

Determining the Effect of Hepatitis C on Mortality: Sorting the Signal From the Noise

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Accepted Manuscript

Hepatitis C is a major cause of morbidity and mortality estimated to affect over 150 to 200 million people worldwide.^{1,2,3} Infection with hepatitis C virus (HCV) carries a large clinical impact and high cost burden to health care systems, and is one of the leading contributing causes of end stage liver disease requiring liver transplantation in the US.⁴ Advancements have been made in areas of both diagnosis and treatment, improving our ability to detect and treat the disease earlier. This carries the potential benefit of decreasing the morbidity and mortality caused by this disease.

This month's issue of *Clinical Infectious Diseases* features two articles which address the impact of hepatitis C, highlighting both the significant mortality it brings as well as the potential underreporting of the disease. Both of these studies utilize data collected from death certificates and either disease reporting/ surveillance systems, or electronic medical records.

The study by Pinchoff et al entitled "Death among people with Hepatitis C in New York City, 2000-2011" examined surveillance data for Hepatitis C reporting, and compared it to cause of death data obtained from death certificates from 2000 to 2011 in New York City (NYC). They evaluated the effect of Hepatitis C on age of death, cause of death (COD), as well as the effect of co-infection with HIV compared to the population without these diseases. This was a well designed study taking advantage of New York City having several robust disease surveillance registries that were able to be cross-matched and then compared to mortality data. By doing the study in NYC, they were able to evaluate a large, well defined, and diverse population with a particularly high incidence of this disease.⁵ This study adds to the literature as it further helps to delineate the natural history of Hepatitis C in the real world. The authors were able to

convincingly demonstrate an increased risk of premature mortality (age <65) in patients infected with hepatitis C, stressing the importance again of early identification and potential treatment of this disease. The study also attempted to further evaluate the cause of death in this population from a review of death certificate data. It is very important to understand when and how people are being diagnosed with the disease and ultimately what they are specifically dying from.

There are however some weaknesses in the study that need to be discussed. Unlike a true cohort, this study only captured people who died in NYC. Patients who were diagnosed and treated in NYC would not be included in the COD analysis if they were to die outside of the city limits. Although the study implies that earlier diagnosis and treatment would likely decrease premature mortality, the study was not able to evaluate the subset of people that were treated for hepatitis C, and with what regimen. Overall the study does an excellent job demonstrating the associated mortality with HCV, but causation is much more difficult to prove. Lastly, the utilization of death certificate data may lead to a classification bias with overrepresentation of certain CODs ie HIV/AIDS and cardiovascular causes.^{6,7,8}

Also in this issue of *Clinical Infectious Diseases*, Mahajan et al publish their findings from The Chronic Hepatitis Cohort Study (CHeCS). This large cohort of 11,703 patients was formed from a review of electronic medical records from four large healthcare systems from 2006-2010, extracting demographics and data from patients diagnosed with HCV. They found a significantly higher than expected effect of hepatitis C on mortality, with a mortality rate twelve times higher in their cohort compared to the general population. An interesting finding of this study, was the paucity of HCV being listed on death certificates of these individuals. In fact, the majority of deaths, whether liver or non-liver related, did not have hepatitis C listed as a COD. Although this finding was specifically for hepatitis C, it reiterates the importance of proper death

certificate completion and accuracy. It also sheds light on the potential impact on other studies such as the article by Pinchoff et al above that utilize death certificate data, to determine the impact on mortality of a certain disease. Potentially the Pinchoff study may be missing large numbers of patients that died from both hepatic and non-hepatic causes related to Hepatitis C. Clearly those that had hepatitis C listed on their death certificates tended to die younger with a higher incidence of premature death, but the full impact is uncertain if we don't have an accurate representation of the deaths that HCV may have contributed to.

This paper by Mahajan et al also has some limitations, and opens the door for many further questions. This study was done with data from four large academic centers and may not necessarily be extrapolated to all hospital systems. Furthermore it would be interesting to know who completed the death certificates, ie attending versus resident or intern, how often it was completed by a covering physician who may not have known the patient as well, and what specific training, if any the completing physician had received in proper death certificate completion. Lastly it would be useful to know what percentage of patients were being treated for Hepatitis C and the impact this may have had on this subset of the cohort.

It's important to note that both of the above studies are only able to take into account HCV cases that were picked up by surveillance. HCV is often under diagnosed, so we don't know if the findings from these studies would apply to all subjects infected with HCV. We can only address the mortality risk, and associations in those with an established diagnosis of hepatitis C. Many of these cases may have been detected because of liver function test abnormalities or exam findings consistent with liver disease. It's important to also consider that hepatitis C infection is associated with several social factors and behaviors that can increase the risk of death. This comes back to an important question of whether people are dying with

hepatitis C or from hepatitis C. To this point, it is also possible that some of the controls who died in both studies may have had HCV, as not everyone who dies is checked for the disease.

As more studies are done to look at the effect of disease, and ultimately determine what Americans or other populations are dying from, the importance of accurate information on death certificates becomes paramount. Based on their data, Mahajan et al propose that 80,000 Americans died with Hepatitis C in 2010 instead of the reported 16,622 secondary to gross underreporting on death certificates. This huge disparity is unlikely unique to Hepatitis C. Wexelman et al in a survey of residents in NYC found that the majority of residents in NYC felt the death certificate reporting system was inaccurate and often knowingly listed inaccurate COD information on death certificates.⁹ Other studies have also documented the general inaccuracies of death certificates, particularly noting cardiovascular disease being overrepresented.^{6,7,8} As less autopsies are being performed, it is becoming more and more important to strive to improve the accuracy and consistency of cause of death reporting.

Increasing education initiatives seem to help,¹⁰ and perhaps with more of these programs we may be moving toward a more reliable system, but this is not the only obstacle. There are system based issues which also need to be further addressed.⁹ For instance, in the Wexelman et al study, residents reported not being able to enter into the Electronic Death Registration System (EDRS) system what they believed was the true COD for a variety of reasons. These issues seem to be multi-factorial and will ultimately need to be addressed on several levels. However, perhaps it is only when you look at studies like these two well designed, interesting papers on hepatitis C, do you really appreciate the importance of getting this right.

The author has no reported conflicts of interest.

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