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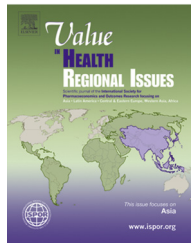

Estimating the Incidence and Prevalence of Chronic Hepatitis C Infection in Taiwan Using Back Projection

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ABSTRACT

Objective: Hepatitis C virus (HCV) infection is the leading cause of liver disease, and Taiwan has among the highest prevalence of HCV infection in the general population in Northeast Asia, estimated at between 2% and 4%. The aim of this study was to estimate the number of patients living with chronic HCV infection in Taiwan and quantify the expected numbers in each of the five Metavir fibrosis stages. **Methods:** We applied a back-projection approach, using observed hepatocellular carcinoma incidence between 1979 and 2008 and a smoothed Expectation-Maximization algorithm to maximize a Poisson likelihood to estimate the previous incidence of HCV infection. The algorithm was coded in Excel and combined with the MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis model (a hepatitis C natural history markov model) to predict the past and future numbers in each Metavir fibrosis stage. **Results:** Incident cases were predicted to have peaked in 1972 at 56,634 annually, with the prevalence peaking in 1986 at 763,737 infections and falling to 578,203 infections in 2012. It was estimated that in 2012, 127,795 (23.0%), 105,545 (19.0%), 81,211 (14.6%), 123,939 (22.3%), and 116,823 (21.1%) subjects were in fibrosis stages F0, F1, F2, F3, and F4, respectively. **Discussion:** Our study provides HCV infection prevalence estimates, stratified by Metavir fibrosis stage, in Taiwan for 2012. This has potential implications for budget planning, particularly with the availability of emerging therapies because fibrosis stage is predictive of both rapid and sustained virological response; therefore, planning expected treatment response in a given population could be enhanced with this additional information.

Keywords: chronic, cirrhosis, fibrosis, hepatocellular, liver.

Introduction

Hepatitis C virus (HCV) infection is the leading cause of liver disease and a major public health burden; approximately 130 to 170 million people are estimated to be infected globally [1]. Incidence rates across the world fluctuate, and accurate estimates are difficult to obtain because of the asymptomatic, often latent nature of the disease before clinical presentation. The World Health Organization estimates that HCV infects 3 to 4 million people every year [2]; of these, approximately 20% to 30% will spontaneously clear the virus; the remaining develop chronic HCV infection and are at risk of progressing to compensated cirrhosis, decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and premature death. Taiwan has among the highest prevalence of HCV infection in the general population in Northeast Asia [3], estimated at between 2% and 4% (463,000 and 927,000) [4].

The period between infection and end-stage liver disease (ESLD) is highly variable [5]. On average, around 10% to 20% of the subjects with HCV infection will progress to ESLD within 10 to 20 years following infection [6]. This has important implications because the current health care burden associated with treating HCV infection and managing ESLD complications is relatively small compared with the potential future cost associated with treating those progressing over the coming years. Furthermore, as patients age and their disease progresses, the number presenting either with ESLD or for treatment will increase substantially. Consequently, knowledge of historic infection rates and disease prevalence estimates is informative for developing effective public health management strategies for screening and treatment. Estimates of the number of subjects living with chronic HCV infection and the extent of fibrosis are important because treatment response is reduced in patients with advanced fibrosis. Identifying treatment-eligible patients and initiating the most cost-effective treatment option will become increasingly relevant in the very near future.

The aim of this study was to estimate the number of patients living with chronic HCV infection in Taiwan and quantify the expected numbers in each of the five Metavir fibrosis stages.

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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Methods

Back Projection

Back projection, also known as back-calculation, is a technique that has been used extensively to estimate historic HIV infection levels given knowledge of AIDS incidence [5]. The technique has also been applied to estimate the incidence and prevalence of hepatitis C infection in the United Kingdom [7], France [8], and Australia [9]. Estimating chronic HCV infection incidence and prevalence via back projection typically uses routinely coded HCV-related ESLD events, such as DC or HCC, together with an estimate of the time between chronic infection and progression to ESLD to calculate the unobserved infections that must have occurred in the past.

The technique can be implemented in a number of ways, ranging from statistical to deterministic [10–12]. The approach taken in this study was to use a smoothed Expectation-Maximization algorithm to maximize a Poisson likelihood. We assume that the incidence of chronic HCV infection cases occurs as an independent random process in which the number of individuals developing chronic HCV infection following infection in period t is denoted as N_t and the number of subjects with HCV-related HCC is denoted as Y_t, where $t=1,2,\ldots,T$. In the current implementation, T represents the last year of recorded HCC included in the analysis (2008) and each t is equivalent to one calendar year. The number of expected HCV-related HCC cases in year t is given by

$$E[Y|N_1,N_2,\ldots,N_t]=\sum_{i=1}^{t} N_i f_{t-i}$$

The mean number of HCC cases in year t is then given by

$$\mu_t=\sum_{i=1}^{t} \lambda_i f_{t-i}$$

where $\mu_i=E[Y_t]$ and $\lambda_i=E[N_i]$

Assuming that all HCV infections are independent Poisson variates, the log likelihood function is given by

$$\log L(\lambda|y)=\sum_{t=1}^{T}[y_t \log(\mu_t)-\mu_t]$$

where μ is given by the second equation.

The Expectation-Maximization algorithm was coded in Visual Basic for Applications within Microsoft Excel.

Data

Data on HCC incidence for the period 1979 to 2008 were obtained from the Taiwan National Cancer Registration Database. Our analysis required HCV-specific HCC event data; therefore, an adjustment was made that accommodated secular trends in hepatitis B virus (HBV) and HCV-associated HCC in line with reported male- and female-specific HBV-related HCC over the period 1981 to 2001 [4]. In men, HBV-related HCC decreased from 81.5% in the period 1981 to 1983 to 66.2% in the period 1999 to 2001. In women, HBV-related HCC decreased from 66.7% in the period 1981 to 1983 to 41.4% in the period 1999 to 2001. We further assumed that 10.5% (males) and 11.3% (females) of the HCC cases were unrelated to either HBV or HCV. Figure 1 shows the unadjusted HCC data alongside estimated HCV-specific HCC incidence data. The upper and lower limits for estimated HCV-specific HCC were obtained by using reported confidence intervals for secular trends in HBV-related HCC in Taiwan.

Back projection is relatively inaccurate at predicting recent infection rates; as such, it was necessary to provide a minimum HCV incidence within the model. Because information on HCV incidence within Taiwan is extremely limited, the infection rate was estimated from US data and applied to the Taiwan population. It was estimated that 5.437 people in every 100,000 are infected with HCV each year [13]. This rate was applied to the Taiwan population to give an annual incidence of 1260.

Model

The natural history of progression from chronic infection to HCC was obtained by using the MOdelling the NAtural histoRy and Cost-effectiveness of Hepatitis model. This is a cohort-based Markov lifetime simulation that has previously been described in detail [14]. In brief, the model iterates a cohort through annual cycles starting at Metavir disease stage F0 (no fibrosis) and progressing though F1 (portal fibrosis with no septa), F2 (portal fibrosis with few septa), F3 (portal fibrosis with numerous septa), and F4 (compensated cirrhosis). The model flow diagram is shown in Figure 2. Progression through fibrosis stages is controlled via stage-specific transition probabilities influenced by the duration of HCV infection, age at infection, sex, genotype, source of infection, and excessive alcohol consumption [15]. Table 1 reports the transition rates used in the model. We assumed that 54% of the infections were genotype 1 [3].

In addition to estimating the number of chronic HCV infection cases (F0), the number of individuals progressing through fibrosis

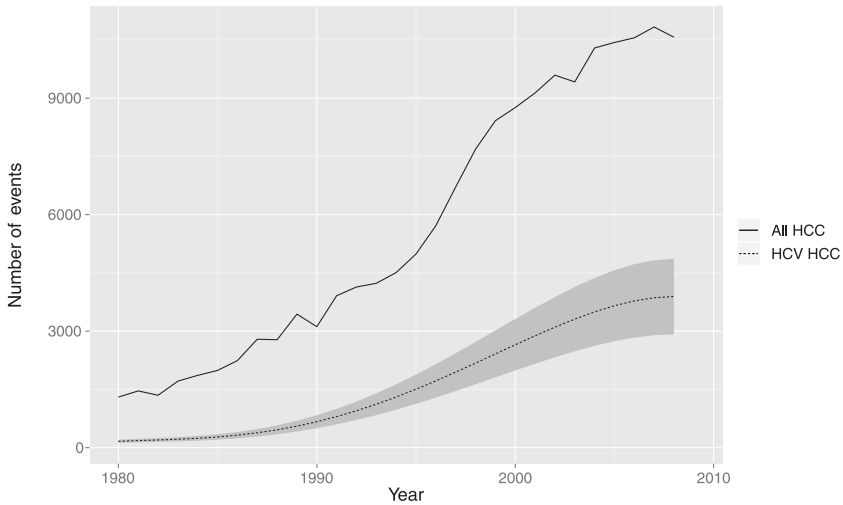

Fig. 1 – Incident cases of confirmed HCC in Taiwan with estimated HCV-related HCC. HCV, hepatitis C virus.