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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".[1] 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 provides 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.[2,3] 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

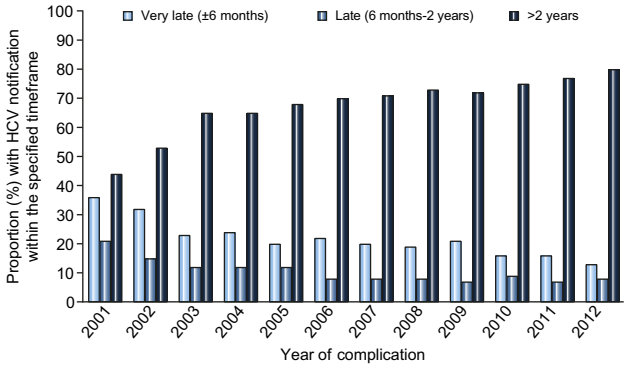

Fig. 1. Proportions of very late and late HCV notification among people with a decompensated cirrhosis or hepatocellular carcinoma diagnosis, by year of complication.

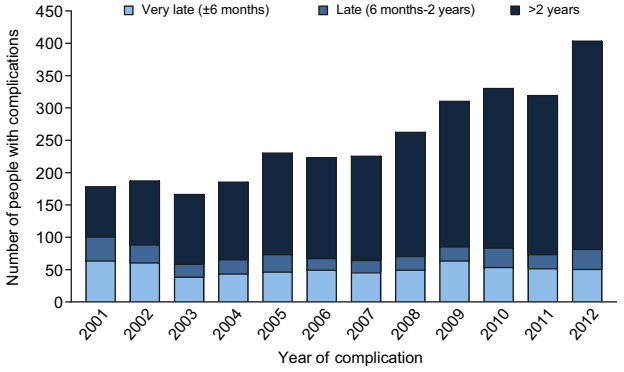

Fig. 2. Numbers of very late and late HCV notifications, by year of complication.

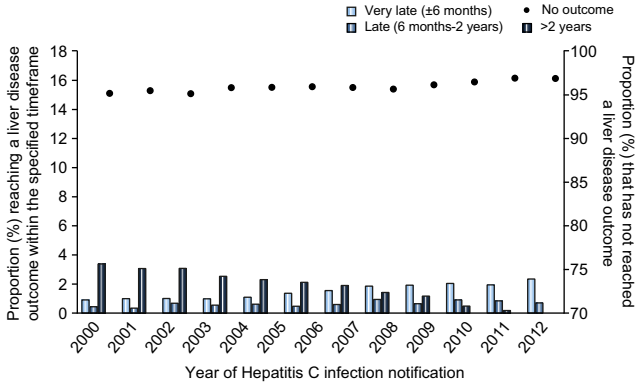

Fig. 3. Proportions of very late and late HCV notifications among all people with an HCV notification, by year of notification.

event. In contrast, in Ontario, in 2001–2014, the proportion with DC or HCC was 20% to 8% and the proportion without an event increased from 80% in 2000 to a high of 93% in 2014. These contrasting trends reflect higher levels of HCV screening and a younger HCV epidemic in Australia, with HCV incidence peaking in the late 1990s, compared to early to mid-1980s in Canada.[3] In NSW, 85% of the chronic HCV population are estimated to be diagnosed.[2] Data among current people who inject drugs indicate very high levels of HCV screening among younger at-risk populations,[4] while we believe our data on the declining, and relatively low, proportion of people with "late HCV diagnosis" among those developing advanced liver disease complications indicate high levels of screening among older populations, including former PWID, blood transfusion-acquired, and migrant populations. Importantly, "late HCV diagnosis" was not associated with country of birth in our previous analyses.

Despite differences in methodologies and findings between the 2 studies, we believe that, in the DAA era it is increasingly important to develop tools for monitoring population-level HCV screening. The "missed opportunity" of "late HCV diagnosis" is more acute in this otherwise optimistic public health and clinical setting.

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Conflict of interest

ML has received research support from Merck, Bristol-Myers Squibb, Boehringer Ingelheim, Janssen-Cilag, Gilead Sciences, and ViiV HealthCare. ML has received consultancy and workshop fees from Gilead Sciences. ML has received Data Safety Monitoring Board Committee fees from Sirtex Pty Ltd. GD has received research support and is a consultant for Gilead Sciences, Merck, and AbbVie. GD has received research support from Gilead Sciences, Merck, Bristol-Myers Squibb, and AbbVie. GD is on the speaker's bureau for Gilead Sciences, Merck, and AbbVie. GD is a member of advisory board for Gilead Sciences, Merck, and AbbVie. GD has received travel support from Gilead Sciences, Merck, and AbbVie. MA has no commercial relationships that might pose a conflict of interest in connection with this manuscript.

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

Authors' contributions

MA and ML contributed to data analysis, interpretation of findings, and drafting of the manuscript; and GD contributed to interpretation of findings and drafting of the manuscript.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.07.011.

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