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## Increasing Prevalence of HCC and Cirrhosis in Patients with Chronic Hepatitis C Virus Infection

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### Abstract

**Background & Aims**—Patients with hepatitis C virus (HCV) infection are at risk for developing additional liver disorders that are costly to treat and have high rates of morbidity, although the actual prevalence of these diseases is not known. We examined time trends in the prevalence of cirrhosis and its related complications, such as hepatic decompensation and hepatocellular cancer (HCC).

**Methods**—We calculated the annual prevalence of cirrhosis, decompensated cirrhosis, and HCC in a national sample of veterans diagnosed with HCV between 1996 and 2006. Patients with HCV who had at least 1 physician visit in a given calendar year were included in the analysis of prevalence for that year. We used direct standardization to adjust the prevalence of cirrhosis and related complications for increasing age of the cohort, as well as sex and changes in clinical characteristics.

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**Results**—In this cohort, the number of individuals with HCV increased from 17,261 in 1996 to 106,242 in 2006. The prevalence of cirrhosis increased from 9% in 1996 to 18.5% in 2006. Similarly, the prevalence of patients with decompensated cirrhosis doubled, from 5% in 1996 to 11% in 2006, whereas the prevalence of HCC increased approximately 20-fold (0.07% in 1996 to 1.3% in 2006). After adjustment, the time trend in the prevalence of cirrhosis (and its complications) was lower than the crude trend, although it still increased significantly.

**Conclusions**—The prevalence of cirrhosis and HCC in HCV-infected patients has increased significantly over the past 10 years, and could increase further. An aging cohort of HCV patients could partly explain our findings. Clinicians and healthcare systems should develop strategies to provide timely and effective care to this high-risk population of patients.

### Keywords

liver cancer; epidemiology; virology

## BACKGROUND

Chronic hepatitis C virus infection (HCV) is a common condition that affects more than 1.3% of the US population.<sup>1</sup> Recent data show that antiviral treatment rates are lower than 30%, and results in a response in only half of the treated patients.<sup>2–5</sup> Thus, a significant proportion of patients with HCV remain at risk for progression to advanced liver disease or cirrhosis.

Cirrhosis develops after prolonged infection in patients with HCV.<sup>6</sup> Because a majority of patients are thought to have acquired their infection as young adults in the 1970's,<sup>7,8</sup> the number of patients chronically infected for more than 20 years continues to rise.<sup>9,10</sup> Due to the coupling of prolonged infection with aging of the HCV cohort, the prevalence of cirrhosis and related complications is expected to increase.<sup>11</sup> Indeed, a recent cohort study found that HCV related mortality has increased substantially from 1995 to 2004, and that this rising burden of mortality is likely related to complications of advanced liver disease.<sup>12</sup> These data, however, do not provide direct population based estimates of the number of patients with cirrhosis and related complications in relation to overall infection with HCV, particularly in the era of modern anti viral therapies. Measuring the burden of cirrhosis in HCV is important as these data can help understand changes in the pattern of care delivery to patients with HCV, provide a critical insight into the magnitude of the problem, and guide both clinicians and the health care system to develop strategies and capacity targeted towards providing timely and effective care to this highly vulnerable group of patients with HCV.

The Veterans Administration (VA) healthcare system is the largest integrated healthcare system in the U.S., and it has a disproportionate number of patients with HCV. A recent study found that more than 5% of a nationally representative cohort of VA System enrollees is chronically infected with HCV.<sup>13</sup> This makes the VA the flagship healthcare system in which to examine changes in the burden of cirrhosis. The VA is also a semi-closed system with relatively stable patient population making long-term studies possible. We conducted a retrospective cohort study of all VA patients with HCV to quantify the changes in the prevalence of cirrhosis and to examine trends in its related complications, such as hepatic decompensation and hepatocellular cancer (HCC).

## METHODS

### Data Source

We used data from the VA HCV Clinical Case Registry (CCR). This database contains health care utilization and clinical data for over 300,000 patients with HCV and allows for sufficient follow up to examine the time trends in cirrhosis and related complications over the last decade. The objectives of this continually updated Registry are to identify all VA patients with HCV infection; monitor and track specific elements of medical care for these patients; review clinical status and medical outcomes; and identify opportunities for improving care. When the Registry was first built, historical information was pulled from each VA facility on patients with at least one positive HCV antibody test result or an International Classification of Diseases 9th Revision (ICD-9 code) for HCV. After the initial Registry build period, the Registry software automatically identifies patients from ICD-9 codes and HCV antibody testing results. A local staff member at each VA site then reviews all patients identified as meeting the electronic criteria to confirm infection, and these patients are added to the CCR.<sup>14</sup> Data elements include demographics, all laboratory tests with results, outpatient and inpatient pharmacy data, inpatient and outpatient utilization, and death dates (if any). Seventy five percent of CCR patients have received a HCV viral load or genotype test, and of these 80% have evidence of chronic infection. The remaining 20% have a negative test—indicating either a false positive anti-HCV test or resolved infection.<sup>14</sup>

### Study Cohort

The study cohort included patients with chronic HCV infection, defined as a positive test for the detection of HCV RNA in plasma by qualitative or quantitative assays or detectable HCV genotype, who visited any of 128 VA medical centers from January 1 1996 to December 31, 2006.

We did not include patients with positive HCV antibody test who had not received any confirmatory test because we wanted to avoid inclusion of patients with a false positive test or those with resolved HCV infection. We defined the index diagnosis date for our patients as the earliest of their first positive HCV antibody test, viremia test, or first appearance of an ICD-9 code for HCV. For each calendar year, we only included those patients who had  $\geq 1$  visit to the VA during that year. We terminated follow up at the time of patient's death.

### Statistical Methods

**Outcomes**—The primary outcomes were time trends in the prevalence of cirrhosis, hepatic decompensation and HCC. We defined cirrhosis based on any inpatient or outpatient ICD-9 code of 571.2, 571.5, or diagnosis codes for hepatic decompensation. We defined hepatic decompensation as ascites, variceal bleeding, hepatic encephalopathy, spontaneous bacterial peritonitis, and hepatorenal syndrome based on an inpatient or outpatient ICD-9 codes 789.5, 456.0–2, 572.4, 572.2, 348.3×, 070.0, 070.2×, 070.4×, 070.6, 070.71. HCC was defined as an inpatient or outpatient ICD-9 code of 155.0. Using these ICD-9 codes, we have previously found high agreement between the VA administrative data and medical records for cirrhosis and HCC diagnoses (cirrhosis: PPV 88%, NPV 92%; HCC: PPV 94%).<sup>15,16</sup> As an additional internal control, we reviewed the laboratory file of the CCR for AST to platelet ratio index (APRI) in our cohort stratified by the presence of cirrhosis codes. These data showed that most of those without cirrhosis (81%) had an APRI  $< 1$  (the latter shown in the initial derivation and validation cohorts to be highly predictive of the absence of cirrhosis).<sup>17</sup> On the other hand, only 5.9% of patients with cirrhosis had an APRI  $< 1$ . We used the date of first appearance of the ICD-9 code in the database as the index date for the corresponding diagnosis. For example, if we found the first ICD-9 code for cirrhosis in 2000, then we assigned “2000” as the index year for cirrhosis diagnosis.

**Factors Associated with Cirrhosis**—We examined the time trends in the following risk factors that may be associated with an accelerated progression to cirrhosis in patients with HCV: age, race, human immunodeficiency virus (HIV) infection, hepatitis B virus (HBV) infection, diabetes, and alcohol use.<sup>18–27</sup> We identified HIV, diabetes, and alcohol use by the presence of 2 outpatient or 1 inpatient ICD-9 diagnosis codes recorded during the study time frame. We used the AHRQ Clinical Classification System to classify all patient ICD-9 codes into the relevant diagnoses.<sup>28</sup> We defined patients with HBV co-infection as subjects with a positive HBV surface antigen test. We used the date of first appearance of the ICD 9 code or, for HBV, date of the first positive HBV surface antigen test, as the index date for the respective comorbidity.

**Statistical methods**—We calculated the crude annual prevalence rate of cirrhosis by dividing the number of HCV patients with either a new or prior diagnosis of cirrhosis by the total number of HCV patients with at least one visit to the VA during that particular year. We used the same method to estimate annual prevalence rates of hepatic decompensation and HCC. We plotted the crude prevalence of cirrhosis and related complications against the calendar years. We compared the prevalence in the first year *versus* the last year using a chi-square test.

We then examined the time trends in the annual mean age as well as the annual prevalence for each of the demographic and clinical characteristics (listed in the section above) in our HCV cohort. We computed the crude annual prevalence of each demographic or clinical characteristic by dividing the number of HCV patients with such a characteristic by the total number of HCV patients with at least one visit to the VA during a particular year. Then we plotted the estimates against year and compared the first year *versus* the last year using a t-test (for mean age) or chi-square test (for proportions).

We used direct standardization to adjust for increasing age of the HCV cohort as well as any gender differences during the study period. We selected the first year (1996) in the study cohort as our reference population. We stratified the reference population by gender and 8 age groups (>25 yrs, 25–34 yrs, 35–44 yrs, 45–54 yrs, ...>85 yrs) and calculated the distribution of patients in each age-gender group. We then calculated the prevalence of cirrhosis (decompensation or HCC) in these groups in each of the subsequent years. We multiplied the age-gender specific prevalence rates with the number of patients in the corresponding gender-age groups in the reference population to obtain the number of expected patients to have cirrhosis (decompensation or HCC) for each successive year. Last, we divided the cumulative sum of expected patients with cirrhosis (decompensation or HCC) by the number of total patients in the reference population to arrive at an overall age and gender adjusted prevalence rate for each year. We then calculated the 95% confidence intervals (CI) for each rate. In order to determine the additional impact of other comorbidities that may be rising over time, we repeated the method above to derive the age and comorbidity adjusted prevalence of cirrhosis (decompensation and HCC) for each year. We compared the adjusted prevalence in the first year *versus* the last year using a weighted chi-square test. All statistical analyses were conducted by SAS software version 9.1.<sup>29</sup>

**Sensitivity Analysis:** HCV infected veterans with newly diagnosed serious medical conditions such as decompensated liver disease and/or HCC that require expensive treatment may be more likely to turn to the VA for their medical care than those in stable health. To examine this possibility, we calculated the percentage of the study cohort who received a diagnosis of cirrhosis, decompensated cirrhosis, or HCC within the first, second, and subsequent years of their VA care as part of a sensitivity analysis.

## RESULTS

### Study Cohort

Figure 1 shows the number of patients with HCV for each of the study year from 1996 to 2006. Our cohort consisted of 17,261 patients in 1996. The cohort size increased steadily (about 10,000 patients annually) between 1996 and 1999 and reached 47,000 patients in 1999. This was followed by a relatively steep rise between 2000 and 2004, and likely reflected the wide implementation of the screening program for HCV among VA users. The trend leveled off in the more recent years, with a cohort size of 106,242 patients in 2006.

### Crude Prevalence of Cirrhosis, Decompensated Cirrhosis, and HCC

Figure 2 displays the trends in the prevalence of cirrhosis, decompensated cirrhosis (left vertical axis), and HCC (right vertical axis) between 1996 and 2006. There was a significant increase in the prevalence of cirrhosis and its related complications over time. For example, the prevalence of cirrhosis doubled from 9% (95% CI, 8.7% to 9.5%) in 1996 to 18.5% (95% CI, 18.3% to 18.7%) in 2006 ( $p < 0.0001$ ). As shown in Figure 2, the prevalence rose steeply from 1996 to 1998, stabilized between 1999 and 2002, and then started rising again in 2003, with the trend still being upwards. Similarly, the prevalence of decompensated cirrhosis rose in parallel with the overall prevalence of cirrhosis, with 2-fold increase from 5% (95% CI, 4.5% to 5.3%) in 1996 to 11% (95% CI, 10.7% to 11.1%) in 2006 ( $p < 0.0001$ ). There was a steady increase in the prevalence of HCC between 1996 and 2002. However, the upward slope became steeper from 2003 onwards. The prevalence of HCC increased 19-fold from 0.07% (95% CI, 0.04% to 0.1%) to 1.3% (95% CI, 1.23% to 1.35%) during the 11 study years ( $p < 0.0001$ ).

We found that approximately 20% of all patients with a diagnosis of cirrhosis with or without decompensation, and only 10% of patients with HCC had their first ICD-9 code in the first year (Table 1 in the online supplementary material). For both cirrhosis and HCC, most of the patients were diagnosed after being in the VA for several years.

As a result of the rising prevalence rates, there were 23294, 13724, and 1619 HCV patients with a diagnosis of cirrhosis, hepatic decompensation, or HCC, respectively in 2006. Moreover, as shown in Figure 3, mortality in patients with cirrhosis increased over time, with a greater proportion of patients dying in the latter than earlier years.

### Crude Prevalence of Demographic and Clinical Characteristics

As expected, the mean age of the cohort increased over time from 46.8 years (standard deviation,  $SD=7.6$ ) in 1996 to 55.4 year ( $SD=7.2$ ) in 2006 ( $p\text{-value} < 0.0001$ ) (Figure 4). Similarly, the proportion of patients with diabetes increased from 12% in 1996 to 23% in 2006 ( $p\text{-value} < 0.0001$ ). Other demographic and clinical characteristics of our HCV cohort either declined or remained stable over the 11 study years. Specifically, the proportion of patients with HIV, HBV, and those with diagnosis of alcohol use declined slightly ( $p\text{-values} < 0.01$ ), whereas the racial composition was relatively stable.

### Adjusted Prevalence of Cirrhosis, Decompensated Cirrhosis, and HCC

As shown in Figure 5, after adjustment for gender and increasing age of the HCV cohort, the upward slopes in the prevalence of cirrhosis and HCC were lower than the corresponding slopes in the crude rates. This divergence was apparent after 1998 for cirrhosis and after 2001 for HCC and became more pronounced with time. For example, the adjusted prevalence of cirrhosis was 20% lower, whereas that of HCC was 47% lower than the corresponding crude prevalence rates in 2006. Nonetheless, the trend remained upwards with a significant increase from 9% (95% CI, 8.7% to 9.5%) in 1996 to 15% (95% CI,

14.3% to 15.3%) in 2006 for cirrhosis and from 0.07% (95% CI, 0.04% to 0.1%) in 1996 to 0.7% (95% CI, 0.6% to 0.8%) in 2006 for HCC (p-values <0.001).

Because diabetes was the only other risk factor that increased over time (Figure 4), we calculated the age-diabetes adjusted trends for the prevalence of cirrhosis, decompensation, and HCC. These trends were very similar to that of the age-gender adjusted trends displayed in Figure 5 (data not shown).

## DISCUSSION

There are few indirect data suggesting a rise in the burden of illness in HCV and the relative contribution of cirrhosis in this rise. Using the U.S. Census and cause of death data, Wise et al reported that age adjusted HCV-related mortality rates increased from 1995 to 2002 but reached a plateau since 2002.<sup>12</sup> Results from mathematical models projected an increase in the proportion of HCV patients with cirrhosis to ~16% in 2000 and 25% in 2010, with an accompanying increase in decompensation, liver cancer, and liver-related deaths.<sup>11</sup> Our data are the first to provide direct and contemporary estimates of the time trends in the burden of cirrhosis from the largest assembled group for HCV patients anywhere in the world.

Our study has two major findings.

First, there was striking increase in the burden of cirrhosis, hepatic decompensation, and HCC in the VA HCV cohort over the past decade. We found that the prevalence of cirrhosis and hepatic decompensation doubled, whereas the prevalence of HCC increased 19-fold between 1996 and 2006. Thus, one of five patients with HCV had cirrhosis and one of 100 patients with HCV had HCC in 2006 calendar year. Our results show that aging of the VA HCV-infected patients explains a significant proportion of the rising trend (20% and 47%) in the prevalence of cirrhosis and HCC, respectively with time. However, even after adjusting for aging, the time trends remained significantly upward, suggesting that other “unmeasured” factors that are in turn associated with the passage of time (such as duration of HCV infection) have a role in explaining the rising burden of cirrhosis and its related complications in HCV. We also found an increase in the proportion of cirrhosis patients who died each year, with annual mortality rates reaching 7% in 2006. Overall, 23294, 13724, and 1619 patients with HCV who sought care at the VA had either a diagnosis of cirrhosis, hepatic decompensation, or HCC in 2006 *versus* 2061, 1012, or 17 patients, respectively in 1996.

Second, we found that the rise in the burden of HCC was significantly greater than predicted by previous mathematical models. Specifically, we found that although only 0.26% of the HCV patients had HCC in 2000—an estimate very similar to that reported in the previous mathematical models this—proportion increased significantly to 1.3% in 2006—an estimate that is remarkably higher than some have previously projected (*e.g.*, 0.39% by Davis et al).<sup>11</sup> It is plausible that transferring care to the VA after development of HCC might have contributed to the its prevalence, but we found that most of the HCC patients were diagnosed after being in the VA for several years, suggesting that care transfer plays a relatively small role. Another explanation is that our patient population may be at a higher risk for progression to cirrhosis and HCC than non-veterans HCV patients because of the high prevalence of several comorbid conditions (such as alcohol use) in our cohort (Figure 4). It is also possible that veterans with HCV acquired their infection earlier than non-veteran HCV patients, and thus would have had their infection for a longer time period compared with non-veterans. If true, then it would mean that the HCC prevalence curve in the general (or non-veteran) population with HCV is lagging behind that of HCV infected veterans, and that there might be a greater epidemic of HCC than we were expecting. Last, it

is also possible that data from previous studies may be an underestimate. In fact, data from recalibrated mathematical models suggest that the projected prevalence of HCC may indeed be higher than previously reported.<sup>30</sup> These new and concurrent estimates, therefore, provide convergent validity to our report. In contrast to the higher than expected prevalence of HCC, we found that the prevalence of cirrhosis to be somewhat lower than previously predicted. Based on previous data, this disconnect is likely related to under-diagnosis of early stage cirrhosis, possibly due to low rates of biopsy in the VA.<sup>2,31</sup> Thus the prevalence of histological cirrhosis may indeed be significantly higher than seen in our analysis.

The morbidity and mortality associated with cirrhosis and HCC may be greatly reduced if potentially life saving interventions—such as liver transplantation and, for HCC, local ablation and surgical resection—are applied in a timely manner. However, liver transplantation is a resource intensive and scarce treatment modality, and only a few patients with HCC are eligible for potentially curative therapy due to advanced stage of HCC at diagnosis. Moreover, recent data show deficits in the care provided to patients with cirrhosis. For example, Julapalli et al found that only 20% of patients with cirrhosis who satisfied AASLD guidelines for referral had a mention of liver transplantation in their medical charts.<sup>32</sup> Wilbur et al found that 94% of patients with variceal bleeding had not received any primary prophylaxis, and Singh et al found that follow-up endoscopy for secondary prophylaxis was arranged for only 65% of patients after the initial bleeding episode.<sup>33,34</sup> In our previous studies, we found that less than one-third of patients who were diagnosed with HCC received screening before their diagnosis.<sup>35</sup> In addition, we have also found that quality of health care given to patients with HCV infection falls far short of that recommended by practice guidelines.<sup>36</sup> These deficits in HCV care in general and cirrhosis care in particular combined with the relative scarcity of available treatment modalities for cirrhosis further limit the effectiveness of these treatments in clinical care. Given the significant increase in the number of patients with cirrhosis, and given the data suggesting marked gaps in the quality of care, the healthcare system may need to re-channel its efforts in patients with HCV to provide timely and effective care to the patients with cirrhosis.

Our study has several strengths including the long period of follow up, use of previously validated definitions of cirrhosis and HCC, and examination of demographic and clinical variables that may impact burden of cirrhosis in HCV. Moreover, most of the HCV patients in the VA are diagnosed as a result of a system wide screening program, rather than after development of complications from liver disease. Presence of this unique screening mechanism makes our sample a relatively unbiased cohort. Availability of laboratory results data allowed us to identify a cohort of patients with chronic HCV infection. To achieve high accuracy of case definitions, we excluded patients without documented viremia from our denominator and therefore the absolute number of patients with cirrhosis might be even higher than reported. However, prevalence estimates are less likely to be affected.

Our study is limited by the observational retrospective nature of its design. Several unmeasured patient characteristics could have affected our results. Specifically, we could not determine presence of co-existing non-alcoholic steatohepatitis (NASH). However, given the strong association between metabolic syndrome and NASH, we hypothesized that diabetes would act as a surrogate for NASH. Although we had information on anti-viral treatment in our database, we opted not to include this variable in our analysis. Conceptually, we expected “anti-viral treatment” variable to have two opposing effects on cirrhosis prevalence—patients with successful anti-viral treatment would be less likely to progress to cirrhosis (negative association); and because patients with cirrhosis are at the highest risk for adverse disease outcomes, they would also be more likely to receive anti-viral treatment (positive association). Given the low rates of anti-viral treatment in our study population (16% of our cohort had ever received at-least one prescription of interferon. Data

not shown), we do not anticipate any bias in our analysis. We did not analyze any care that occurred before 1/1/1996 and it is possible that some patients, particularly those included in the database during the earlier years, might have been diagnosed with HCV prior to 1996. This might have caused an over-estimation of cirrhosis prevalence in the earlier years. However, we believe that this effect is likely small because most of the HCV patients in the VA were diagnosed as a result of a widely implemented screening program for HCV in the late 1990's (Figure 1 depicts the impact of this screening program). Our analysis was not designed to identify causative elements that lead to progression of liver disease and, therefore, we cannot imply causative relationships about progression from this study. Instead, we planned this analysis to shed light on the burden of illness and its related implications from the perspective of a healthcare system that is managing a large cohort of patients with HCV. Our results are derived from diagnosed HCV infected patients who sought care in the VA healthcare system, and although the generalizability of the biologic process of cirrhosis progression probably extends from these veterans to other HCV infected individuals in the VA as well as nonveterans, further research would be needed to confirm that. We are also limited by the ICD-9 coding system's sensitivities and specificities for our outcomes, which may vary between the VA and non VA practitioners, thus limiting the generalizability of overall rates of cirrhosis and its complications to HCV patients outside of the VA.

Our analysis highlights that the prevalence of cirrhosis has reached very high proportions among veterans with HCV infection. Given low anti-viral treatment rates for HCV, we believe that the burden of cirrhosis will continue to grow as the HCV cohort ages unless effective treatment can be provided to HCV patients in a timely manner. In light of the increasing burden of cirrhosis and HCC in patients with HCV, clinicians and healthcare system may need to develop strategies targeted to provide timely and effective care to this high-risk patient population.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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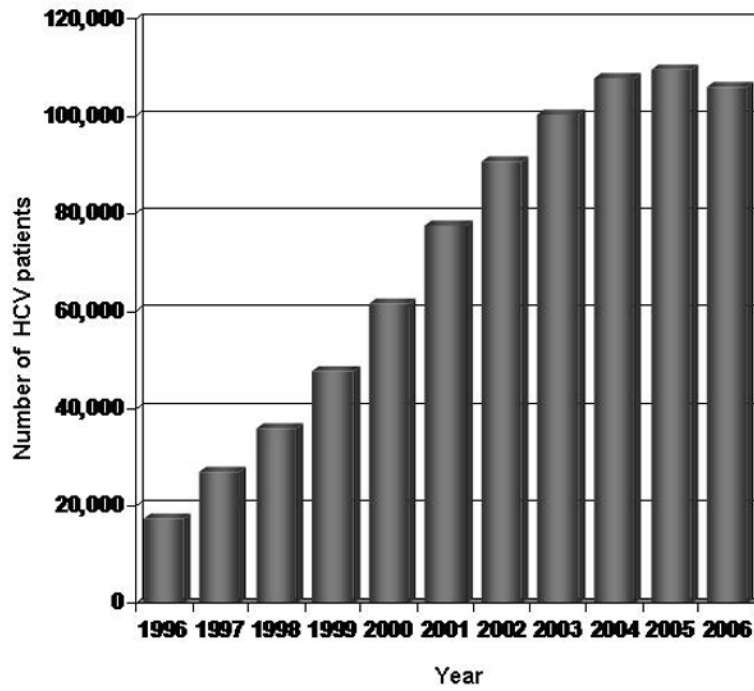
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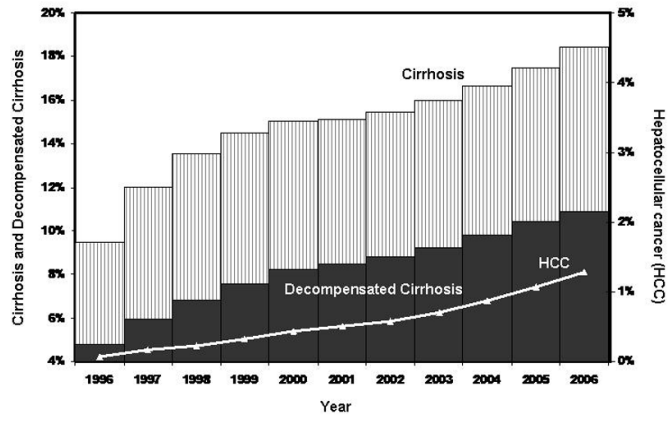


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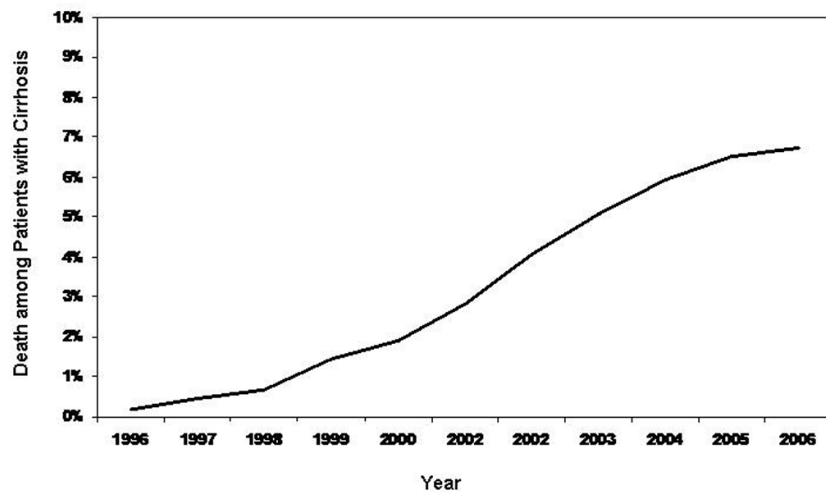
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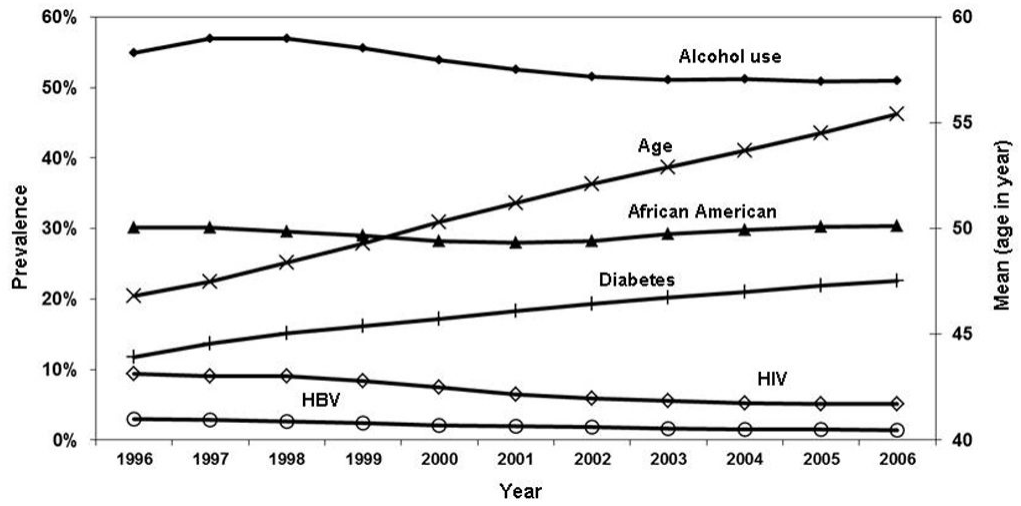
**Figure 1.**  
Change in Hepatitis C (HCV) Cohort Size 1996–2006



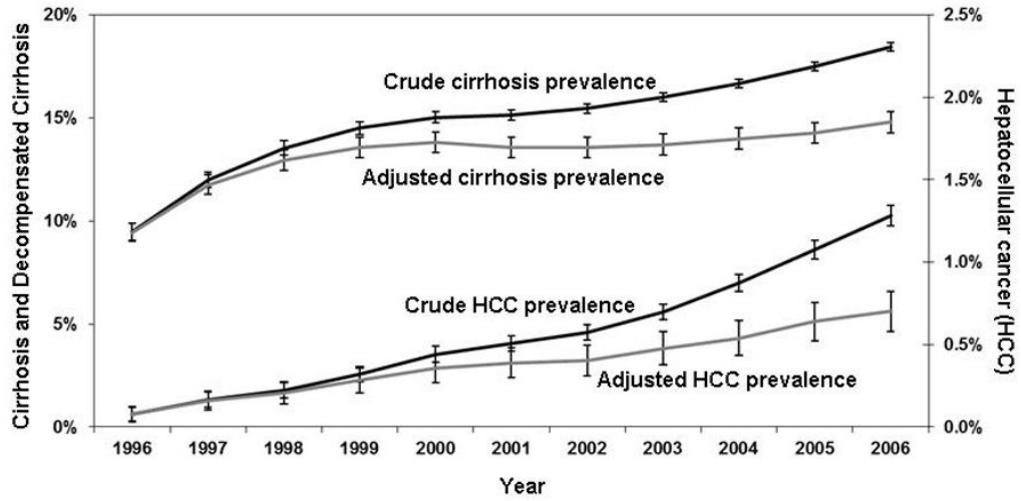
**Figure 2.** Crude Prevalence of Cirrhosis, Decompensated Cirrhosis, and Hepatocellular Cancer---1996–2006.



**Figure 3.**  
Annual Mortality in Patients with Cirrhosis—1996–2006



**Figure 4.** Changes in the Demographic and Clinical Characteristics 1996–2006. We plotted the crude prevalence of demographic (such as race) and clinical (such as diabetes, HIV, alcohol use, etc.) characteristics (left vertical axis) and mean age (right vertical axis) against each year from 1996 to 2006.



**Figure 5.** Age and Gender Adjusted Prevalence of Cirrhosis and Hepatocellular Cancer. The error bars represent 95% confidence intervals. Reference population is the HCV-infected VA cohort in 1996.