CLINICAL ADVANCES IN LIVER, PANCREAS, AND BILIARY TRACT

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

FASIHA KANWAL,[*,‡] TUYEN HOANG,[§] JENNIFER R. KRAMER,[‖,¶] STEVEN M. ASCH,[§,#,**] MATTHEW BIDWELL GOETZ,[§,**] ANGELIQUE ZERINGUE,[*] PETER RICHARDSON,[‖,¶,#] and HASHEM B. EL–SERAG[‖,¶,#]

[*]Department of Gastroenterology and Hepatology, John Cochran VA Medical Center, St Louis, Missouri, [‡]Saint Louis University School of Medicine, St Louis, Missouri; [§]Department of Medicine and Health Services Research, Greater Los Angeles VA Healthcare System, Los Angeles, California; [‖]Houston VA HSR&D Center of Excellence, Health Services Research and Development Service, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; Sections of [¶]Health Services Research and [#]Gastroenterology, Department of Medicine, Baylor College of Medicine, Houston, Texas; and [**]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California

This article has an accompanying continuing medical education activity on page e14. Learning Objective: Upon Completion of this CME exercise, successful learners will be able to indentify recent temporal trends in cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma among veterans with chronic hepatitis C infection in the United States.

See related article, Stättermayer AF et al, on page 344 in *CGH*.

BACKGROUND & AIMS: Patients with hepatitis C virus (HCV) infection are at risk for developing costly and morbid complications, although the actual prevalence of these complications is unknown. We examined time trends in the prevalence of cirrhosis and its related complications, such as hepatic decompensation and hepatocellular carcinoma (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 one 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. **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. 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. An aging cohort of patients with HCV could partly explain our findings. Clinicians and health care systems should develop strategies to provide timely and effective care to this high-risk population of patients.**

Keywords: Liver Cancer; Epidemiology; Virology.

Chronic hepatitis C virus (HCV) infection is a common condition that affects more than 1.3% of the US population.[1] Recent data show that antiviral treatment rates are lower than 30% and such treatment results in a response in only half of the treated patients.[2–5] 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.[6] Because a majority of patients are believed to have acquired their infection as young adults in the 1970s,[7,8] the number of patients chronically infected for more than 20 years continues to rise.[9,10] Due to the coupling of prolonged infection with aging of the HCV cohort, the prevalence of cirrhosis and related complications is expected to increase.[11] 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.[12] 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 antiviral therapies. Measuring the burden of cirrhosis in HCV is impor-

Abbreviations used in this paper: CCR, Clinical Case Registry; CI, confidence interval; ICD-9, International Classification of Diseases, Ninth Revision; VA, Veterans Administration.

0016-5085/$36.00
doi:10.1053/j.gastro.2010.12.032

tant because these data can help us 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 toward providing timely and effective care to this highly vulnerable group of patients with HCV.

The Veterans Administration (VA) health care system is the largest integrated health care system in the United States and 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 are chronically infected with HCV.[13] This makes the VA the flagship health care system in which to examine changes in the burden of cirrhosis. The VA is also a semiclosed system with a relatively stable patient population, making long-term studies possible. We conducted a retrospective cohort study of all VA patients with HCV to quantify changes in the prevalence of cirrhosis and examine trends in its related complications, such as hepatic decompensation and hepatocellular carcinoma (HCC).

Subjects and Methods

Data Source

We used data from the VA HCV Clinical Case Registry (CCR). This database contains health care utilization and clinical data for more than 300,000 patients with HCV and allows for sufficient follow-up to examine the time trends in cirrhosis and related complications over the past 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, Ninth 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.[14] 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 patients in the CCR have received an HCV viral load or genotype test; of these, 80% have evidence of chronic infection. The remaining 20% have a negative test result, indicating either a false-positive anti-HCV test result or resolved infection.[14]

Study Cohort

The study cohort included patients with chronic HCV infection, defined as a positive test result 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 a positive HCV antibody test result who had not received any confirmatory test result because we wanted to avoid inclusion of patients with a false-positive test result or resolved HCV infection. We defined the index diagnosis date for our patients as the earliest of their first positive HCV antibody test result, viremia test result, or first appearance of an ICD-9 code for HCV. For each calendar year, we only included patients who had $\geq$1 visit to the VA during that year. We terminated follow-up at the time of the 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 or 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 inpatient or outpatient ICD-9 codes 789.5, 456.0-2, 572.4, 572.2, 348.3x, 070.0, 070.2x, 070.4x, 070.6, and 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: positive predictive value, 88%; negative predictive value, 92%; HCC: positive predictive value, 94%).[15,16] As an additional internal control, we reviewed the laboratory file of the CCR for aspartate aminotransferase to platelet ratio index in our cohort stratified by the presence of cirrhosis codes. These data showed that most of those without cirrhosis (81%) had an aspartate aminotransferase to platelet ratio index $<$1 (the latter shown in the initial derivation and validation cohorts to be highly predictive of the absence of cirrhosis).[17] On the other hand, only 5.9% of patients with cirrhosis had an aspartate aminotransferase to platelet ratio index $<$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 diagnosis of cirrhosis.

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 infection, hepatitis B virus (HBV) infection, diabetes, and alcohol use.[18–28] We identified human immunodeficiency virus, 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 Agency for Healthcare Research and Quality Clinical Classification Sys-

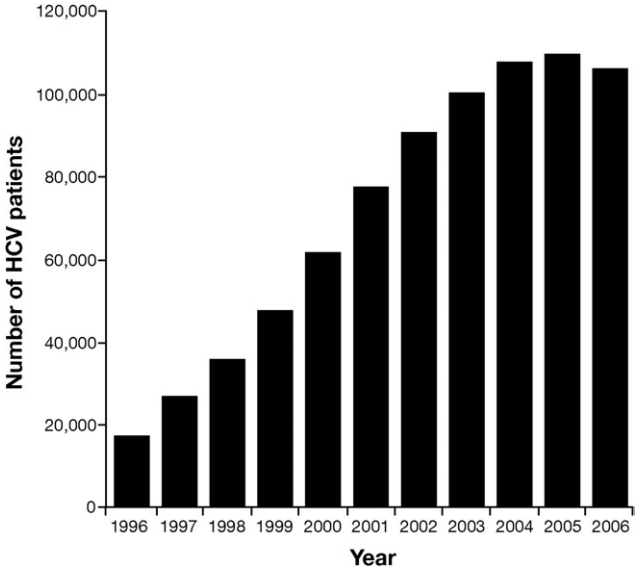

Figure 1. Change in HCV cohort size, 1996–2006.

tem to classify all patient ICD-9 codes into the relevant diagnoses (Available at: http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp). We defined patients with HBV coinfection as subjects with a positive HBV surface antigen test result. We used the date of first appearance of the ICD-9 code or, for HBV, date of the first positive HBV surface antigen test result as the index date for the respective comorbidity.

Statistical analyses. We calculated the crude annual prevalence rate of cirrhosis by dividing the number of patients with HCV with either a new or prior diagnosis of cirrhosis by the total number of patients with HCV 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 with that in the last year using an χ^2 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 previous section) in our HCV cohort. We computed the crude annual prevalence of each demographic or clinical characteristic by dividing the number of patients with HCV with such a characteristic by the total number of patients with HCV with at least one visit to the VA during a particular year. Then we plotted the estimates against year and compared the first year with the last year using a t test (for mean age) or χ^2 test (for proportions).

We used direct standardization to adjust for increasing age of the HCV cohort as well as any sex 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 sex and 8 age groups (younger than 25 years, 25–34 years, 35–44 years, 45–54 years and so on to older than 85 years) and calculated the distribution of patients in each age/sex group. We then calculated the prevalence of cirrhosis (decompensation or HCC) in these groups in each of the subsequent years. We multiplied the age/sex-specific prevalence rates by the number of patients in the corresponding age/sex 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 sex-adjusted prevalence rate for each year. We then calculated the 95% confidence intervals (CIs) for each rate. To determine the additional impact of other comorbidities that may be rising over time, we repeated the method previously described 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 with that of the last year using a weighted χ^2 test. All statistical analyses were conducted using SAS software version 9.1 (SAS Institute, Cary, NC).

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 years 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

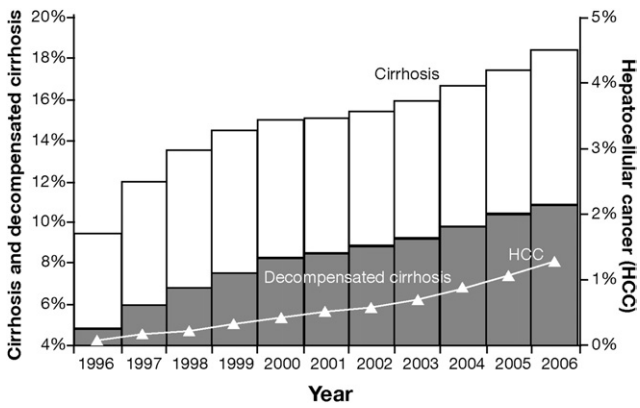

Figure 2. Crude prevalence of cirrhosis, decompensated cirrhosis, and HCC, 1996–2006.

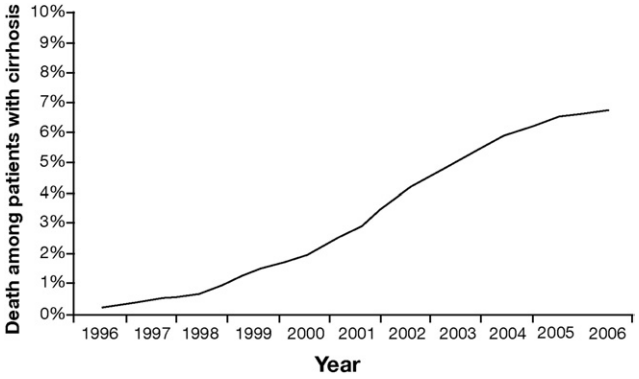

Figure 3. Annual mortality in patients with cirrhosis, 1996–2006.

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%–9.5%) in 1996 to 18.5% (95% CI, 18.3%–18.7%) in 2006 ($P < .0001$). 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 upward. Similarly, the prevalence of decompensated cirrhosis rose in parallel with the overall prevalence of cirrhosis, with a 2-fold increase from 5% (95% CI, 4.5%–5.3%) in 1996 to 11% (95% CI, 10.7%–11.1%) in 2006 ($P < .0001$). There was a steady increase in the prevalence of HCC between 1996 and 2002. However, the upward slope became steeper from 2003 onward. The prevalence of HCC increased 19-fold from 0.07% (95% CI, 0.04%–0.1%) to 1.3% (95% CI, 1.23%–1.35%) during the 11 study years ($P < .0001$).

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 (Supplementary Table 1). 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 23,294, 13,724, and 1619 patients with HCV 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 (SD, 7.6) in 1996 to 55.4 years (SD, 7.2) in 2006 ($P < .0001$) (Figure 4). Similarly, the proportion of patients with diabetes increased from 12% in 1996 to 23% in 2006 ($P < .0001$). 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 human immunodeficiency virus, HBV, and a diagnosis of alcohol use declined slightly ($P < .01$), whereas the racial composition was relatively stable.

Adjusted Prevalence of Cirrhosis, Decompensated Cirrhosis, and HCC

As shown in Figure 5, after adjustment for sex 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 up-

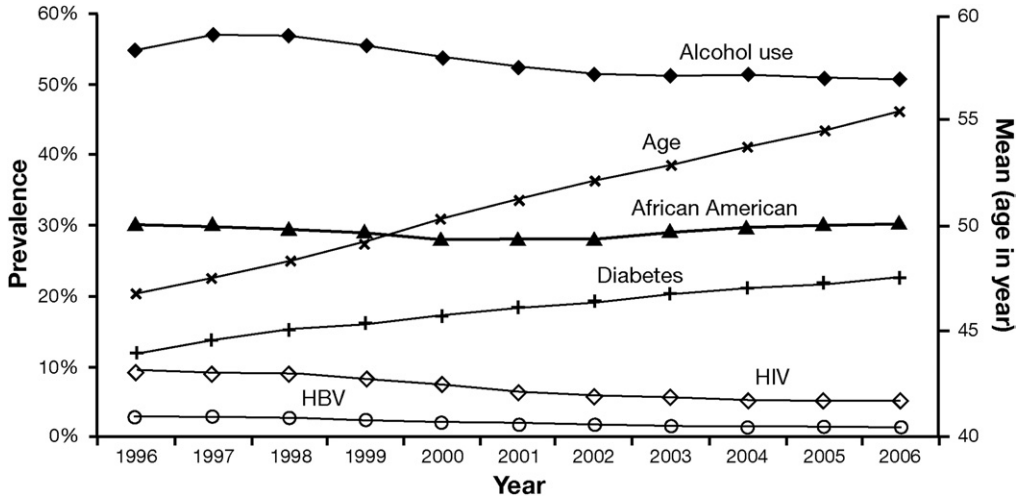

Figure 4. Changes in demographic and clinical characteristics. We plotted the crude prevalence of demographic (such as race) and clinical (such as diabetes, human immunodeficiency virus, alcohol use, and so on) characteristics (*left vertical axis*) and mean age (*right vertical axis*) against each year from 1996 to 2006.

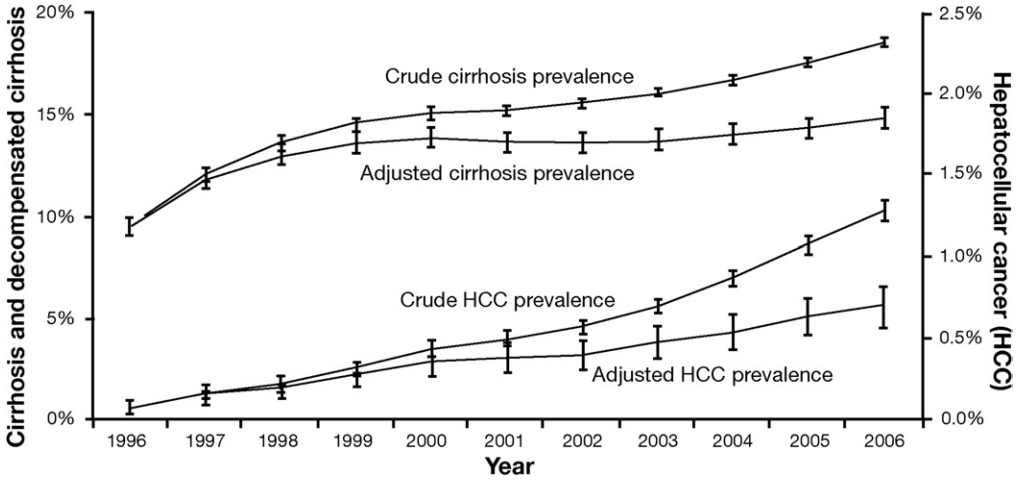

Figure 5. Age and sex-adjusted prevalence of cirrhosis and HCC. The *error bars* represent 95% CIs. The reference population is the HCV-infected VA cohort in 1996.

ward with a significant increase from 9% (95% CI, 8.7%–9.5%) in 1996 to 15% (95% CI, 14.3%–15.3%) in 2006 for cirrhosis and from 0.07% (95% CI, 0.04%–0.1%) in 1996 to 0.7% (95% CI, 0.6%–0.8%) in 2006 for HCC ($P < .001$).

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 those of the age/sex-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 US 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.[12] Results from mathematical models projected an increase in the proportion of patients with HCV who have cirrhosis to ~16% in 2000 and 25% in 2010, with an accompanying increase in decompensation, liver cancer, and liver-related deaths.[11] 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 of patients with HCV anywhere in the world.

Our study has 2 major findings. First, there was a 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, 1 of 5 patients with HCV had cirrhosis and 1 of 100 patients with HCV had HCC in 2006. 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 patients with cirrhosis who died each year, with annual mortality rates reaching 7% in 2006. Overall, 23,294, 13,724, and 1619 patients with HCV who sought care at the VA had a diagnosis of cirrhosis, hepatic decompensation, or HCC in 2006 vs 2061, 1012, and 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 patients with HCV 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, which is an estimate that is remarkably higher than some have previously projected (eg, 0.39% by Davis et al[11]). It is plausible that transferring care to the VA after development of HCC might have contributed to the prevalence, but we found that most of the patients with HCC had their condition 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 higher risk for progression to cirrhosis and HCC than nonveteran patients with HCV 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 nonveteran patients with HCV and thus would have had their infection for a longer time compared with nonveterans. If true, then it would mean that the HCC prevalence curve in the general (or nonveteran) 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.[29] These new and concurrent estimates, therefore, provide convergent validity to our report. In contrast to the higher than expected

prevalence of HCC, we found the prevalence of cirrhosis to be somewhat lower than previously predicted. Based on previous data, this disconnect is likely related to underdiagnosis of early-stage cirrhosis, possibly due to low rates of biopsy in the VA.[2,30] Thus, the prevalence of histologic 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 American Association for the Study of Liver Diseases guidelines for referral had a mention of liver transplantation in their medical charts.[31] 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.[32,33] In our previous studies, we found that less than one-third of patients who were diagnosed with HCC received screening before their diagnosis.[34] In addition, we have found that the quality of health care given to patients with HCV infection falls far short of that recommended by practice guidelines.[35] 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 health care system may need to rechannel 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 the burden of cirrhosis in HCV. Moreover, most of the patients with HCV in the VA are diagnosed as a result of a system-wide screening program, rather than after development of complications from liver disease. The presence of this unique screening mechanism makes our sample a relatively unbiased cohort. The availability of laboratory 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; 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 the presence of coexisting nonalcoholic steatohepatitis. However, given the strong association between metabolic syndrome and nonalcoholic steatohepatitis, we hypothesized that diabetes would act as a surrogate for nonalcoholic steatohepatitis. Although we had information on antiviral treatment in our database, we opted not to include this variable in our analysis. Conceptually, we expected the antiviral treatment variable to have 2 opposing effects on the prevalence of cirrhosis: (1) patients with successful antiviral treatment would be less likely to progress to cirrhosis (negative association), and (2) because patients with cirrhosis are at the highest risk for adverse disease outcomes, they would also be more likely to receive antiviral treatment (positive association). Given the low rates of antiviral 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 January 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 before 1996. This might have caused an overestimation of the prevalence of cirrhosis in the earlier years. However, we believe that this effect is likely small because most of the patients with HCV in the VA were diagnosed as a result of a widely implemented screening program for HCV in the late 1990s (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; 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 health care 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 health care 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 sensitivities and specificities of the ICD-9 coding system for our outcomes, which may vary between VA and non-VA practitioners, thus limiting the generalizability of overall rates of cirrhosis and its complications to patients with HCV outside of the VA.

Our analysis highlights that the prevalence of cirrhosis has reached very high proportions among veterans with HCV infection. Given low antiviral 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 patients with HCV in a timely manner. In light of the increasing burden of cirrhosis and HCC in patients with HCV, clinicians and the health care system may need to develop strategies targeted to provide timely and effective care to this high-risk patient population.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at doi: 10.1053/j.gastro.2010.12.032.

References

1. Armstrong GL, Wasley A, Simard EP, et al. The prevalence of hepatitis C virus infection in the United States, 1999 through 2002. Ann Intern Med 2006;144:705–714.
2. Kanwal F, Hoang T, Spiegel BM, et al. Predictors of treatment in patients with chronic hepatitis C infection—role of patient versus non-patient factors. Hepatology 2007;46:1741–1749.
3. Shatin D, Schech SD, Patel K, et al. Population-based hepatitis C surveillance and treatment in a national managed care organization. Am J Manag Care 2004;10:250–256.
4. Falck-Ytter Y, Kale H, Mullen KD, et al. Surprisingly small effect of antiviral treatment in patients with hepatitis C. Ann Intern Med. 2002;136:288–292.
5. Backus LI, Boothroyd DB, Phillips BR, et al. Predictors of response of US veterans to treatment for the hepatitis C virus. Hepatology 2007;46:37–47.
6. Seeff LB, Buskell-Bales Z, Wright EC, et al. Long-term mortality after transfusion-associated non-A, non-B hepatitis. N Engl J Med 1992;327:1906–1911.
7. Alter MJ, Hadler SC, Judson FN, et al. Risk factors for acute non-A, non-B hepatitis in the United States and association with hepatitis C virus infection. JAMA 1990;264:2231–2235.
8. Sanchez-Tapias JM, Barrera JM, et al. Hepatitis C virus infection in patients with nonalcoholic chronic liver disease. Ann Intern Med 1990;112:921–924.
9. Alter MJ. The epidemiology of acute and chronic hepatitis C. Clin Liver Dis 1997;1:559–568.
10. Armstrong GL, Alter MJ, McQuillan GM, et al. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. Hepatology 2000;31:777–782.
11. Davis GL, Albright JE, Cook SF, et al. Projecting future complications of chronic hepatitis C in the United States. Liver Transpl 2003;9:331–338.
12. Wise M, Bialek S, Finelli L, et al. Changing trends in hepatitis C-related mortality in the United States, 1995-2004. Hepatology 2008;47:1128–1135.
13. Dominitz JA, Boyko EJ, Koepsell TD, et al. Elevated prevalence of hepatitis C infection in users of United States veterans medical centers. Hepatology 2005;41:88–96.
14. Backus LI, Gavrilov S, Loomis TP, et al. Clinical case registries: simultaneous local and national disease registries for population quality management. J Am Med Inform Assoc 2009;16:775–783.
15. Kramer JR, Davila JA, Miller ED, et al. The validity of viral hepatitis and chronic liver disease diagnoses in Veterans Affairs administrative databases. Aliment Pharmacol Ther 2008;27:274–282.
16. Kramer JR, Giordano TP, Souchek J, et al. The effect of HIV coinfection on the risk of cirrhosis and hepatocellular carcinoma in U.S. veterans with hepatitis C. Am J Gastroenterol 2005;100:56–63.
17. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38:518–526.
18. Poynard T, Ratziu V, Charlotte F, et al. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. J Hepatol 2001;34:764–767.
19. Wiley TE, Brown J, Chan J. Hepatitis C virus infection in African Americans: its natural history and histological progression. Am J Gastroenterol 2002;97:700–706.
20. Harris DR, Gonin R, Alter HJ, et al. The relationship of acute transfusion-associated hepatitis to the development of cirrhosis in the presence of alcohol abuse. Ann Intern Med 2001;134:120–124.
21. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus infected patients. Hepatology 1999;30:1054–1058.
22. Thomas DL. Hepatitis C and human immunodeficiency virus infection. Hepatology 2002;36(Suppl 1):S201–S209.
23. Tsai JF, Jeng JE, Ho MS, et al. Independent and additive effect modification of hepatitis B and C virus infection on the development of chronic hepatitis. J Hepatol 1996;24:271–276.
24. Pontisso P, Gerotto M, Benvegnu L, et al. Co-infection by hepatitis B virus and hepatitis C virus. Antivir Ther 1998;3:137–142.
25. Hourigan LF, MacDonald GA, Purdie D, et al. Fibrosis in chronic hepatitis C correlates significantly with body mass index and steatosis. Hepatology 1999;29:1215–1219.
26. Powell EE, Cooksley WG, Hansen R, et al. The natural history of nonalcoholic steatohepatitis: a follow-up study of forty-two patients for up to 21 years. Hepatology 1990;11:74–80.
27. Mason AL, Lau JY, Hoang N, et al. Association of diabetes mellitus and chronic hepatitis C virus infection. Hepatology 1999;29:328–333.
28. El-Serag HB, Everhart JE. Diabetes increases the risk of acute hepatic failure. Gastroenterology 2002;122:1822–1828.
29. Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. Gastroenterology 2010;138:513–521.
30. Crocker JA, Lyon WW, Sterling RK, et al. Detecting undiagnosed cirrhosis and monitoring quality of surveillance for hepatocellular carcinoma using stored data from computerized patient records: a pilot study. Hepatology 2008:51:358A.
31. Julapalli VR, Kramer JR, El-Serag HB; American Association for the Study of Liver Diseases. Evaluation for liver transplantation: adherence to AASLD referral guidelines in a large Veterans Affairs center. Liver Transpl 2005;11:1370–1378.
32. Wilbur K, Sidhu K. Beta blocker prophylaxis for patients with variceal hemorrhage. J Clin Gastroenterol 2005;39:435–440.
33. Singh H, Targownik LE, Ward G, et al. An assessment of endoscopic and concomitant management of acute variceal bleeding at a tertiary care centre. Can J Gastroenterol 2007;21:85–90.
34. Davila JA, Weston A, Smalley W, et al. Utilization of screening for hepatocellular carcinoma in the United States. J Clin Gastroenterol. 2007;41:777–782.
35. Kanwal F, Schnitzler MS, Bacon BR, et al. Quality of care in patients with chronic hepatitis C virus infection: a cohort study. Ann Intern Med 2010;17:231–239.

Received December 20, 2009. Accepted December 10, 2010.

Reprint requests

Address requests for reprints to: Fasiha Kanwal, MD, MSHS, Saint Louis VA Medical Center, 915 N Grand, 111/JC-GI, St Louis, Missouri 63141. e-mail: fasiha.kanwal@va.gov; fax: (310) 289-7035.

Acknowledgments

The authors thank the Hepatitis C Clinical Case Registry for the data used in this study.

Conflicts of interest

The authors disclose no conflicts.

Funding

Supported in part by Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs, grant IIR-07-111 (to F.K.) and K24DK078154-03 and R01CA125487-03 (to H.B.E.).

Supplementary Table 1. Timing of Diagnosis of Cirrhosis and HCC in Relation to the Duration of Follow-up in the VA Health Care System

Time of diagnosis	Cirrhosis (%)	HCC (%)
First year	20.6	10.2
Second year	9.5	7.5
Third year	8.4	8.3
Fourth year	11.4	10.2
Fifth year or later	50.1	63.6

NOTE. For this analysis, we primarily focused on patients who were diagnosed with cirrhosis or HCC on or after January 1, 2000. We used this cutoff to allow for a sufficient washout period between 1996 and diagnosis of cirrhosis or HCC and thus minimized the possibility of misclassification of the patients' first visit to the VA.