

**Supplementary data**

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2019.08.022>.

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Author names in bold designate shared co-first authorship

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## Pitfalls in measuring temporal trends for late diagnosis of viral hepatitis

To the Editor:

To monitor the prevention and treatment of chronic diseases, the World Health Organization and others report age-standardized death rates, years of life lost, and disability-adjusted life years.<sup>1</sup> However, these measures do not capture information on how late in their disease course patients first present for care. This information can be useful to gauge the adequacy of disease screening efforts. Clinical stage at presentation, as used in oncology research, can be used as a measure of late diagnosis,<sup>2,3</sup> but the detailed clinical information used to stage liver disease is lacking from health administrative data sources, which are increasingly used to study the real-world outcomes of patients with liver disease.<sup>4,5</sup>

Comparing the time of diagnosis to the time of development of a complication may be an indirect way to determine the proportion of individuals who are inadequately served by current disease screening efforts. When diagnosis and complications occur very close together in time, inferences can be made about the clinical stage at diagnosis. Two previous studies have reported on late diagnosis of hepatitis B and C infection in Canada and Australia.<sup>6,7</sup> Both studies included plots of the pro-

portion of patients with late diagnosis over time, and reported that late diagnosis was becoming less common. Because of the potential policy importance of such findings, we attempt here to illustrate how the choice of methods used to identify late diagnosis can determine the direction of observed trends. It is essential to consider possible sources of bias in this measurement, to avoid making erroneous inferences.

### Methods and results

We undertook a cohort study of patients diagnosed with hepatitis C virus (HCV) infection based on laboratory tests in Ontario between 2000 and 2014. Using data from Public Health Ontario, we identified all patients with positive anti-HCV antibody or HCV RNA. We excluded patients who had a positive antibody but negative HCV RNA, signalling a previous (now cleared) infection. We also excluded those with an HCV diagnosis before January 1st 2000 or within 1 year of their earliest health insurance eligibility. Because we relied on health administrative data to detect outcomes, we excluded those whose HCV testing data could not be linked to health administrative data holdings. Ontario health administrative data were accessed in accordance

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with the protocols of and with permission from ICES in Toronto, Canada.

Outcomes detected were the earliest of: (1) decompensated cirrhosis; (2) hepatocellular carcinoma; or (3) liver transplant. These were identified through a combination of administrative data codes for inpatient and outpatient diagnoses and procedures, as well as pathological and death certificate information, as described elsewhere.<sup>8</sup> We followed individuals for outcomes until March 31st 2017.

We separated the cohort into the following 4 groups according to the timing and presence of complications: (1) patients with a complication within  $\pm 6$  months of HCV diagnosis, termed “very late diagnosis”; (2) patients with a complication 6 months to 2 years after HCV diagnosis, termed “late diagnosis”; (3) patients with a complication  $>2$  years after HCV diagnosis; and (4) patients who did not reach a complication during the observation period.

Results were plotted according to the following 3 methods:

**Method 1**

Method 1, used by Samji *et al.* and Alavi *et al.*, restricts the analytic sample to those individuals who experienced a complication. Individuals are categorized according to the year in which the complication occurred. Then, for each year, the proportion of those experiencing a complication who also had a very late diagnosis is computed and plotted.<sup>6,7</sup> This was repeated for those experiencing a late diagnosis and for those experiencing neither a late nor very late diagnosis. For each year, all percentages sum to 100%. Results with this method can be interpreted as follows for any given year: “among patients with hepatitis C infection who presented with a complication in xxxx year, xx% were diagnosed very late and xx% were diagnosed late.”

When we plot the results this way, we note that the proportion of late diagnoses appears to be decreasing consistently over the study period (Fig. 1). A potential explanation for this trend is the longer observation time for those who have developed complications in more recent years, compared to those developing complications in earlier years. Simply put, the more years of look-back observation time prior to the date of complication occurrence, the greater the potential for an increasing number of individuals in the “ $>2$  years” category. The percentage of patients in this category grows with each subsequent year, leading to a shrinking effect on the proportions with very late and late diagnoses.

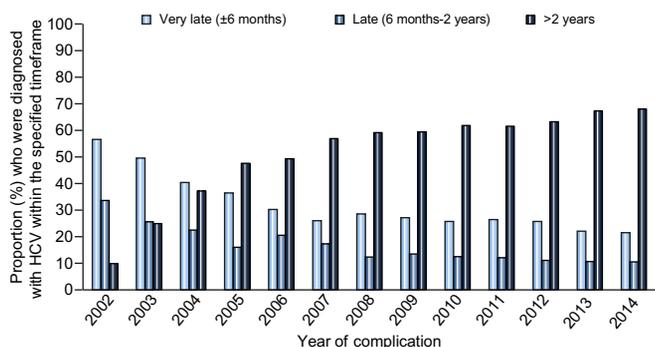


Fig. 1. Very late and late diagnosis of HCV infection among those with a complication, by year of complication.

**Method 2**

Method 2, like Method 1, uses all patients reaching a complication as the denominator. In this method, individuals are categorized according to the year in which they are first diagnosed with hepatitis, instead of the year that a complication is diagnosed. Then, for each year of hepatitis diagnosis, the proportion that experienced a very late diagnosis is computed and plotted. In this case, we note that the proportion of late diagnoses appears to be increasing over time (Fig. 2). Results with this method can be interpreted as follows for any given year: “among patients diagnosed with hepatitis C infection in xxxx year who later developed a complication, xx% were diagnosed very late and xx% were diagnosed late.”

A potential explanation for this trend is the longer observation times for groups that were diagnosed with viral hepatitis in the earliest years, compared to those diagnosed with viral hepatitis in later years. The more years of follow-up observation, the greater the potential for an increased number of individuals in the “ $>2$  years” band. The percentage of patients in this category decreases every year, leading to an inflationary effect on the proportions with very late and late diagnoses.

**Method 3**

Method 3 differs from the first 2 methods in that the denominator is all patients diagnosed with hepatitis, rather than being restricted to only patients who have reached a complication at some point in the study follow-up period. Here, we plot the proportion with a late diagnosis by year of hepatitis diagnosis. Results with this method can be interpreted as follows for any given year: “among all patients newly diagnosed with hepatitis C infection in xxxx year, xx% were diagnosed very late and xx% were diagnosed late.”

With this method, we note that the “ $>2$  years” category shrinks over time as a result of shorter follow-up observation periods for patients diagnosed with HCV in more recent years (Fig. 3). However, this is accompanied by an increasing proportion of patients in the “have not reached a complication” category in more recent years. Consequently, there is no distortion of the proportion with very late or late diagnoses.

**Discussion**

We have demonstrated that the method for calculation and display of the proportion of late diagnoses greatly impacts observed temporal trends. In 2 previous studies, plots of the

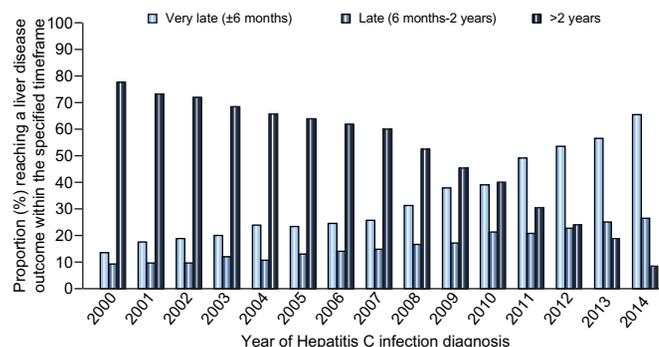
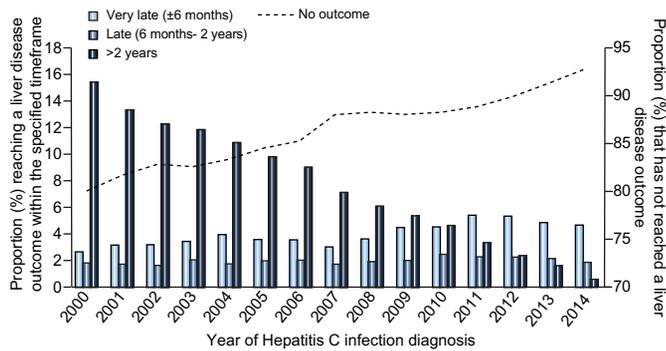


Fig. 2. Very late and late diagnosis of HCV infection among those with a complication, by year of infection diagnosis.



**Fig. 3. Very late and late diagnosis among all those with HCV infection, by year of infection diagnosis.**

proportion with late diagnosis included only those who reached a complication in the denominator, rather than all patients diagnosed with hepatitis.<sup>6,7</sup> The longer patients are observed, the more likely they are to develop a complication. As a result, the denominator is growing over time (when plotted by year of complication) and shrinking over time (when plotted by year of hepatitis diagnosis). Therefore, the proportion of late diagnoses appears to be either shrinking in the first instance, or growing in the latter case. With both of these methods, inferences made about the effect of evolving prevention and/or screening strategies would be incorrect.

In our study, patients diagnosed with hepatitis in early years are observed throughout the entire 14-year study, yet those diagnosed in 2012 are only observed for 4 years. In order to make valid comparisons over time, the denominator must not be susceptible to inflation or shrinkage due to different observation periods. In this case, the most suitable denominator is all HCV diagnosed cases, by year. This denominator includes very late or late diagnosed, others with complications, and the group of patients who have not yet developed a complication (but might if observed longer). The graph obtained with this third method demonstrates that the group with complications more than 2 years from diagnosis appears to be shrinking over time. Yet, because the denominator is all hepatitis cases, and because we have at least 2 years of follow-up time for all cohort members, the proportion with a very late or late diagnosis is not similarly distorted.

While Samji *et al.* and Alavi *et al.* reported decreases in late diagnosis of HBV and HCV over time in Canadian and Australian populations, our findings suggest that was not the case for HCV in the Canadian province of Ontario.<sup>6,7</sup> After comparing 3 analytic approaches to the study of time trends in late diagnosis, we conclude that, to avoid bias due to different follow-up times, comparisons across years must consider all patients at risk instead of only those who have already developed a complication. Using this approach, we found that among patients newly diagnosed with hepatitis C infection, the proportion who are diagnosed very late is increasing. It would be interesting to see whether similar trends are observed in the data from Samji *et al.* and Alavi *et al.* if re-analysed in this way. Understanding the optimal way to analyse and present data on late diagnoses will be critical to develop policies addressing this important clinical issue.

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### Conflict of interest

JJF reports grants and personal fees from Abbvie, grants and personal fees from Gilead, grants and personal fees from Merck, grants from Janssen, personal fees from Enanta, personal fees from Combivir, all outside the submitted work. The remaining authors declare no potential conflicts of interest.

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

### Authors' contributions

LL-S, PCA, BS, JCK and JJF conceived and designed the study. LL-S and HC analysed and interpreted the data. LL-S drafted the manuscript. All authors critically revised the manuscript for important intellectual content.

### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2019.06.015>.

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## Reply to: “Pitfalls in measuring temporal trends for late diagnosis of viral hepatitis”

To the Editor:

We appreciate the correspondence of Lapointe-Shaw *et al.* on our study “Time to decompensated cirrhosis and hepatocellular carcinoma after an HBV or HCV notification: A population-based study”.<sup>1</sup> They make important points in relation to possible sources of bias in the evaluation of late hepatitis C virus (HCV) diagnosis. We have therefore undertaken further analyses to clarify the role of monitoring trends in “late HCV diagnosis” and to highlight key differences in the epidemiology of HCV and population-level HCV screening in New South Wales (NSW) and Ontario.

In our original study, we had proposed a definition of “late HCV diagnosis”, to monitor population-level HCV screening, particularly among older people and those with longer duration of HCV who are at higher risk of advanced liver disease. Low levels of HCV screening in these populations would be reflected by a relatively high proportion of people diagnosed with decompensated cirrhosis (DC) or hepatocellular carcinoma (HCC) who had recent HCV diagnosis (within 2 years prior or following the event) or “late HCV diagnosis”. The 2-year period was chosen to cover both a symptomatic period and a period of “lost opportunity” for potential prevention of the event. Our findings showed declining proportions with “late HCV diagnosis” among people with DC and HCC, from 56% in 2001, to 20% in 2012 (compared to 35% in Ontario in 2012) (Fig. 1). Lapointe-Shaw *et al.* argued this reduction is due to the increasing proportion of DC and HCC diagnosis among people with longer look-back observation time in later years. In our study, HCV diagnoses 1995–1999 comprised 47% of all diagnoses and were included to reduce overestimation of late HCV diagnosis in the early 2000s; however, the look-back observation time was shorter for people with a DC and HCC diagnosis in the early 2000s, compared to the later time periods. This is a limitation of our study and has been acknowledged in the manuscript. Plotting the crude numbers of “late HCV diagnoses” by year of DC and HCC diagnosis pro-

vides further insight (Fig. 2). Due to the ageing cohort of people with HCV and limited impact of HCV treatment in the era prior to direct-acting antiviral (DAA) therapy, the total number of advanced liver disease events steadily increased, doubling over the period 2001–2012, but the number of late diagnosis events was stable.

To avoid distortion of the proportions with “late HCV diagnosis”, Lapointe-Shaw *et al.* proposed including all people with an HCV diagnosis in the denominator and plotting the proportions by year of HCV diagnosis, accompanied by the proportion of people who have not yet reached an advanced liver disease complication (Fig. 3). This method produced markedly different results in NSW, a setting with higher HCV diagnosis and a younger (lower advanced disease risk) epidemic, compared to Canada.<sup>2,3</sup> In NSW, in 2001–2012, the proportion with DC or HCC was never more than 5%; each year, 95–97% of those with an HCV diagnosis had not developed an advanced liver disease

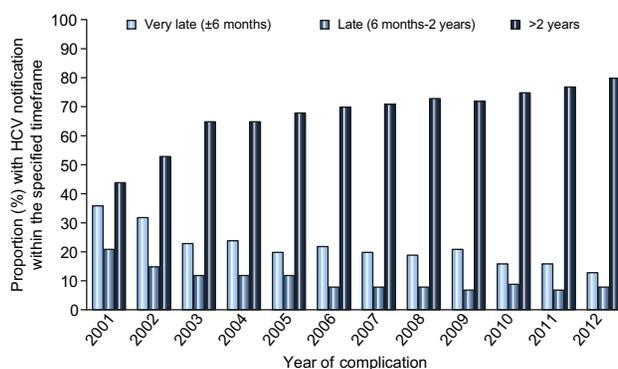


Fig. 1. Proportions of very late and late HCV notification among people with a decompensated cirrhosis or hepatocellular carcinoma diagnosis, by year of complication.