to any time after DC/HCC). (B) Prevalence of late diagnosis using Approach 2 (Late diagnosis = DC/HCC any time before to within 2 years after HCV diagnosis) and prevalence of ultrasound assessment for liver complications (record of abdominal ultrasound within 2 years after HCV diagnosis). Data source = BC Hepatitis Testers Cohort (Table S1 contains more information on data source). DC, decompensated cirrhosis. HCC, hepatocellular carcinoma. Years 2014 and 2015 removed from (B) to avoid truncation bias.

Exclusion of unassessed individuals from late diagnosis analyses may be important to obtain unbiased absolute estimates and trends over time, yet to our knowledge has not been done in other studies. Exclusion is difficult for several reasons. First, many assessment tests (*e.g.* ultrasound, fibroscan, endoscopy *etc.*) are used for both screening and diagnostic purposes, and the intended use is difficult to tease apart in administrative data. Second, DC conditions are generally severe and mostly diagnosed through hospitalization rather than asymptomatic screening. Finally, exclusion of unassessed individuals could introduce bias if their risk of late diagnosis differs to those assessed. Of note, removal of unassessed individuals is not necessary or possible for Approach 1, as the research question specifically relates to the proportion of *diagnosed* DC/HCC.

In further analysis of our data, we found that the proportion of individuals receiving an abdominal ultrasound within 2 years after HCV diagnosis (light blue dotted line in Fig. 1B) follows a similar trend as late diagnoses in Approach 2 (dark blue solid line in Fig. 1B). While this suggests improved screening could be partly driving late diagnosis trends, the inverse could be true (*i.e.*, increased late diagnoses may be necessitating more frequent diagnostic ultrasound tests to confirm late stage disease). When unassessed individuals were excluded, the burden of late diagnoses was higher and the trend over time more variable (black solid line in Fig. 1B).

Our crude exploratory analysis suggests that unassessed individuals warrant consideration when interpreting trends using Approach 2. We are currently working to create a more comprehensive assessment measure that includes other liver function and fibrosis tests (*e.g.* endoscopy), in addition to abdominal ultrasounds.

Death

Misclassification may also arise if individuals die from HCV-related liver complications before the complication is diagnosed by a physician. Use of death data to identify DC and HCC may therefore be important, but was not done in our original analysis or in other studies (with the exception of Lapointe-Shaw *et al.*[2,7]). In the current analysis described in this letter, inclusion of death codes did not affect trends but did increase the prevalence of late diagnosis in Approach 2 by 0.1–0.4% absolute percentage points (data not shown).

Time window

Time window around the anchor point also varies across studies (Table 1). Decisions on window length must consider a variety of factors, including the time it can take to diagnose complications (*e.g.* delays related to linkage to care or diagnostic machine wait times). Too short of a time window may be unfeasible and lead to misclassification. A key consideration for window length in Approach 1 is the time needed to prevent development of complications through medical intervention.

A difference between our and Lapointe-Shaw *et al.*'s analysis is the window length for detection of complications prior to HCV diagnosis (anytime *vs.* 6 months, respectively). Use of an open cut-off in our study may increase the potential for

truncation bias, while 6 months may be too short. Using Lapointe-Shaw *et al.*'s definition with our data did not change overall conclusions regarding trends over time for either approach, but it did decrease prevalence by 0–0.6% absolute percentage points in Approach 2 (data not shown).

Immigration

Immigrants from high prevalence countries have a higher risk of HCV infection, but can be difficult to identify in administrative data without linkage to immigration records. These individuals may be important to consider for stratification in analyses or potential exclusion. Some of these individuals have been infected for a long time prior to immigration and present with late stage disease in Canada. Therefore, late diagnosis may be indicative of poor screening for HCV in countries outside of Canada. However, screening of immigrants from high prevalence countries is usually poor and many have a very long interval (10–15 years) between arrival and HCV screening in Canada.[8] Improving screening at arrival could identify individuals with HCV infection at an early stage.

Moving forward

Linked administrative datasets are an important tool for monitoring progress towards HCV elimination goals. However, assessment of late diagnosis in administrative data as an indicator of effectiveness of screening strategies requires additional guidance and consensus on methods. The next International Liver Meeting would be an ideal opportunity to move this agenda forward.

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Conflict of interest

MK has received grant funding via his institution from Roche Molecular Systems, Boehringer Ingelheim, Merck, Siemens Healthcare Diagnostics and Hologic Inc.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

NJ, JW, AY, HS participated in the study design. JW and AY performed the statistical analysis. JW & NJ wrote the first draft. All authors contributed in the interpretation of results, manuscript preparation and revisions. All authors read and approved the final manuscript.

Ethnical approval and data availability statement

Data linkage to establish the British Columbia Hepatitis Testers Cohort (BC-HTC; Table S1) was performed under the auspices of the British Columbia Centre for Disease Control's public health mandate. This study was reviewed and approved by the Behavioral Research Ethics Board at the University of British Columbia (H14-01649). This study used administrative data collected as part of routine healthcare encounters. Investigators did not have contact with individual patients for data collection and hence consent is not needed for the study. Data is available through British Columbia Centre for Disease Control's data access request process.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.09.015.

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