Natural History of HCV Infection

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Module 2: Evaluation, Staging, and Monitoring of Chronic Hepatitis C
Lesson 2: Natural History of HCV Infection

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Spontaneous Clearance versus Chronic Infection

Most persons who acquire hepatitis C virus (HCV) will develop chronic infection.[1] Following acute infection, HCV is very successful in establishing persistent infection by evading the immune system. Although the mechanism for the high rate of viral persistence is not completely understood, several viral and host factors play a significant role.[2,3] The actual rate of chronicity following initial infection with HCV is not well established in prospective studies, primarily because of the high percentage of persons who have asymptomatic or unrecognized early infection.[4] The chronicity rate has been estimated from cross-sectional population-based studies, such as the National Health and Nutrition Examination Survey (NHANES), as well as numerous retrospective studies.[5] Overall, it is estimated that 55 to 85% of persons who acquire HCV will develop chronic HCV infection.[6]

Role of Immune Response in Outcome of Early Infection

The rate of HCV production is high, 10^{10} to 10^{12} virions per day, and the lack of proofreading by the viral polymerase leads to enormous genetic diversity, which in turn creates a major challenge for the host immune response. This broad viral genetic diversity contributes to the high likelihood of developing chronic infection, whereas certain host factors play an important role in whether an individual will go on to spontaneously clear HCV.[7,8,9] Human and animal studies indicate that clearance of HCV is associated with strong and persistent HCV-specific cytotoxic T-lymphocyte and CD4 lymphocyte responses.[10,11] In addition, persons who clear HCV generally have limited viral diversity, which also points to enhanced immune-mediated response to acute infection.[12]

Host Factors Associated with Viral Clearance

The reason HCV infection persists in most patients but resolves spontaneously in others is not well understood. The following characteristics have been associated with a lower rate of chronicity.

- **Younger Age**: The rate of developing chronic HCV infection may be lower in younger persons, including those who acquire HCV during childhood.[13] In one study of 67 children infected with HCV through contaminated blood transfusions, only 55% developed chronic infection.[14] Similarly, in a prospective cohort that assessed viral clearance among 919 persons aged 17 years or older, there was a marginal association between age younger than 45 years and HCV viral clearance.[6]
- **Female Sex**: In a large retrospective analysis of more than 704 women who acquired HCV after receiving contaminated Rh immune globulin, 55% of the 704 women developed chronic HCV infection, a rate on the lower end of that typically reported.[15] In addition, several multicenter prospective studies of patients with acute HCV have reported women were more likely than men to experience

spontaneous clearance of HCV.[8,16]

- **Race**: In the NHANES study, the rate of developing chronic HCV infection was determined by the prevalence of HCV RNA positivity among persons who had a positive HCV antibody test.[5] Overall, HCV viremia was present in 74% of persons with a positive HCV antibody test; however, the rate was 98% for African American men.[5] In a prospective cohort study involving 1,667 persons who inject drugs, African Americans were more likely to develop chronic infection than other races (91% versus 64%).[6] This racial difference in spontaneous clearance may be accounted for, at least in part, by differences in the IL28B gene (presence of CT and TT alleles) and other variations in alleles, which have been associated with a lower rate of spontaneous clearance and may be more prevalent among persons of African descent.[17,18,19]
- **Symptomatic Acute HCV Infection**: In a variety of studies, individuals who presented with clinical symptoms of acute HCV infection, particularly those who developed jaundice, were less likely to develop chronic infection.[3,4] It is believed that severe acute infection reflects a more vigorous immune response that results in higher clearance of HCV and thus a lower rate of chronicity.
- **Absence of HIV Coinfection**: In a prospective study of persons who inject drugs (PWID) who acquired HCV, those with HIV were more likely to develop chronic infection than those who did not have HIV.[20] In a subsequent study that enrolled persons with early HCV infection, HCV persisted in 95% of those with HCV and HIV coinfection and persistence was associated with relatively weak HCV-specific T cell responses.[21] Other studies have similarly shown relatively lower clearance of HCV in persons with HIV coinfection and one prospective study of viral clearance among 9,191 persons age 17 years and older found an association between lower CD4 count and decreased odds of HCV clearance.[22,23]
- **IL28B CC Genotype**: The single nucleotide polymorphism (SNP) rs12979860 is located upstream from the IL28B gene that encodes for interleukin 28 (also referred to as interferon lambda). Variations in the rs12979860 SNP have been associated with the probability of clearance of HCV.[17,24,25] Individuals with the CC allele of IL28B genotype are more likely to spontaneously clear HCV than those with CT or TT genotypes. In one report involving 1,008 individuals, those with CC genotype cleared the virus 53% of the time compared with a clearance rate of 23% for those with the TT genotype (Figure 1).[17]

Variable Outcomes of Chronic Infection

Studies Related to Natural History

The natural history of chronic HCV infection has not been fully delineated. It is difficult to design studies that convincingly define the natural history of chronic HCV infection for multiple reasons, including the difficulty of accurately establishing the time of initial HCV infection, which sets the timeline for determining duration of infection, and the necessity of following persons with HCV for decades to see clinical complications.[13,26]

Timing of Development of Liver Complications

Once chronicity is established, available data suggest the process runs an indolent course for the first two decades after infection. If serious liver disease related to chronic HCV infection (e.g., cirrhosis, end-stage liver disease [ESLD], and/or hepatocellular carcinoma [HCC]) develop, such complications are more likely to emerge in the third and fourth decades after initial infection (Figure 2).

Estimates of Frequency of Liver Complications

Among those with chronic HCV, an estimated 20 to 30% will develop cirrhosis, and among those with HCV-related cirrhosis, there is an approximately 1 to 4% annual risk of developing HCC and a 2 to 5% annual risk of progressing to ESLD (Figure 3).[2,27,28]

Fibrosis and Cirrhosis

Annual rates of progression to cirrhosis increase with older age at the time of HCV acquisition and longer duration of infection, but the relationship is not linear.[29] It is estimated that approximately 20 to 30% of those infected with HCV will develop cirrhosis during the 20- to 30-year period after HCV acquisition.[27,30] This progression is variable, and it is impossible to predict the expected outcome for an individual early in the course of their disease. There are no predictive models that can accurately estimate the risk of disease progression, which is mediated by host, viral, and environmental factors.[31]

Host Factors that Impact Rate of Fibrosis Progression

Multiple factors can influence the natural history, rate of fibrosis progression, and survival of persons with chronic HCV infection, including host factors.[27,32]

Age

The progression of liver fibrosis in persons infected with chronic HCV appears to accelerate at a faster rate in persons older than 40 years of age, when compared to younger individuals. The reason for this age-related difference in fibrosis progression is not known, but may relate to reduced regenerative capacity of the liver or decreased hepatic blood flow in older persons.[27,32] In addition, older age at acquisition of HCV is associated with a more rapid rate of fibrosis progression (Figure 4).[33,34,35] In one study, development of cirrhosis within 20 years of HCV infection occurred in only 2% of participants who acquired HCV before the age of 20, but it developed in 63% of the individuals who acquired HCV after the age of 50.[36]

Rate of Progression by Sex

Multiple studies in persons with chronic HCV have shown that males experience a more rapid fibrosis progression than females.[33,37,38] Even when controlling for alcohol consumption, duration of infection, and age, men still have a fibrosis progression rate approximately twice that of women.[33] The explanation for the more rapid progression in men is not clear, but may relate to differences in sex hormones.[27] Several studies have shown an association between increased serum testosterone levels and advanced hepatic inflammatory activity in men.[39] More recently, investigators have reported that certain variants in genes involved in androgen and estrogen biosynthesis correlate with increased risk of accelerated hepatic fibrosis and inflammation in males.[40]

Metabolic Factors (Obesity, Insulin Resistance, and Hepatic Steatosis)

The relationship between body weight, insulin resistance, and hepatic steatosis is complex. Hepatic steatosis has been strongly associated with fibrosis progression and risk of HCC (Figure 5).[41,42,43] In addition, insulin resistance and diabetes mellitus are independently associated with increased fibrosis progression.[44,45] Given that persons with chronic HCV are more likely than healthy controls to have insulin resistance and diabetes mellitus, it is difficult to tease out the relative importance of obesity on the progression of fibrosis independent of hepatic steatosis and insulin resistance.

Viral Factors that Impact Rate of Fibrosis Progression

Several viral factors may significantly impact the rate of fibrosis progression.

HCV Factors

In general, the HCV RNA level and HCV genotypes do not appear to influence the progression of liver disease.[6] One exception is the impact of chronic infection with HCV genotype 3. Multiple studies have shown that persons infected with genotype 3 have a higher prevalence of hepatic steatosis on liver biopsy, which has been associated with a greater likelihood of progression to cirrhosis and HCC.[46,47,48,49,50]

Coinfection with HIV

Coinfection with HIV accelerates the course of HCV-related liver damage and progression to cirrhosis (Figure 6), ESLD, HCC, and death.[51,52,53] A meta-analysis of studies examining the impact of HIV on the course of HCV infection (using cirrhosis and decompensated liver disease as their endpoints) yielded an adjusted relative risk of 2.92 for persons with HCV and HIV coinfection compared with persons who have HCV monoinfection.[54] In this same review, studies that only examined decompensated liver disease showed an even higher relative risk of 6.14 with coinfection.[54] In persons with HIV infection, CD4 count less than 200 cells/mm^3, alcohol consumption, and older age at the time of HCV acquisition are independently associated with accelerated fibrosis progression.[52] The mechanism whereby HIV causes accelerated hepatic fibrosis in persons with HCV remains unclear, but may result from an alteration in the host cytokine milieu that favors fibrosis, possibly related to HIV-related depletion in gut-associated lymphoid tissue and enhanced microbial translocation.[53] Unfortunately, it appears that fully suppressive therapy for HIV only partially neutralizes the negative impact of HIV on HCV-related progression of liver disease.[53,55]

Coinfection with Hepatitis B

Approximately 2 to 10% of persons with chronic HCV infection have coinfection with hepatitis B.[27] Most studies, although small and mostly retrospective, suggest that coinfection with HBV and HCV accelerates liver disease progression, increases the risk of cirrhosis, HCC, and death.[56,57] The adverse impact of HBV coinfection only occurs in patients with ongoing HBV replication (viremia).[57]

Environmental Factors that Impact Rate of Fibrosis Progression

Several environmental factors have been shown to impact the rate of fibrosis progression in persons with chronic HCV infection.

Alcohol

Use of alcohol in the setting of HCV has consistently been associated with an increased risk of progression to cirrhosis. Most studies that have examined the impact of alcohol on fibrosis progression quantify alcohol intake based on the number of grams of alcohol ingested on a daily basis. As a rough guide, the National Institute on Alcohol Abuse and Alcoholism defines “a standard drink of alcohol” as approximately 14 grams of alcohol, with the following considered one standard drink equivalent: 12 ounces of regular beer, 8 to 9 ounces of malt liquor, 5 ounces of table wine, or 1.5 ounces of hard liquor. In a study of more than 2,000 persons living with HCV infection in France, daily consumption of over 50 grams of alcohol was associated with a 38% increase in fibrosis progression.[36] Another study involving persons with HCV infection found accelerated fibrosis progression in persons with excessive alcohol intake (greater than 40 grams per day for women and greater than 60 grams per day for men) (Figure 7).[58] In addition, alcohol use has also been associated with development of HCC and mortality.[59,60] In a study using population-based mortality data, heavy alcohol use in the setting of HCV infection was strongly associated with premature death.[61]

Cannabis

Data on cannabis intake and its impact on the natural history of HCV are conflicting.[62,63,64,65] In several studies, daily use of cannabis (marijuana) has been associated with accelerated fibrosis progression.[63,64,66] In one study, a strong independent association was found between heavy use of marijuana and hepatic steatosis, and the authors postulated a possible steatogenic role of marijuana on the endogenous cannabinoid system.[64] Other studies, however, have shown that regular use of cannabis in persons with chronic HCV reduces insulin resistance and the risk of hepatic steatosis.[62,65] Ultimately, the evidence base is mixed and not supportive of an overt association between cannabis use and fibrosis.

Coffee

In a prospective study of HCV patients with bridging fibrosis or cirrhosis, regular coffee consumption was associated with slower fibrosis progression (Figure 8).[67] In a separate study, investigators showed that persons with chronic HCV infection who drank 3 or more cups per day had relatively reduced liver histologic activity.[68] In addition, several studies, including two meta-analyses, have found an inverse relationship between coffee consumption and the risk of developing HCC among patients with cirrhosis.[69,70] Taken together, available data suggest that higher levels of coffee consumption are associated with lower hepatic necroinflammatory injury, slower rate of fibrosis progression, and decreased risk for developing HCC. The mechanism whereby coffee provides hepatoprotective properties remains unknown.

Summary Points

- Approximately 55 to 85% of persons who acquire HCV will develop chronic HCV infection.
- Factors associated with spontaneous clearance of HCV include younger age at infection, female sex, race other than African American, IL28B CC genotype, and symptomatic acute HCV infection.
- The natural history of HCV infection has not been clearly defined because of the lack of prospective studies. Our understanding of the natural history of hepatitis C is primarily based on retrospective studies.
- Among those who develop chronic HCV infection, an estimated 20 to 30% will develop cirrhosis.
- It is impossible to predict the rate of fibrosis progression in an individual early on in their infection, but there are several host, viral, and environmental factors that have been shown to influence disease progression.
- Factors associated with an increased rate of fibrosis progression include acquisition of HCV at an older age, increased age independent of duration of infection, male sex, heavy alcohol use, coinfection with HIV or HBV, hepatic steatosis, and insulin resistance.
- Individuals who develop HCV-related cirrhosis have an approximately 1 to 4% risk per year of developing HCC.

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[PubMed Abstract] -

- Westbrook RH, Dusheiko G. Natural history of hepatitis C. J Hepatol. 2014;61:S58-68.
[PubMed Abstract] -

- Wirth TC, Manns MP. The impact of the revolution in hepatitis C treatment on hepatocellular carcinoma. Ann Oncol. 2016;27:1467-74.
[PubMed Abstract] -

Figures

Figure 1 IL28B and Spontaneous Clearance of HCV

This graphic shows the percentage of persons with spontaneous clearance of HCV after initial infection in relation to the individual's IL28B genotype. Clearance rates are highest among persons with the CC genotype.

Source: Thomas DL, Thio CL, Martin MP, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461:798-801.

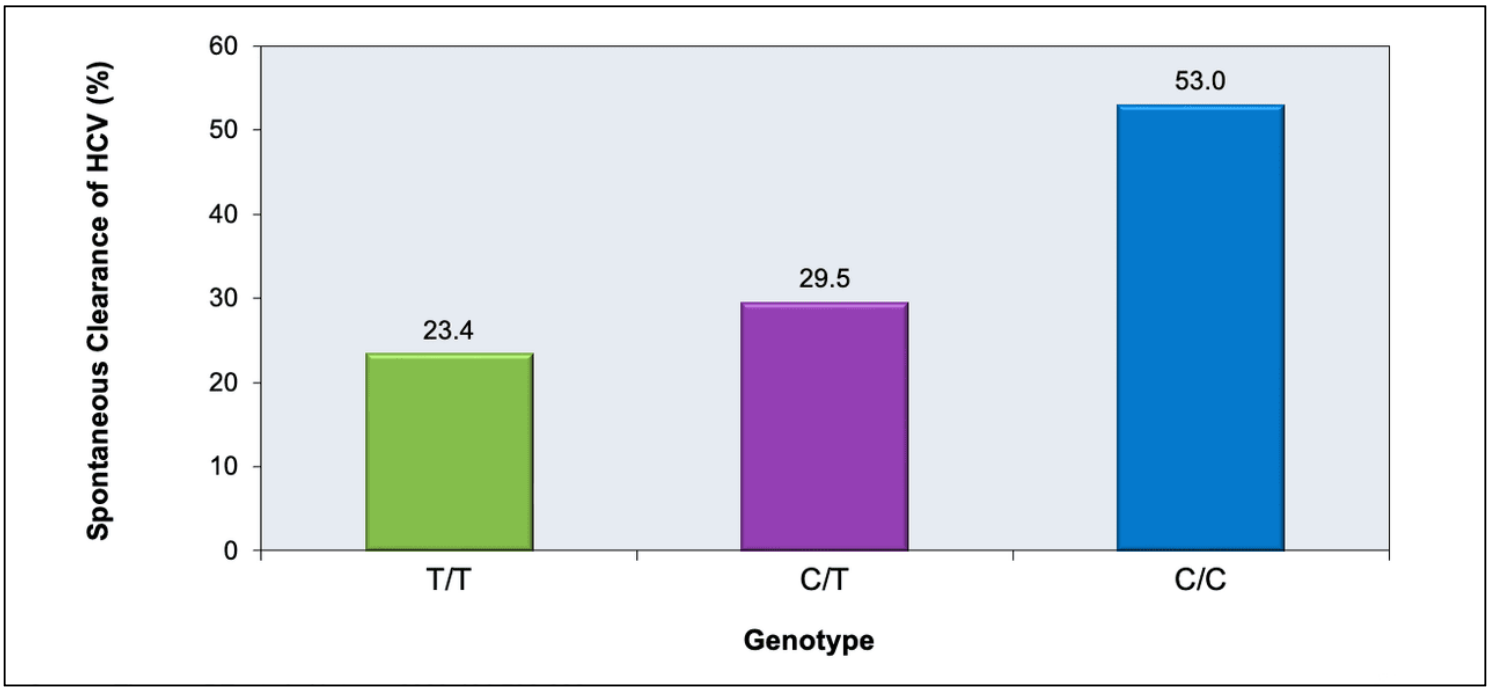


Figure 2 Time Course of Progression with Chronic Hepatitis C Infection

Abbreviations: HCC = hepatocellular cancer; ESLD = end-stage liver disease

Illustration: David H. Spach, MD

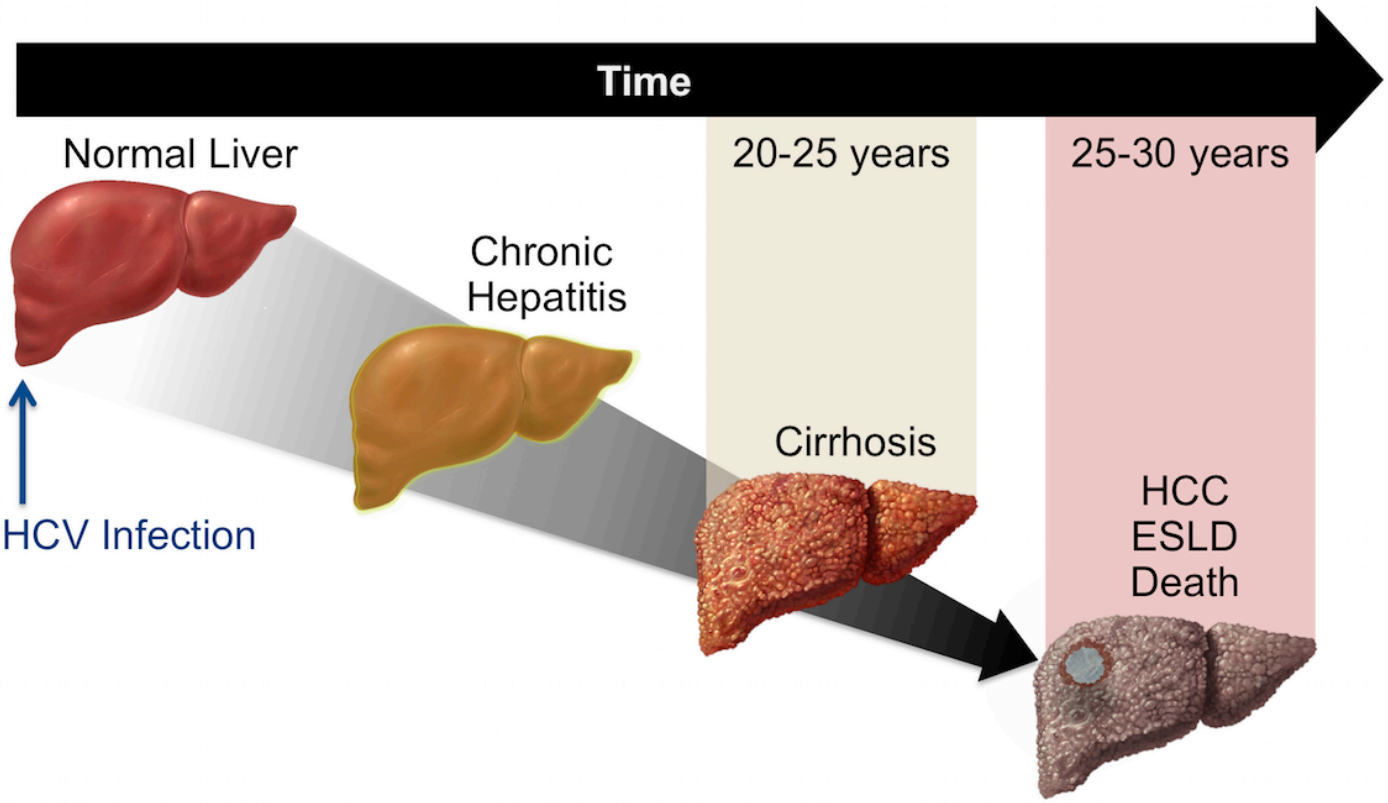


Figure 3 Natural History Following Initial Infection with HCV

Abbreviations: ESLD = end-stage liver disease HCC = hepatocellular carcinoma

Source: Lingala S, Ghany MG. Natural History of Hepatitis C. Gastroenterol Clin North Am. 2015;44:717-34.

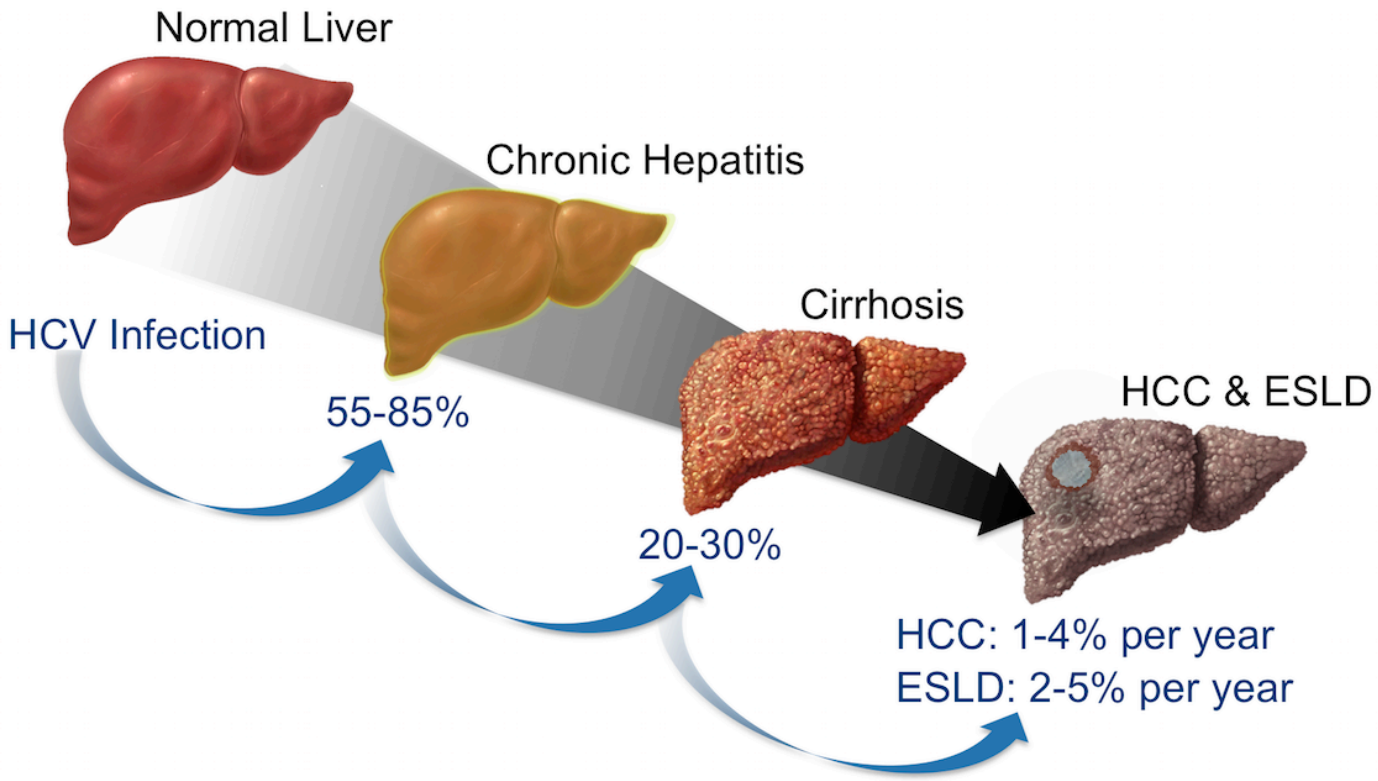


Figure 4 Impact of Age at the Time of Initial HCV Infection and Rate of Fibrosis

Source: Poynard T, Bedossa P, Opolon P. Lancet. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. Lancet. 1997;349:825-32.

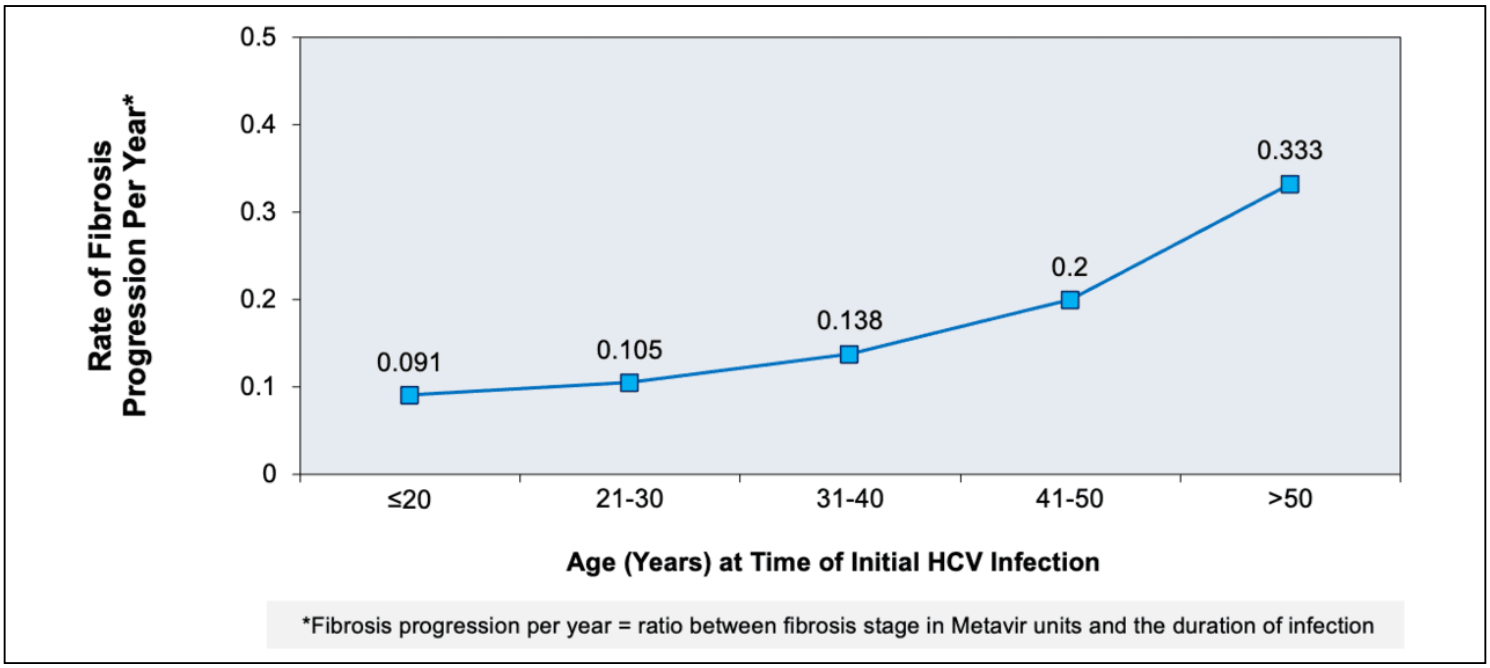


Figure 5 Impact of Steatosis on Progression of Hepatic Fibrosis

This graphic shows a correlation of degree of steatosis at initial biopsy with cumulative risk of hepatic fibrosis. The trends are clearly seen on both the year 4 (blue bars) and year 6 (orange bars) follow-up periods.

Source: Fartoux L, Chazouillères O, Wendum D, Poupon R, Serfaty L. Impact of steatosis on progression of fibrosis in patients with mild hepatitis C. Hepatology. 2005;41:82-7.

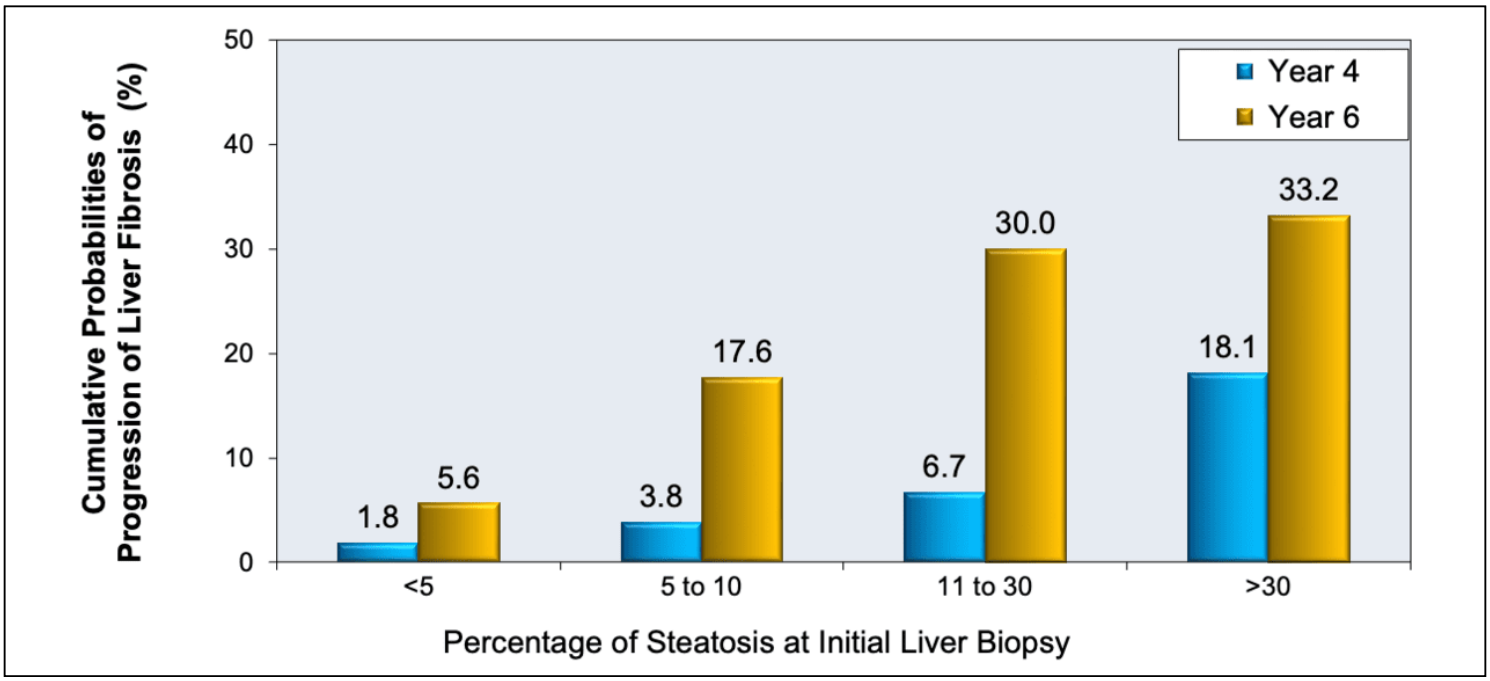


Figure 6 Impact of Coinfection with HIV and Progression of Hepatic Fibrosis

This graphic compares the progression of hepatic fibrosis over a 25-year period among individuals with HCV monoinfection compared with those with HCV and HIV coinfection. As shown, coinfection with HIV accelerates the progression of hepatic fibrosis.

Source: Di Martino V, Rufat P, Boyer N, et al. The influence of human immunodeficiency virus coinfection on chronic hepatitis C in injection drug users: a long-term retrospective cohort study. Hepatology. 2001;34:1193-9.

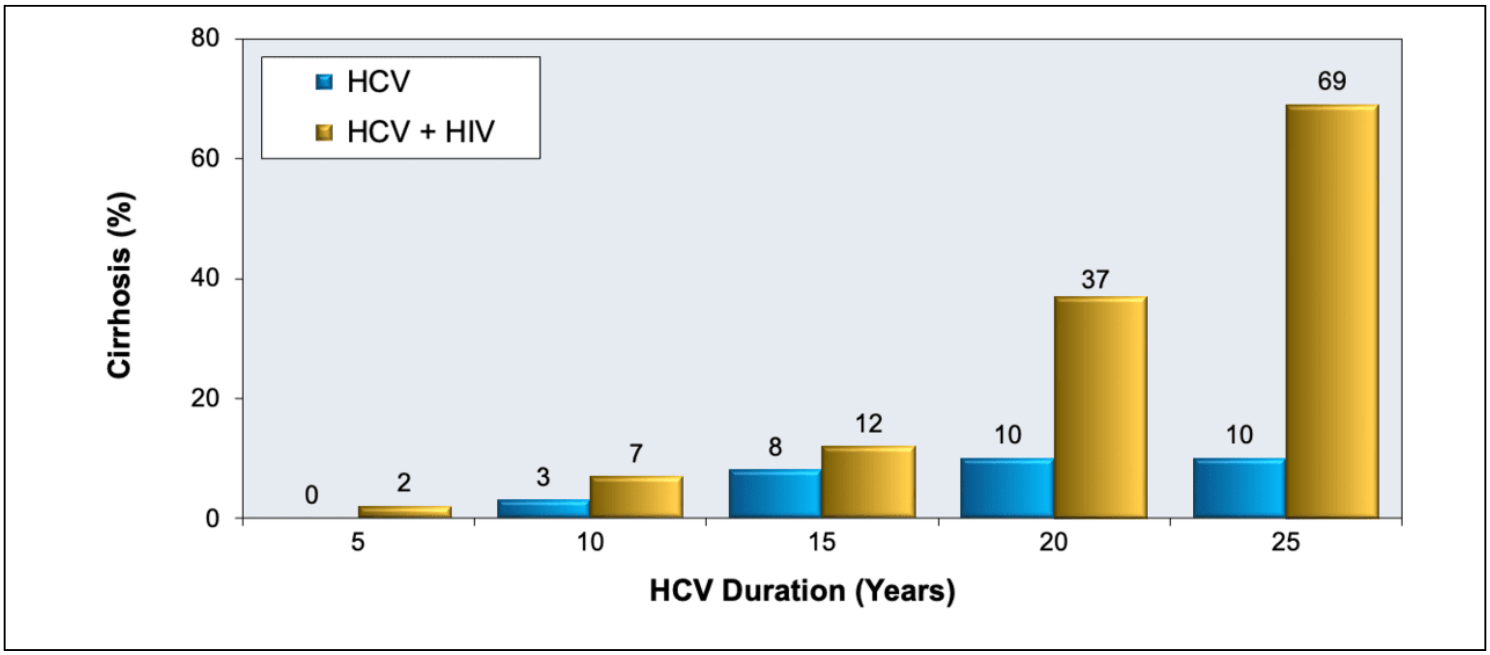


Figure 7 Impact of Alcohol Consumption and Excessive Alcohol Use* on Progression of Hepatic Fibrosis

This graphic compares the progression of hepatic fibrosis over a 40-year period in persons without excessive alcohol use compared with those who had excessive alcohol use. Individuals with excessive alcohol use clearly had a greater risk of developing cirrhosis.

Source: Wiley TE, McCarthy M, Breidi L, McCarthy M, Layden TJ. Impact of alcohol on the histological and clinical progression of hepatitis C infection. Hepatology. 1998;28:805-9.

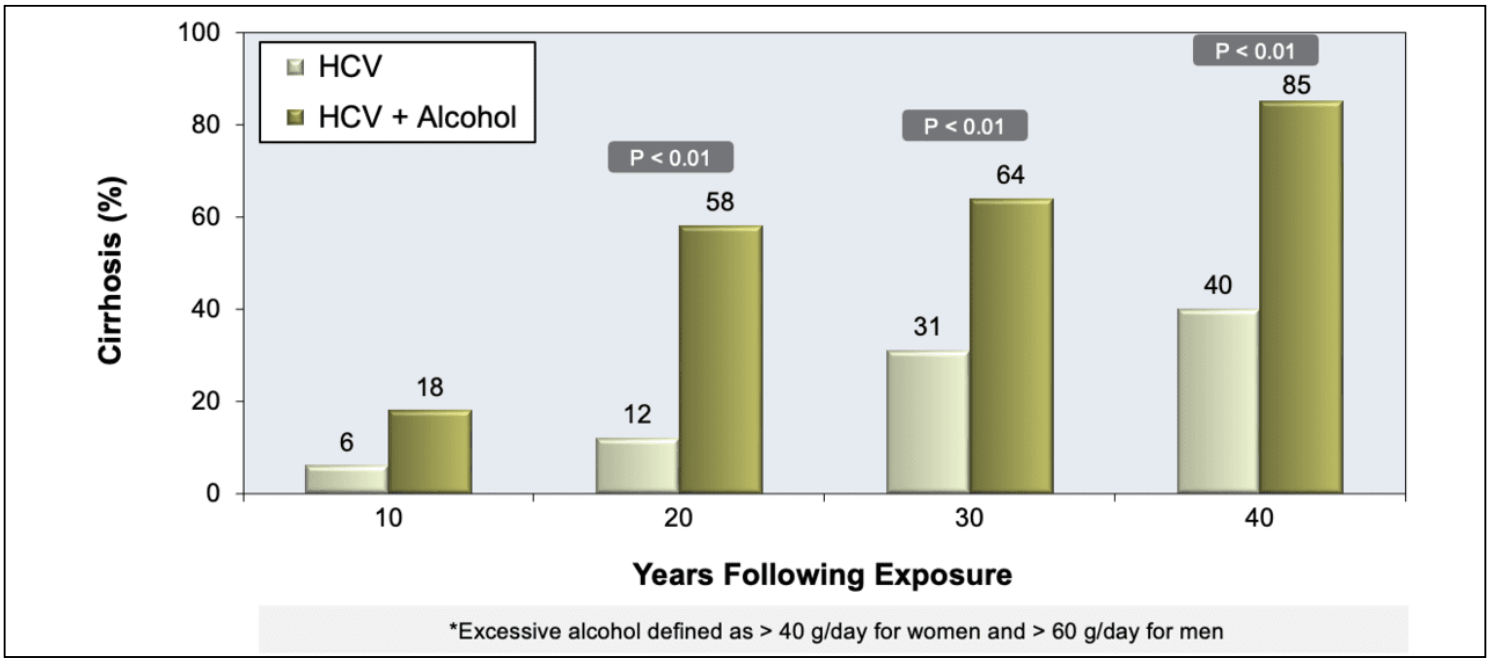
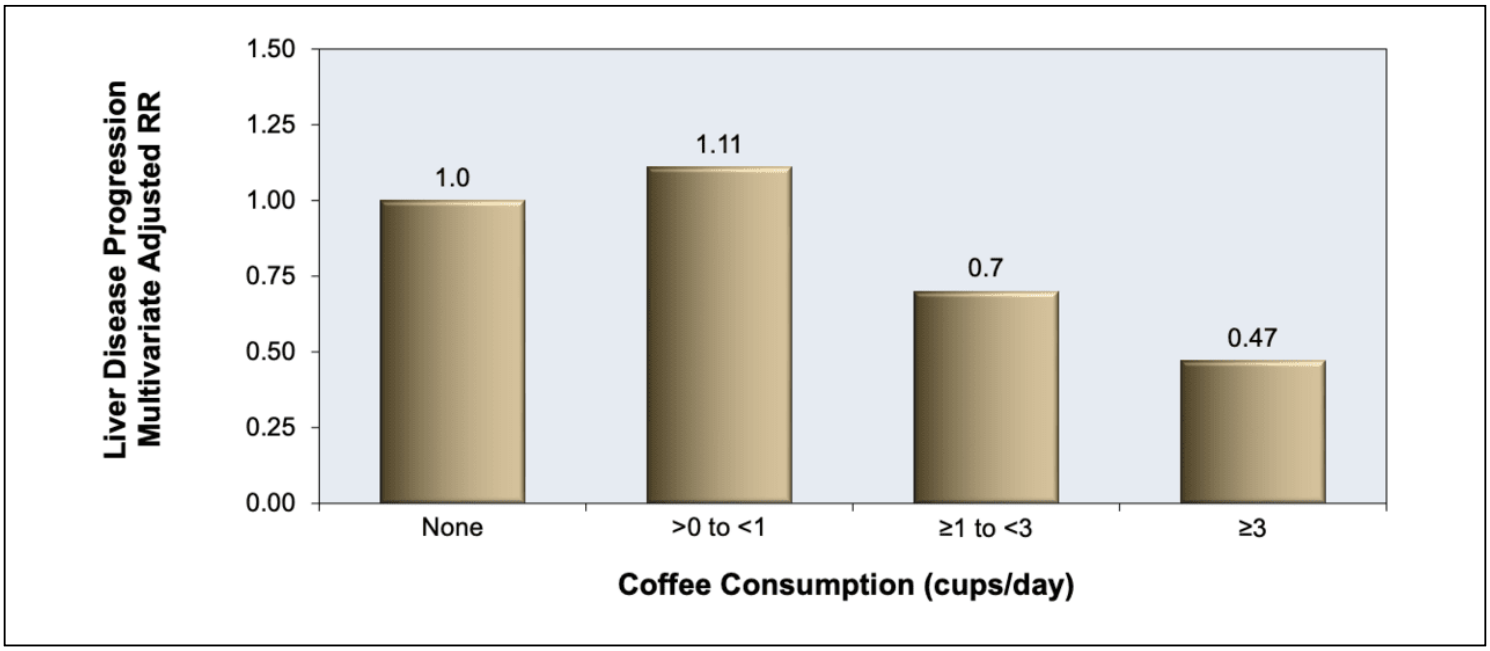


Figure 8 Impact of Coffee Consumption on Liver Disease Progression

In this study, investigators examined the relationship of coffee intake and progression of liver disease in 766 patients with chronic hepatitis C. They found that regular coffee consumption of more than 1 cup per day was associated with a lower risk of liver disease progression.
RR= relative risk

Source: Freedman ND, Everhart JE, Lindsay KL, et al. Coffee intake is associated with lower rates of liver disease progression in chronic hepatitis C. Hepatology. 2009;50:1360-9.