Projected Future Increase in Aging HCV-Infected Liver Transplant Candidates: A Potential Effect of HCC

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Abbreviations

HCV, hepatitis C virus

US, United States

HCC, hepatocellular carcinoma

OPTN, Organ Procurement and Transplantation Network

Background: In the US, the peak hepatitis C (HCV) antibody prevalence of 4% occurred in persons born in calendar years 1940 to1965. **Aim:** To examine observed and projected age-specific trends in the demand for liver transplantation (LTx) among patients with HCV-associated liver disease stratified by concurrent hepatocellular carcinoma (HCC). **Methods**: All new adult LTx candidates registered with the Organ Procurement and Transplantation Network for LTx between 1995 and 2010 were identified. Patients who had primary, secondary, or text field diagnoses of HCV with or without HCC, were identified. **Results:** There were 126,862 new, primary registrants for LTx, 52,540 (41%) with HCV. The number of new registrants with HCV was dramatically different by age at calendar year, suggesting a birth cohort effect. When stratified by birth year in 5-year intervals, the birth cohorts with the highest frequency of HCV in decreasing order were those born 1951-1955, 1956-1960, 1946-1950, and 1941-1945. These four birth cohorts, spanning 1941 to1960 accounted for 81% of all new registrants with HCV. A 4-fold increase in new registrants with HCV and HCC occurred between calendar years 2000 to 2010 in the 1941-1960 birth cohorts. By 2015, we anticipate an increasing proportion of new registrants with HCV will have HCC and be over the age of 60 (born on or before 1955). **Conclusions:** The greatest demand for LTx due to HCV-associated liver disease is occurring among individuals born between 1941 and1960. This demand appears to be driven by the development of HCC in patients with HCV. Over the coming decade, the projected increase in demand for LTx from an aging HCV infected population will challenge the transplant community to reconsider current treatment paradigms.

Introduction

Hepatitis C virus (HCV) is the most common blood-borne infection and a leading cause of liver disease in the United States (US). [1] An estimated 1.3% of the total US population is chronically infected with HCV. [1] Among individuals who have been infected with chronic HCV for 20 to 30 years, 10-20% will develop cirrhosis and 1-5% will develop hepatocellular cancer. [2] This high burden of HCV disease in the US has made HCV the leading indication for liver transplantation (LTx) in the US. [3]

Several studies have characterized the epidemiology and estimated future burden of HCV disease in the US. The leading modes of transmission are injection drug use and transfusion of HCV infected blood products. The peak incidence of new cases occurred during the calendar years of 1970 to 1989 with an observed 85% drop in incidence after 1989 attributable to improved screening of blood products and interventions targeting prevention of human Immunodeficiency virus. [1, 4] The peak HCV antibody prevalence of 4% occurred in persons born in calendar years 1940 to1965. [5] This birth cohort, born between 1940 and 1965, passed through their high-risk period (ages 20 to 35) during the period of high incidence of HCV infection (1970 to 1989). [5] As the duration of HCV infection in this high HCV prevalence birth cohort increases, the prevalence of complications related liver disease is projected to increase dramatically over the next 10 to 20 years. [2, 5] Based on US population data, Davis *et al* project that from 2000 to 2030, the number patients with HCV related cirrhosis will climb nearly 2 fold, from 472,000 to over 879,000. [2] Age-specific trends were not included in these projections of the burden of HCV disease in the US. In a subsequent study, Wise *et al*. reported age-specific trends in HCV associated mortality in the US showing increased rates in 55 to 64 year

olds as of 2004. [6] Importantly, HCV is the leading risk factor associated the development of hepatocellular carcinoma in the US, implicated in up to 47% cases. [7] Modeled simulations of the complications of chronic HCV infection predict a peak incidence of cirrhosis occurring in 2020 with a continued increase in the incidence of hepatic decompensation and HCC for the next 10-13 years. [8]

In this paper, we aim to examine observed and projected age-specific trends in the burden of HCV and HCV complicated by HCC on LTx in the US. Given the dire projected trends for HCV related complications in the general population, further understanding of age-specific trends on the demand for LTx are needed.

Patients and Methods

Study Data

Data on all adult patients (≥ 18 years) who were registered for primary LTx on the waiting list in the US from 1995-2010 were obtained from the Organ Procurement and Transplantation Network. These data were available from the Standard Transplant Analysis and Research File created June 3rd 2011. New adult registrants for calendar years 1995 to 2010 were used to calculate observed annual trends and the complete data were used to generate projections. Retransplantations were excluded. Demographics, including age at registration, and liver disease diagnosis were evaluated. New registrants with a primary or secondary diagnosis of HCV or other text field entry for HCV infection at registration were analyzed as having HCV related liver disease. Similarly, new registrants with a primary or secondary diagnosis of HCC or other text field entry for HCC or at registration were analyzed as having HCC. Through this process, we identified primary LTx registrants with HCV and HCV complicated by HCC. Year of birth was calculated based on age at registration and calendar year of

registration. To facilitate comparison of new LTx registrants to published US population data, we chose age categories based on those selected by Wise et al. [6]

Statistical Analysis

Study populations were described using counts, proportions, and medians with ranges. Age specific rates for new registrants by calendar year were calculated. Poisson regression was used to examine the associations between LTx registration and birth cohort among patients with HCV related liver disease, with and without HCC. Projections of predicted counts of new registrants for calendar years outside of the range of observed data were based on extrapolation of natural cubic splines fitted to observed trends in Poisson regression models. All statistical analyses were performed using SAS v9.2 (SAS Institute, Cary, NC), and R v2.12 (R Foundation for Statistical Computing).

Results

During the study period from 1995 to 2010 there were 126,862 new registrants for liver transplantation of which 52,540 (41%) were for HCV associated liver disease. New registrants with HCV associated liver disease had a median (range) age of 52 (18 to 83), 71% were male and 10,345 (20%) also had HCC.

HCV-related liver disease: US Mortality Rates and Demand for Liver Transplantation

Previously, Wise *et al* evaluated age-specific mortality rates in the general US population among HCV infected persons between 1995 and 2004. [6] Mortality rates were increasing for persons aged 55-64 years in 2004 but flat or decreasing in persons aged 35-44, 45-54 and 65+. We evaluated these same age groups for frequency of new registrants for LTx with HCV-related liver disease. (Figure 1a) In our analyses, we found strikingly

similar age-specific trends for the demand for LTx in HCV-related liver disease as Wise *et al* found for HCV associated mortality. In calendar years 2004 to 2009, the number of new registrants with HCV increased among patients aged 55-64 years but remained flat or decrease among in patients aged 35-44, 45-54 and 65+ years. Next, we examined the rates of new registrations with and without HCC. The age-specific trends for new registrants with HCV and without HCC were similar to that seen in the whole group. (Figure 1b) However, in patients whose HCV was complicated by HCC, this trend was more evident with a dramatic rise in the rate of new registrants in patients between the ages of 55 to 64 years and a decline in those between the ages of 45 to 54 years. (Figure 1c) This pattern of a decline in the 45-54 year old age group and rise in the 55-64 year old age group is suggestive of a birth cohort effect in which patients transition between age categories across calendar years.

In figure 2, we use 5-year age cohorts to present the age-specific trends for new registrants for liver transplantation with HCV-related liver disease. Overall, the absolute number of new registrants with HCV climbed each year from 1995 to 1999, reaching a relatively stable rate apart from a brief decline during 2002 and 2003. Similar to the mortality data reported by Wise *et al* [6], in recent calendar years, the proportion of new registrants with HCV increased in patients 50-54 and 55-59 years old and stabilized or decreased in patients 40-44 and 45-49 years old. Trends of age-specific rates of new registrants with HCV were significantly different in these age groups ($p<0.01$), and again consistent with a birth cohort effect.

Peak new HCV liver transplant registrants: 1941-1960 Birth Cohort

We stratified new registrants for LTx with HCV-related liver disease by birth cohort and age at registration. (Figure 3) Over 82% of the patients were between the ages of 40 and

59 years at the time of registration. The frequency of HCV related liver disease among birth cohorts was highest in those born from 1951-1955 followed by 1956-1960, then 1946-1950, and lowest in those born from 1941-1945. These four birth cohorts, spanning 1941 to1960 accounted for 81% of the new registrants with HCV related liver disease during the calendar years 1995 to 2010. Across calendar years, the 1941-1960 birth cohort (representing individuals aged 50-69 years in the year 2010) consistently dominates the new registrants for LTx with HCV. Interestingly, the 1961-1965 birth cohort shows a small yet increasing number of new registrants with HCV related liver disease in more current calendar years.

Hepatocellular carcinoma and observed age-specific trends

Among new registrants with HCV-related liver disease but without HCC, the 1941-1960 birth cohort is the dominant proportion of individuals yet the absolute number in this birth cohort was relatively stable (Figure 4a). When examining rates in patients with HCC, there is a dramatic increase in both the number and proportion of new registrants with HCV and HCC in the 1941-1960 birth cohort (Figure 4b); increasing approximately 4 fold between calendar years 2000 and 2010.

Projected age specific trends in new registrants for liver transplantation

Next we plotted observed and projected age-specific trends by birth cohort, stratifying patients by the absence or presence of a concurrent diagnosis of HCC. (Figures 5a and 5b) Based on rates observed up to 2010, the rates of new registrations without HCC that were born from 1941-1955 are expected to decline, with projected stability of rates in those born 1956-1960. However, for those with hepatocellular carcinoma the rates of new registrations are expected to be steady in patients born from 1941-1950, and projected to increase in patients born from 1951-1960. By 2015, patients born on or

before 1955 will be 60 years old or older. Figure 6 shows the projected rates of new HCV registrants with and without HCC born on or before1955. Largely based on a projected decline in new HCV registrants without HCC who are over age of 60 in 2015, the relative proportion of new registrants with HCC is expected to increase. By 2015, up to 40% of all new registrants with HCV who are over the age of 60 are expected to have HCC.

Discussion

Our analyses identified the 1941-1960 US birth cohort with HCV related disease as generating the greatest demand for LTx. Additionally, within this birth cohort of individuals with HCV related liver disease we found a dramatic increase in the rate of new registrants for LTx due to HCC. Interestingly, our observed and projected analyses suggest that older patients (≥60 years) with HCC will increasingly contribute to the proportion HCV infected liver transplant candidates, unless current patterns of care change dramatically.

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Prior studies of HCV epidemiology and HCV age-specific mortality have identified that the peak prevalence of HCV and mortality associated with HCV occurs in the 1940 to 1965 US birth cohort. [5, 6] Our current study identifies a similar US birth cohort effect among LTx registrants with HCV related liver disease. Specifically, individuals born from 1941-1960 dominate the demand for LTx in the US. HCC is increasing in frequency in the US, and HCV infection is the leading contributing risk factor, implicated in up to 47% cases.[7] The incidence rates of HCC in the US has more than doubled between calendar years 1985 and 1998 with point estimates increasing from 1.3 to 3.0 per 100,000 persons and reaching 4.1 per 100,000 persons in 2000. [9, 10] Adjusting for age, Kim *et.al* found an increasing incidence of HCC in new registrants for liver transplantation with

HCV. [11] Our study, using a birth cohort analysis confirms this finding and demonstrates that the increasing incidence of HCC is a significant contributor to an increase in the demand for LTx among the 1941 to 1960 birth cohort infected with HCV. Additionally, a recent study from Asahina *et al* reported that increasing age in a cohort of patients treated for HCV had a strong independent association with the incidence of HCC, particularly in those over the age of 65. [12] In this context, as the 1941-1960 birth cohort observed in our study ages, the demand for LTx among patients with HCV and HCC is unlikely to decline until other age-specific comorbidities preclude transplantation.

When complications of end-stage liver disease occur in the setting of HCV there are two likely results, death or LTx. Unlike the analyses Wise *et al* [6] that used mortality with HCV as their measure of HCV disease burden in the US, we used listing for LTx as our HCV disease burden measure. These two HCV disease burden measures showed similar age-specific trends that we demonstrate are likely a birth cohort effect occurring in the US and previously attributed to HCV transmission due to injection drug use and unavailability of tests to adequately screen blood products for HCV during the years 1970-1990.[5] In our study using listing for LTx as the HCV disease burden measure, we observed different birth cohort patterns in the rates of new registration LTx among individuals with HCV related disease depending on their HCC status. There are at least two potential epidemiologic explanations for this: 1) HCC incidence is higher in older patients; and 2) older patients with non-HCC indications for LTx (*i.e.* ascites, hepatic encephalopathy or portal hypertensive bleeding) are less likely to be referred or listed for LTx. Our study is unable to determine which or to what degree these or other explanations resulted in our observations. Another potential influence on our findings is a possible ascertainment bias related to improved documentation of HCC after 2002 with the implementation of MELD based allocation that included additional priority of patients

with HCC. Importantly, dependent on the knots in the natural cubic spline calculations, the projections of the observed data are largely based on data in the most recent 5-7 year period (ie since 2003-2005).

Characterization of observed trends and projected changes in the demographics of patients seeking liver transplantation in the US may allow for proactive planning by the US liver transplant community to adapt current treatment approaches and policies to future needs. Prior epidemiologic projections of HCV-related mortality and need for LTx predicted peak event rates in the 2014 and 2015 calendar years, respectively. [13] Using more contemporary data, our analyses demonstrate a steady rise in the demand for LTx in an increasingly older population with HCV infection driven primarily by patients with HCC. Absent an abrupt reversal of our observed rate of new registrants through 2010, the peak demand stemming from the 1941-1960 birth cohort is likely to extend beyond 2015, but increasing age and other age-related comorbidities may have a significant influence on liver transplant candidacy assessments in this birth cohort who will be 60 to 79 years old in 2020.[14] The Center for Disease Control[15-17] and others[18, 19] are currently considering expansion of HCV screening to all persons in the 1945-1965 birth cohort in the US, an approach that may increase the HCV testing rate[19, 20]. In the near term such a policy may increase HCV diagnosis rates and potentially HCC diagnosis rates but subsequently would be expected to reduce the occurrence of HCV-related liver disease[19] and associated complications such as HCC. Additionally, advances in treatment of HCV or HCC which have the potential to alter the disease course could result in lower observed HCV related disease burden, particularly over longer time horizons and if the interventions have improved tolerability in elderly patients.

Although LTx can be performed safely in highly selected candidates who are over 70 years old, [21] alternative treatment strategies may be more appropriate particularly in patients infected with HCV. The strong adverse effect of donor age on graft and patient survival after LTx is amplified in HCV infected recipients.[22, 23] But the practice of preferentially using younger donors for HCV recipients[23-26] may not be appropriate in the elderly. For patients with HCV who develop HCC, local-regional therapies or surgical resection for compensated cirrhotics may be a more efficacious use of resources than LTx. [27-33] Over the coming decade, the projected increase in demand for LTx from an aging HCV infected population will challenge the liver transplant community to reconsider current treatment paradigms.

Figures:

Figure 1a: US Age-specific new registrants for liver transplantation with HCV

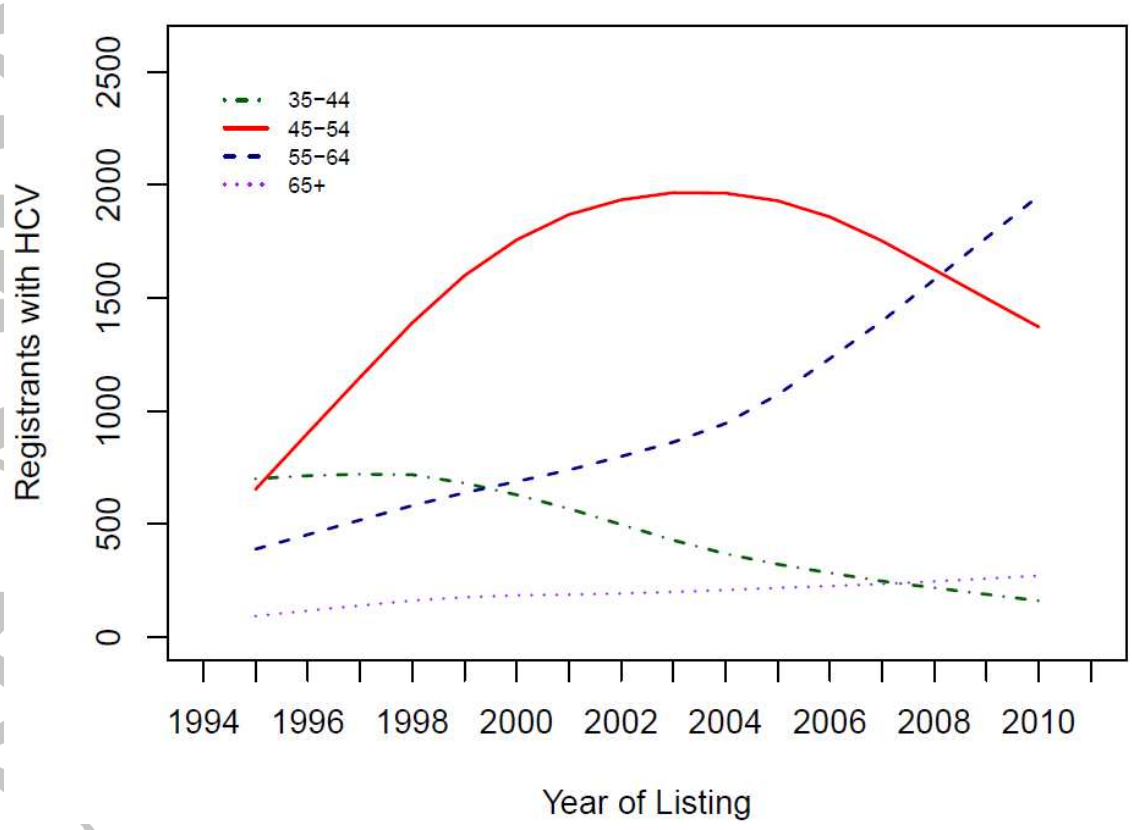


Figure 1b: US Age-specific new registrants for liver transplantation with HCV and without HCC

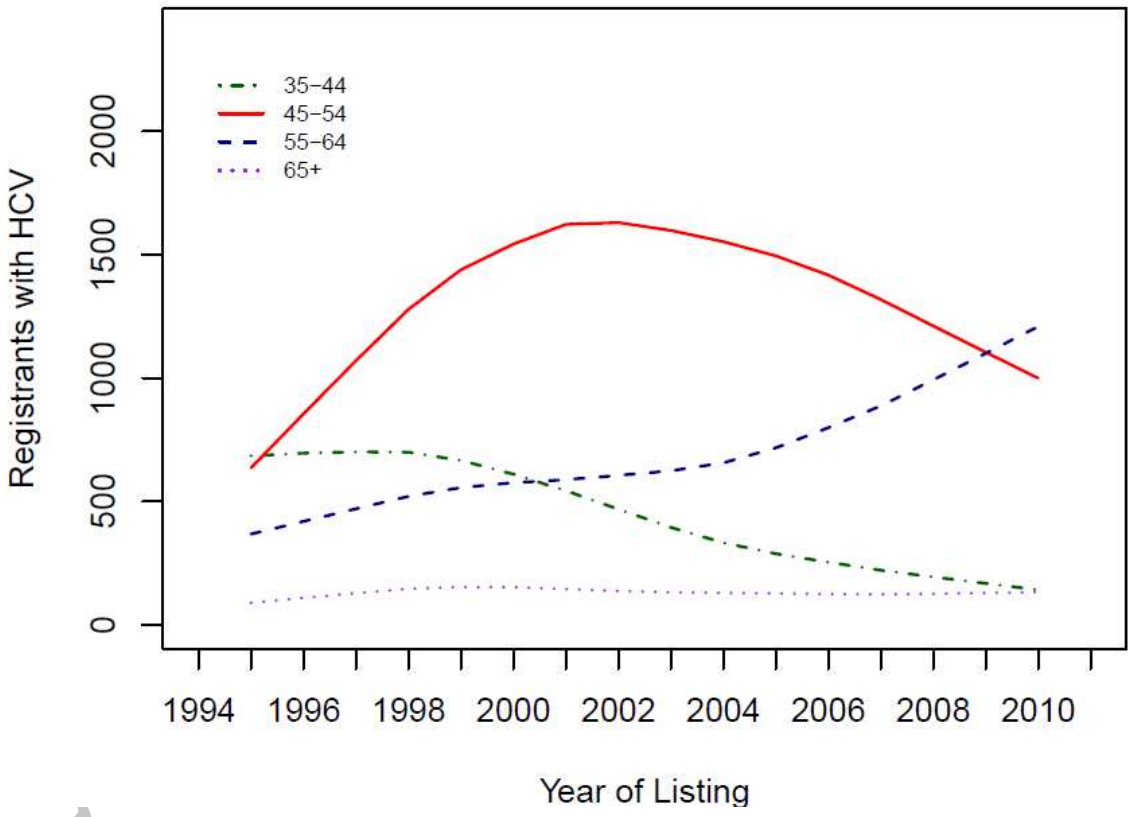


Figure 1c: US Age-specific new registrants for liver transplantation with HCV and HCC

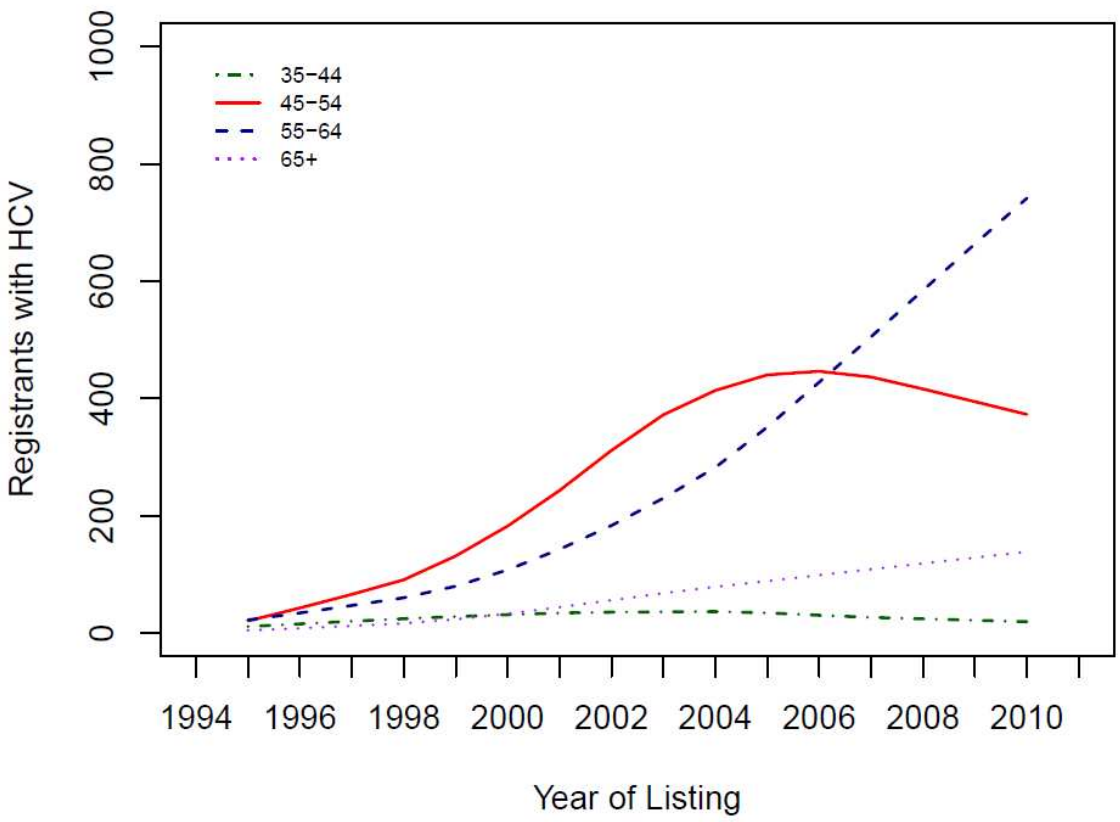


Figure 2 HCV + by listing year and age at listing for liver transplantation

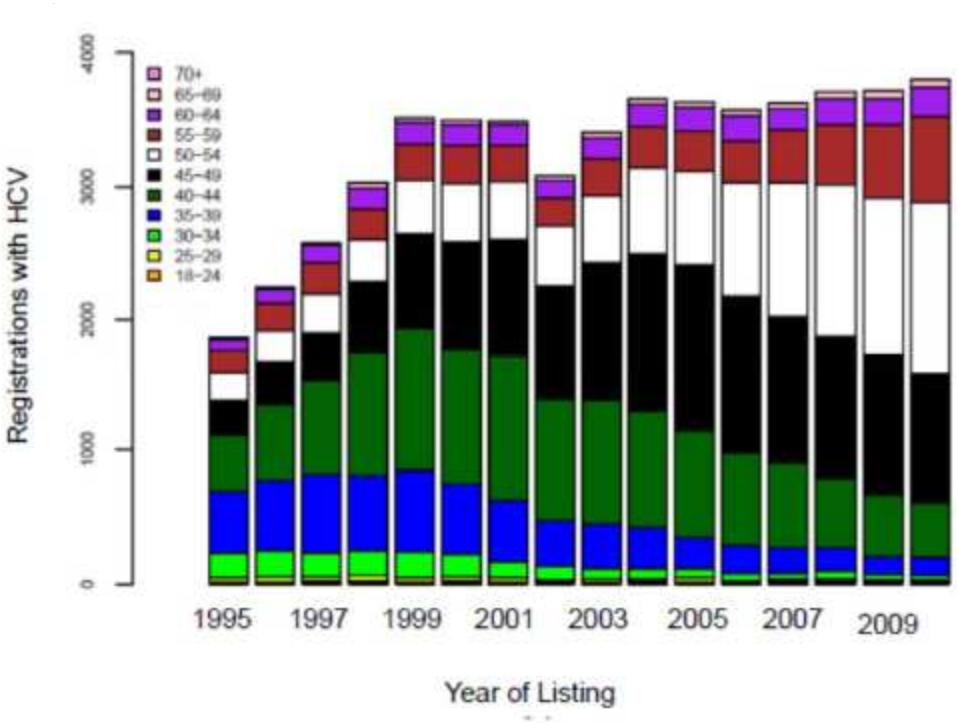


Figure 3 All new registrants for liver transplantation with HCV by listing year and birth cohort

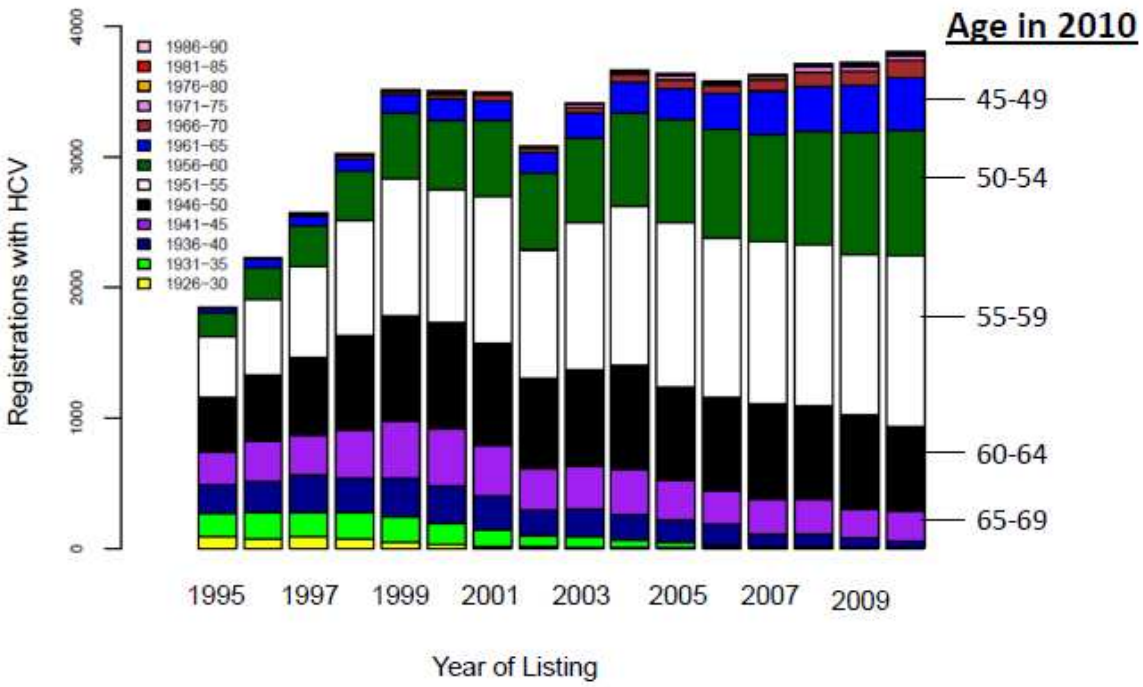


Figure 4a: HCV+ by listing year and birth cohort-without HCC

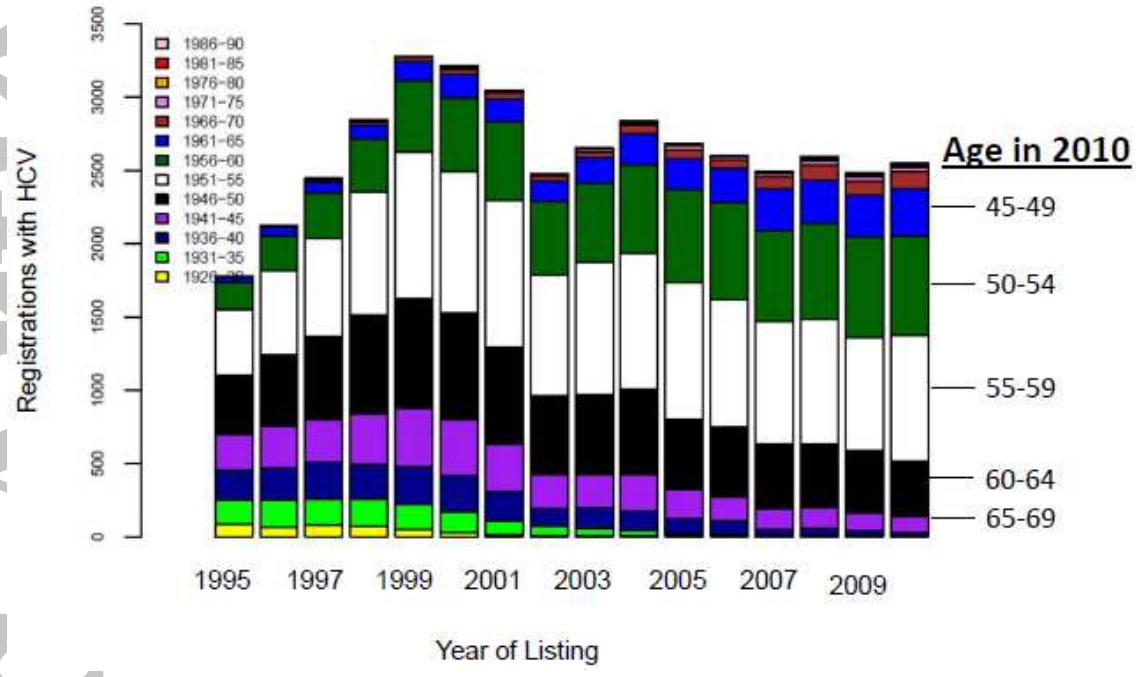


Figure 4b HCV+ by listing year and birth cohort with HCC

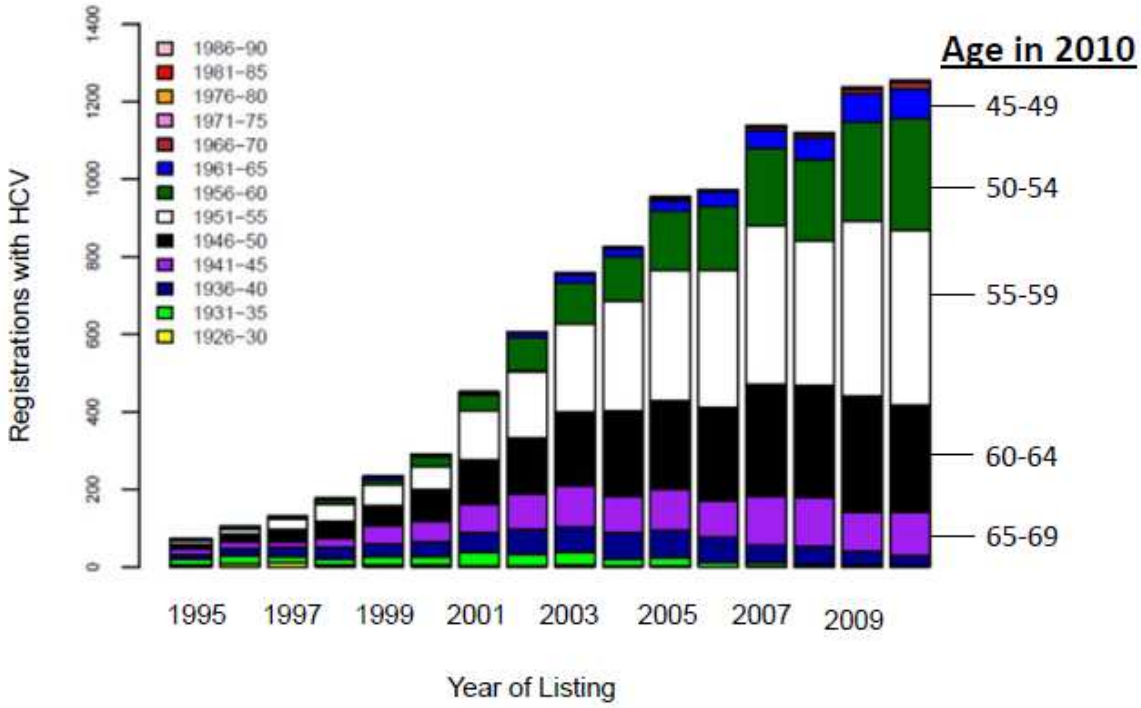


Figure 5a: Projected new registrants with HCV without hepatocellular carcinoma

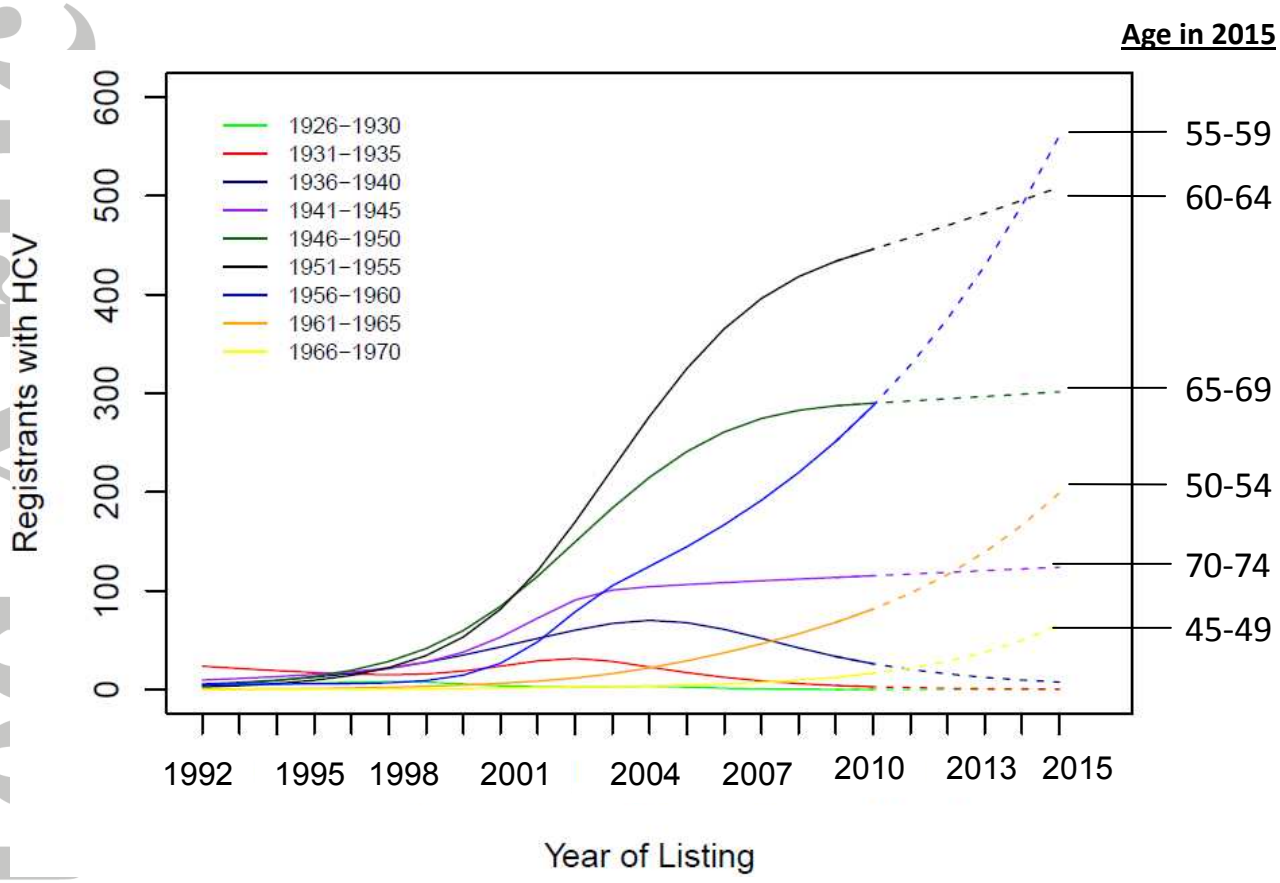


Figure 5 b: Projected new registrants with HCV with hepatocellular carcinoma

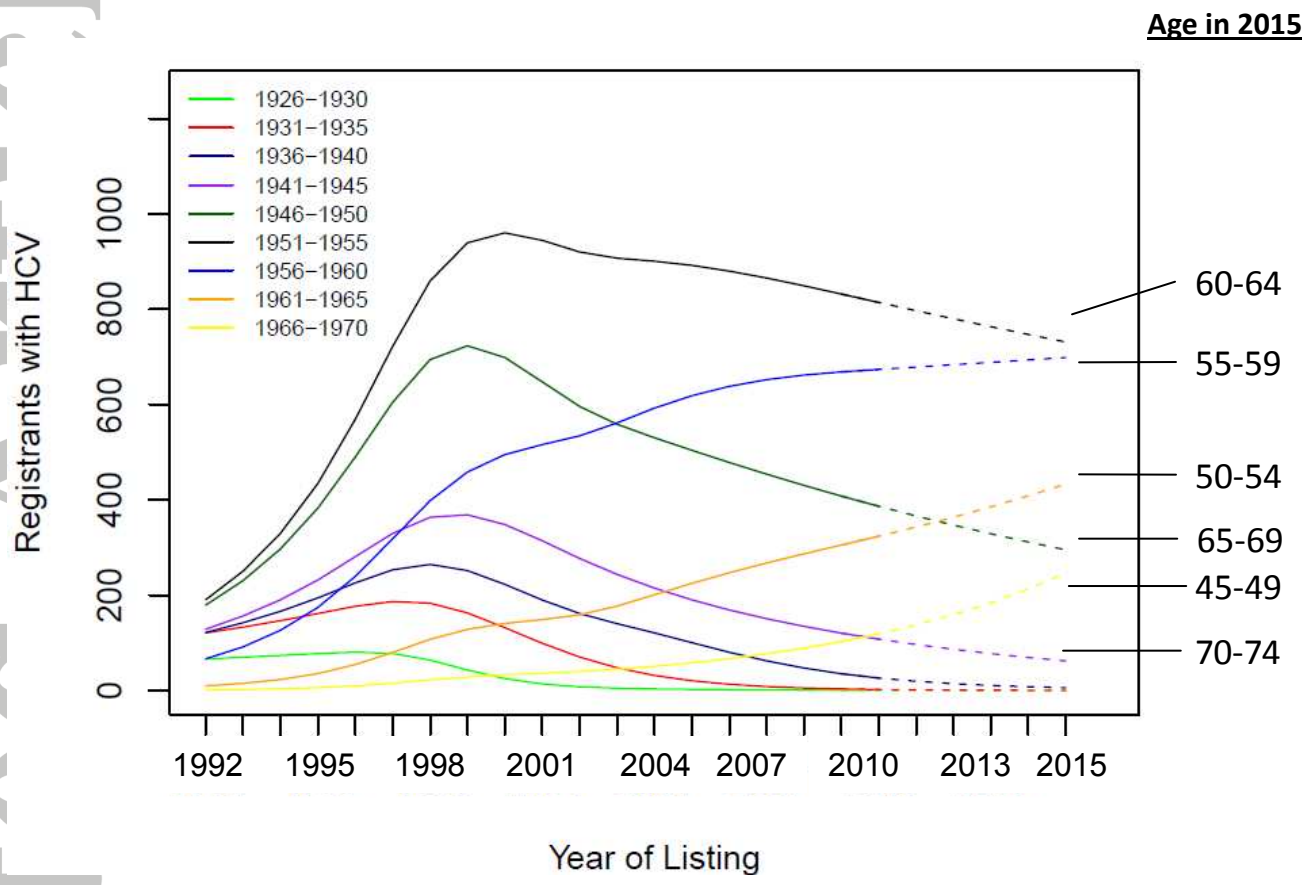
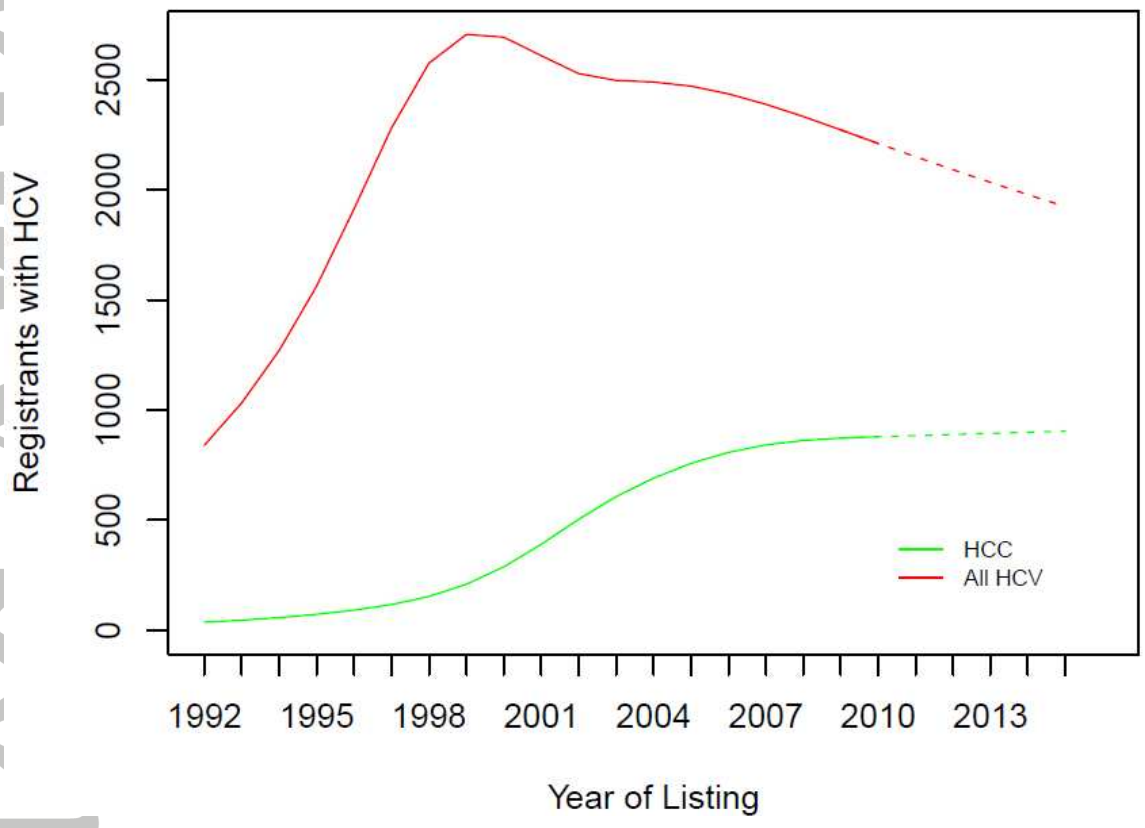


Figure 6: Observed and projected trends for new HCV registrants born on or before 1955 with and without HCC.



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