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Assessing Hepatitis C Spontaneous Clearance and Understanding Associated Factors: A Systematic Review and Meta-Analysis

Running title: Hepatitis C Spontaneous Clearance Predictors

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Abstract

New advances in the treatment of hepatitis C provide high levels of sustained viral response but their expense limits availability in publicly funded health systems. The aim of this review is to estimate the proportion of patients who will spontaneously clear HCV and to identify factors that are associated with clearance, to support better targeting of directly acting antivirals. We searched Ovid Embase, Ovid Medline and Pubmed from 1st January 1994 to 30th June 2015 for studies reporting hepatitis C spontaneous clearance and/or demographic, clinical, and behavioural factors associated with clearance. We undertook meta-analyses to estimate the odds of clearance for each predictor. 43 studies met the inclusion criteria, representing 20,110 individuals and six of these studies included sufficient data to estimate spontaneous clearance. The proportion achieving clearance within 3, 6, 12 and 24 months following infection were respectively 19.8% (95%CI: 2.6-47.5%), 27.9% (95%CI: 17.2-41.8%), 36.1% (95%CI: 23.5-50.9%), and 37.1% (95%CI: 23.7-52.8%). Individuals who had not spontaneously cleared by 12 months were unlikely to do so. The likelihood of spontaneous clearance was lower in males and individuals with: HIV co-infection, absence of HBV co-infection, asymptomatic infection, black or non-indigenous race, non-genotype 1 infection, older age, and alcohol or drug problems. This study suggests that patients continue to spontaneously clear HCV for at least 12 months following initial infection. However,

injecting drug users are comparatively less likely to achieve clearance thus they should be considered a priority for early treatment given the continuing risks that these individuals pose for onwards transmission.

Keywords: HCV, predictors, demographic factor, clinical, behaviour

Introduction

During the acute phase of infection, Hepatitis C Virus (HCV) may completely resolve without treatment (spontaneous clearance) which is confirmed by the disappearance of HCV RNA in the serum. The proportion of HCV spontaneous clearance varies between studies, but it is believed to range from 20% to 30%. Factors nominated as predictors of clearance include female sex (1-4), ethnicity, variation of immune responses (5, 6), and host genetics (7, 8). Polymorphisms in the interleukin-28 (IL28B) gene region are recognised as the strongest genetic factor associated with clearance.(7-9)

New direct-acting antiviral agents (DAA) represent a major advancement in hepatitis C treatment with cure rates above 90% for all HCV genotypes, shorter duration of therapy, less toxicity and fewer side effects.(10) There is major potential to substantially reduce the future burden of HCV cases if treatment can be targeted effectively to high-risk individuals such as people who inject drugs (PWID) to prevent onward transmission and the progression of disease within these individuals. However, DAA's are expensive, ranging from $25,000 in Spain to $54,000 in the UK and $51,000-$84,000 in the USA for a 12 week course of treatment.(11) In England, for example, treatment with DAA is restricted to approximately 10,000 patients in 2016-2017 due to the large numbers of potential patients and the very high aggregate cost of the treatments involved.(12) However, the major burden of HCV is in PWID who are often not in contact with treatment services and under this policy only patients who attend clinic are eligible for treatment. Knowledge of variation between population sub-groups in terms of the natural history of infection and the prevalence of spontaneous clearance could inform policy decisions on the use of DAA's.

A systematic review published in 2006 estimated that 26% of HCV infected patients achieve spontaneous viral clearance.(1) However, the study population was very heterogeneous, and it is likely that a wide range of further studies have been published since this study was conducted. The aim of this review was to ascertain precise estimates of spontaneous viral clearance, and establish factors which are associated with spontaneous clearance to inform policy regarding the use of anti-viral agents for HCV.

Methods

Search Strategy and Selection Criteria

We considered any studies that reported the proportion of spontaneous clearance in hepatitis C infected patients AND/OR investigated factors associated with clearance as eligible for inclusion in the analysis. We conducted a systematic search using Ovid Embase, Ovid Medline and Pubmed, by using the terms "hepatitis C" or "HCV" AND "natural history" or "clearance" or "vir* negativ*". We included studies that were published in English after January 1994 (5 years since hepatitis C virus was discovered and when more sensitive testing was already available) up to June 2015. A protocol for this review can be accessed at http://www.crd.york.ac.uk/PROSPERO/ with registration number: CRD42015023499. We defined HCV clearance as the absence of HCV RNA in blood. In studies that included both treated and untreated individuals, we only included untreated individuals. We excluded case reports, reviews, and studies in very specific groups (e.g. patients with lichen planus). We only included adult patients.

Estimation of Spontaneous Viral Clearance for HCV

To estimate the proportion of patients who achieved HCV spontaneous viral clearance, we identified longitudinal cohort studies with a minimum of one year follow-up which reported the time of infection (estimated as the midpoint between the last negative HCV antibody test result and the first evidence of HCV infection) and measured HCV RNA at baseline. Patients achieved spontaneous clearance if they had at least 2 consecutive serum samples with undetectable HCV RNA after the estimated date of infection. To determine the minimum follow-up time required to estimate the proportion of patients achieving spontaneous clearance, we fitted a weighted regression line plotting the proportion of patients achieving spontaneous clearance over time.

Identification of Factors that Associated with HCV Spontaneous Clearance

For the analysis of factors associated with HCV clearance, we included all studies irrespective of whether the time of infection was known. Studies including cross-sectional and case control designs were eligible for inclusion. We included studies in this analysis provided HCV RNA was measured at least once during follow-up and that the study included data from at least 40 patients and reported the association between spontaneous clearance and at least one demographic, clinical, behavioural or host genetic risk factor.

Two independent reviewers conducted an initial screening of publication titles and abstracts to identify publications for full text review. We included the most recent publication if results were reported in more than one article. If we identified articles where the same participants may have contributed data to multiple studies we contacted the study author where possible to clarify the study population. For the full text review two independent researchers reviewed relevant articles against the pre-defined inclusion and exclusion criteria. We preserved the records of included and excluded publications for audit purposes, indicating reasons for any exclusion. We performed and reported this systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

We used a standardised data extraction form to record the relevant data fields for each study, including: (1) study characteristics: setting, study design, method of data-analysis, duration of follow up, country, method of recruitment; (2) participants: study population, number of participants, research participants characteristics such as age and gender, mode of HCV acquisition; and (3) outcomes: proportion of HCV clearance, factors associated with clearance. Given the scale of this review, we present results in full for the association between demographic, clinical and behavioural factors and spontaneous clearance and summarise the key findings for the association between host genetic factors and spontaneous clearance. Full details of the host genetic factors review are available in a separate publication.

Statistical Analysis

For the subset of studies in which the time of infection was known precisely we estimated the proportion of patients achieving HCV clearance at 3, 6, 12, and 24 months following the initial infection. To examine the relationship between demographic, clinical, and behavioural factors and HCV spontaneous clearance, we calculated odds ratios comparing the risk of clearance in patients with each risk factor to the risk of clearance in patients who lacked each risk factor. We included demographic factors (gender, age, and ethnicity); clinical factors (viral co-infection, HCV genotype, and symptomatic infection); and behavioural factors (alcohol consumption and PWID). We used meta-analysis to summarise the relationship between each risk factor and outcome. Odd Ratios were calculated and forest plots generated using Comprehensive Meta Analysis (CMA) version 3.0. For host genetic determinants, after we found predictors which have strongest association with HCV clearance, we performed meta-analysis to summarise the allele's frequency of those predictors among HCV patients with spontaneous clearance, HCV patients with persistent infection, healthy population and patients with HCV infection to see if the alleles are common. And finally, we tabulate the odds ratio and alleles's frequency to identify which genetic determinants were both common and has highest impact on clearance. We investigated heterogeneity using I^2 and assessed publication bias using a funnel plot of proportions of clearance against the study size. If there was evidence of heterogeneity (I^2 >50%), we used random effect models.

Results

After excluding duplicates, we retrieved 9,357 publications from three databases. 483 publications met the criteria for full text review. We identified six studies where the precise time of infection was recorded for the assessment of spontaneous clearance. Forty three studies met the inclusion criteria for assessing demographic, clinical and behavioural risk factors, and 86 assessed host genetic factors for clearance, representing a total of 53,185 individuals (see Figure 1).

Of the 117 studies we included in the review, there were 45 prospective and 6 retrospective cohort studies, 58 case control and 8 cross-sectional studies. Study participants were recruited from hospitals or related health centres (80 studies) and included patients who were transfusion dependent (4 studies), IDU (11 studies), general population (5 studies), HIV positive patients (8 studies), and blood donors (9 studies). A total of 65 studies were published between 2010 and 2015. The majority of studies were conducted in European countries (42), followed by North America (30), Asia (21), Middle East (9), South America (5), Africa (4 studies), Australia (1), and 5 multi-national studies. Characteristics of included publications were described in Appendix 1.

HCV Spontaneous Clearance

We restricted our estimate of the proportion of patients achieving spontaneous clearance to 6 studies (3, 13-17) which provided precise information on clearance at specific time intervals following the acute infection, representing a total of 998 subjects. Meta-analysis revealed the proportion of spontaneous viral clearance to be 19.8% (95% CI: 2.6-47.5%), 27.9% (95% CI: 17.2-41.8%), 36.1% (95% CI: 23.5-50.9%), and 37.1% (95% CI: 23.7-52.8%) within 3, 6, 12, and 24 months after infection respectively (Figure 2). The detailed meta-analysis output can be seen in Appendix 2.

Demographic, Clinical and Behavioural Factors Associated with Clearance

Forty three studies (2-4, 13-52) were included in the analysis of demographic, clinical and behavioural factors associated with HCV clearance, representing a total of 20,110 individuals. The following groups were significantly less likely than others to spontaneously clear hepatitis C virus: males (OR=0.68, 95% CI: 0.59-0.81), those with asymptomatic infection (OR=0.38, 95% CI: 0.27-0.55), black race (OR=0.38, 95% CI: 0.20-0.75), older adults (age ≥45 years, OR=0.52, 95% CI: 0.64-0.97), those with HIV co-infection (OR=0.50, 95% CI: 0.37-0.67), those without hepatitis B co-infection (OR=0.24, 95% CI: 0.19-0.32), patients with non-genotype 1 infection (OR=0.63, 95% CI: 0.45-0.89), non-aboriginal groups (OR=0.47, 95% CI: 0.36-0.62), and those with excess alcohol use (OR=0.67, 95% CI: 0.47-0.95) and those with a history of injecting drug use (OR=0.59, 95% CI: 0.37-0.93). We show forest plots for these associations in Figures 3-5. When we restricted the analysis of risk factors to patients with a minimum of 12 months follow-up we found similar associations between risk factors and HCV (see Appendix 3).

Host Genetic Factors Associated with Clearance

We included a total of 86 studies to assess host genetic factors associated with HCV spontaneous clearance, representing data from 38,341 participants. There were a total of 146 genetic factors identified from the systematic search. From meta-analysis results, we identified 24 host genetic predictors associated with spontaneous clearance. The genetic factors most strongly associated with spontaneous clearance included IL28B rs12979860 (OR=3·27, 95% CI: 2·68-3·98), IL28B rs8099917 (OR=2·83, 95% CI: 2·36-3·39), IL28B rs8103142 (OR=4·06, 95% CI: 2·64-6·25). Forest plots for each host genetic predictors are shown in Appendix 4. We found similar results when the analysis of risk factors was restricted to studies with a minimum of 12 months follow-up (data not shown). We tabulated the odds ratio for spontaneous clearance among 24 strongest genetic predictors against allele frequency in those who spontaneously cleared. This highlights the importance of IL28B rs8103142, IL28B rs12979860, and IL28B rs8099917 (Figure 6).

Discussion

In this systematic review and meta-analysis of hepatitis C spontaneous clearance, we included data from 43 studies, representing 20,110 individuals. We found that patients with HCV continue to spontaneously clear HCV for at least 12 months following initial infection but those who have not cleared by this point are unlikely to do so. Notably PWID, who represent the majority of HCV cases and pose a risk for ongoing HCV transmission were less likely to achieve spontaneous clearance compared to individuals with no history of injection drug use. Other factors that reduce the risk of spontaneous clearance included: HIV co-infection, non-genotype 1 infection, asymptomatic, black or indigenous race, and those with excess alcohol.

To the best of our knowledge, this is the first meta-analysis examining how the proportion of spontaneous clearance varies over time combined with an assessment of demographic, clinical, and behavioural determinants of HCV clearance. We also undertook a separate analysis of host-genetics factors associated with spontaneous clearance which confirmed the strong association between polymorphisms in IL28B and spontaneous clearance (manuscript submitted). The strengths of our study are that we used a robust and systematic approach based on the PRISMA guidelines to perform an extensive literature search. In addition, we used sensitivity analyses to investigate whether the relationship between risk factors and outcome varied according to duration of follow up.

We used strict inclusion criteria to select studies which had minimum 2 sequential negative RNA samples as well as reported the initial time of infection for estimating spontaneous clearance because most studies did not report the precise timing of infection. Failure to take account of this would introduce bias because patients with a longer duration of follow-up are more likely to clear infection. A further problem is the tendency to underestimate spontaneous clearance because patients who successfully clear infection, and especially those with asymptomatic infection, are less likely to present to hospital and be included in research studies. Furthermore, most studies could not distinguish between continued infection and re-infection, potentially underestimating spontaneous clearance in populations who are frequently re-exposed to HCV such as PWID. Although some authors performed multivariate analyses to minimize the impact of potential confounding effects, some studies only reported univariate analyses. We could not undertake meta-regression to adjust for potential confounders due to lack of individual level data.

Our results suggest that the HCV spontaneous clearance at 12 months is 36.1%, higher than previous estimates from a study conducted by Micallef et.al (1) which did not consider time since infection and only included studies with at least had one follow-up assessment within 24 months of initial HCV infection. We only included studies which reported the precise timing of infection and verified spontaneous clearance through at least 2 consecutive serum samples with undetectable HCV RNA. We found a wide range of factors that affected viral clearance including HIV co-infection and injection drug use. Previous studies have suggested that HIV associated immunodeficiency may weaken immune control, allowing substantial hepatitis C virus replication following initial infection.(53, 54) which is supported by the observation that HCV-specific circulating CD4 and CD8 T cells are usually present in higher concentrations in individuals that go on to clear HCV.(55) There are considerable methodological challenges associated with assessing clearance rates among PWID in cohort studies. PWID have higher rates of loss to follow-up compared to individuals who do not inject drugs, potentially biasing estimates of spontaneous clearance within these individuals. Alternative explanations for the reduced clearance HCV in PWID might reflect that these patients do clear the virus but are re-infected due to ongoing injecting before being re-tested. Reinfection rates in PWID have been found to vary between 1.8 to 46.8 per 100 person-years in PWID (56) which may increase the risk of new drug resistance (57-59).

We found that decreased clearance was associated with male sex, non-HBV co-infection, asymptomatic infection, non-genotype 1, and older age. There is a range of evidence suggesting sex hormones influence immunity (60, 61). However, the mechanism and the data of sex-based difference in HCV clearance are still very limited. A study conducted by Tang et.al has discovered the association of estrogen receptor alpha, ESR2 rs4986938 AA genotype, was strongly associated with HCV clearance among the Chinese Han population.(62) Further studies are needed to examine the association between sex and HCV clearance as well as the underlying mechanisms.

The reasons why co-infection with hepatitis B co-infection increases the spontaneous HCV clearance also remain unclear. It is believed that there is a biological interaction between HBV and the HCV specific T-cell response leading to production of interferons which may trigger a suppressive effect on HCV infection.(63)

People with asymptomatic infection seemed to have lower clearance compared to those that were symptomatic. It is speculated that persons with strong basal immune response are likely to produce jaundice or clinical manifestation hence have better likelihood to eradicate the HCV and control the infection.(64, 65) In addition, our results suggest individuals infected with HCV non-genotype 1 were less likely to clear compare to genotype 1. Only a few studies have reported the association between HCV genotype and clearance due to the difficulties involved in recruitment and follow up of acutely HCV infected individuals. Many studies have reported that HCV interferon treatment is less effective for patients with genotype 1 infection.(66-68) However, patients with DAA treatment showed higher effectiveness for genotype 1 compared to genotype 3.(69, 70) Further studies are needed to explore the relationship between host viral mechanisms of genotype 1 infection and HCV clearance.

Many studies have investigated the association between age at time of infection and HCV clearance with conflicting findings. Based on our sub-group analysis, older age appeared to be associated with lower clearance. This might be due to younger people having a more vigorous immune response to viral infection.(71) However, since most of HCV patients were asymptomatic, some studies could not clarify the true initial time of infection which might produce bias at estimating the age at time of infection.

Our analysis found that alcohol drinkers or people who had history of drinking excess alcohol appeared to have a lower clearance. It has been recognized that alcohol consumption is associated with liver disease progression among chronic HCV patients, increases progression of HCV to cirrhosis and HCC.(72, 73) Furthermore, high alcohol consumption has been demonstrated to have several immunosuppressive effects for example studies in mice have shown that alcohol ingestion was related with impaired immune response to HCV protein.(74, 75) Our study strongly suggests that people with HCV infection and ongoing treatment should avoid alcohol consumption although more research is needed to define what level of alcohol consumption affects the risk of clearance or treatment outcomes.

The specific association between race and HCV clearance is not well understood and may be confounded by other factors such as prevalence of injecting drug user. Some studies have proposed differences in natural killer (NK) cell populations (76) and frequencies of HLA Class II alleles (77) may explain the dissimilarity of hepatitis C natural history, spontaneous clearance rate, and response to antiviral treatment among racial groups. It is also indicated that ethnicity associated with IL28B polymorphism which is believed as the strongest host genetic predictor of HCV clearance. (9, 78, 79) Again, more studies are needed to better explain the racial differences in HCV immunity.

Furthermore, in common with previous studies, we found several host genetic predictors of HCV spontaneous clearance. Polymorphism in the interleukin 28 (IL28B) gene regions, specifically from IL28B rs12979860, IL28B rs8099917 and IL28B rs8103142 were the strongest candidates. Patients with favourable IL28B rs12979860 genotype CC were found have better response to HCV treatment.(80, 81) Further studies are required to investigate mechanisms of these SNPs and IL28B involvement in HCV spontaneous clearance.

Overall, this study confirms a proportion of spontaneous clearance following acute HCV infection of over 35% at 1 year post infection. Risk factors analysis demonstrated significantly reduced rates in individuals with: HIV co-infection, active injection drug-use and excessive alcohol intake. These data provide support for a strategy of early treatment for high risk groups who are less likely to achieve spontaneous clearance, may pose a higher risk of onward transmission and who may be more likely to be lost to follow up. These groups also represent the major burden of HCV. The European Association for the Study of the Liver (EASL) have recently made similar recommendations.(82) Considering the challenges to outreach these higher risk groups, active engagement with drug and alcohol liaison services is required to address addiction problems and reinforce harm minimisation approaches such as safe injecting practices and use of condoms that will reduce the risk of transmission and reinfection. It also important to support adherence as irregular treatment may increase the risk of drug resistance.

Statement of interest:

DNA, LS, AJH, AOB, AH declare that they have no relevant conflicts of interest.

Declaration of funding interest:

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References

1. Micallef J, Kaldor J, Dore G. Spontaneous viral clearance following acute hepatitis C infection: a systematic review of longitudinal studies. Journal of viral hepatitis. 2006;13(1):34-41.
2. van den Berg CHBS, Grady BPX, Schinkel J, van de Laar T, Molenkamp R, van Houdt R, et al. Female sex and IL28b, a synergism for spontaneous viral clearance in hepatitis c virus (HCV) seroconverters from a community-based cohort. PLoS ONE. 2011;6(11).
3. Wang CC, Krantz E, Klarquist J, Krows M, McBride L, Scott EP, et al. Acute hepatitis C in a contemporary US cohort: modes of acquisition and factors influencing viral clearance. Journal of Infectious Diseases. 2007;196(10):1474-82.
4. Page K, Hahn JA, Evans J, Shiboski S, Lum P, Delwart E, et al. Acute hepatitis C virus infection in young adult injection drug users: a prospective study of incident infection, resolution, and reinfection. Journal of Infectious Diseases. 2009;200(8):1216-26.
5. Post J, Ratnarajah S, Lloyd A. Immunological determinants of the outcomes from primary hepatitis C infection. Cellular and molecular life sciences. 2009;66(5):733-56.
6. Lemon SM. Induction and evasion of innate antiviral responses by hepatitis C virus. Journal of Biological Chemistry. 2010;285(30):22741-7.
7. Tillmann HL, Thompson AJ, Patel K, Wiese M, Tenckhoff H, Nischalke HD, et al. A polymorphism near IL28B is associated with spontaneous clearance of acute hepatitis C virus and jaundice. Gastroenterology. 2010;139(5):1586-92. e1.
8. Grebely J, Petoumenos K, Hellard M, Matthews GV, Suppiah V, Applegate T, et al. Potential role for Interleukin-28B genotype in treatment decision-making in recent hepatitis C virus infection. Hepatology. 2010;52(4):1216-24.
9. Thomas DL, Thio CL, Martin MP, Qi Y, Ge D, O'hUigin C, et al. Genetic variation in IL28B and spontaneous clearance of hepatitis C virus. Nature. 2009;461(7265):798-801.

10. Asselah T, Boyer N, Saadoun D, Martinot-Peignoux M, Marcellin P. Direct-acting antivirals for the treatment of hepatitis C virus infection: optimizing current IFN-free treatment and future perspectives. Liver International. 2016;36(S1):47-57.

11. Andrieux-Meyer I, Cohn J, de Araújo ESA, Hamid SS. Disparity in market prices for hepatitis C virus direct-acting drugs. The Lancet Global health. 2015;3(11):e676-e7.

12. Huskinson P, Foster G. Offering real hope for people with hepatitis C United Kingdom: NHS; 2016 [cited 2016 5 October 2016]. Available from: https://www.england.nhs.uk/2016/03/peter-huskinson-graham-foster/.

13. Lewis-Ximenez LL, Lauer GM, Schulze Zur Wiesch J, de Sousa PS, Ginuino CF, Paranhos-Baccala G, et al. Prospective follow-up of patients with acute hepatitis C virus infection in Brazil. Clinical Infectious Diseases. 2010;50(9):1222-30.

14. Sharaf Eldin N, Ismail S, Mansour H, Rekacewicz C, El-Houssinie M, El-Kafrawy S, et al. Symptomatic acute hepatitis C in Egypt: diagnosis, spontaneous viral clearance, and delayed treatment with 12 weeks of pegylated interferon alfa-2a. PLoS ONE [Electronic Resource]. 2008;3(12):e4085.

15. Grebely J, Page K, Sacks-Davis R, van der Loeff MS, Rice TM, Bruneau J, et al. The effects of female sex, viral genotype, and IL28B genotype on spontaneous clearance of acute hepatitis C virus infection. Hepatology. 2014;59(1):109-20.

16. Jauncey M, Micallef JM, Gilmour S, Amin J, White PA, Rawlinson W, et al. Clearance of hepatitis C virus after newly acquired infection in injection drug users. Journal of Infectious Diseases. 2004;190(7):1270-4.

17. Gerlach JT, Diepolder HM, Zachoval R, Gruener NH, Jung MC, Ulsenheimer A, et al. Acute hepatitis C: high rate of both spontaneous and treatment-induced viral clearance. Gastroenterology. 2003;125(1):80-8.

18. Santantonio T, Medda E, Ferrari C, Fabris P, Cariti G, Massari M, et al. Risk factors and outcome among a large patient cohort with community-acquired acute hepatitis C in Italy. Clinical Infectious Diseases. 2006;43(9):1154-9.
19. Seaberg EC, Witt MD, Jacobson LP, Detels R, Rinaldo CR, Young S, et al. Differences in hepatitis C virus prevalence and clearance by mode of acquisition among men who have sex with men. Journal of Viral Hepatitis. 2014;21(10):696-705.
20. Morard I, Clement S, Calmy A, Mangia A, Cerny A, De Gottardi A, et al. Clinical significance of the CCR5delta32 allele in hepatitis C. PLoS ONE. 2014;9(9).
21. Shores NJ, Maida I, Soriano V, Nunez M. Sexual transmission is associated with spontaneous HCV clearance in HIV-infected patients. Journal of Hepatology. 2008;49(3):323-8.
22. Soriano V, Mocroft A, Rockstroh J, Ledergerber B, Knysz B, Chaplinskas S, et al. Spontaneous viral clearance, viral load, and genotype distribution of Hepatitis C Virus (HCV) in HIV-infected patients with anti-HCV antibodies in Europe. Journal of Infectious Diseases. 2008;198(9):1337-44.
23. Tobler LH, Bahrami SH, Kaidarova Z, Pitina L, Winkelman VK, Vanderpool SK, et al. A case-control study of factors associated with resolution of hepatitis C viremia in former blood donors (CME). Transfusion. 2010;50(7):1513-23.
24. Clausen LN, Weis N, Schonning K, Fenger M, Krarup H, Bukh J, et al. Correlates of spontaneous clearance of hepatitis C virus in a Danish human immunodeficiency virus type 1 cohort. Scandinavian Journal of Infectious Diseases. 2011;43(10):798-803.
25. Rolfe KJ, Curran MD, Alexander GJM, Woodall T, Andrews N, Harris HE. Spontaneous loss of hepatitis C virus RNA from serum is associated with genotype 1 and younger age at exposure. Journal of Medical Virology. 2011;83(8):1338-44.
26. Murphy EL, Fang J, Tu Y, Cable R, Hillyer CD, Sacher R, et al. Hepatitis C virus prevalence and clearance among US blood donors, 2006-2007: Associations with birth cohort, multiple pregnancies, and body mass index. Journal of Infectious Diseases. 2010;202(4):576-84.

27. Grebely J, Raffa JD, Lai C, Krajden M, Conway B, Tyndall MW. Factors associated with spontaneous clearance of hepatitis C virus among illicit drug users. Canadian Journal of Gastroenterology. 2007;21(7):447.

28. Moqueet N, Infante-Rivard C, Platt RW, Young J, Cooper C, Hull M, et al. Favourable IFNL3 genotypes are associated with spontaneous clearance and are differentially distributed in Aboriginals in Canadian HIV-hepatitis C co-infected individuals. Int J Mol Sci. 2015;16(3):6496-512.

29. Shah DP, Grimes CZ, Brown E, Hwang LY. Demographics, socio-behavioral factors, and drug use patterns: What matters in spontaneous HCV clearance? Journal of Medical Virology. 2012;84(2):235-41.

30. Kim AY, Kuntzen T, Timm J, Nolan BE, Baca MA, Reyor LL, et al. Spontaneous control of HCV is associated with expression of HLA-B *57 and preservation of targeted epitopes. Gastroenterology. 2011;140(2):686-96.

31. Sarkar M, Bacchetti P, Tien P, Mileti E, French AL, Edlin BR, et al. Racial/ethnic differences in spontaneous HCV clearance in HIV infected and uninfected women. Digestive Diseases and Sciences. 2013;58(5):1341-8.

32. Thomas DL, Astemborski J, Rai RM, Anania FA, Schaeffer M, Galai N, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA. 2000;284(4):450-6.

33. Ibrahim GH, Khalil FA, El-Abaseri TB, Attia FM, El-Serafi AT. Impact of Interleukin-28B gene polymorphism (rs12979860) on Egyptian patients infected with hepatitis C virus genotype-4

Impact du polymorphisme du gene de l'interleukine-28b (rs12979860) chez des patients Egyptiens infectes par le virus de l'hepatite C de genotype-4. Eastern Mediterranean Health Journal. 2013;19(SUPPL.2).

34. Dong Y, Qiu C, Xia X, Wang J, Zhang H, Zhang X, et al. Hepatitis B virus and hepatitis C virus infection among HIV-1-infected injection drug users in Dali, China: prevalence and infection status in a cross-sectional study. Archives of Virology. 2015;160(4):929-36.

35. Busch MP, Glynn SA, Stramer SL, Orland J, Murphy EL, Wright DJ, et al. Correlates of hepatitis C virus (HCV) RNA negativity among HCV-seropositive blood donors. Transfusion. 2006;46(3):469-75.
36. Wawrzynowicz-Syczewska M, Kubicka J, Lewandowski Z, Boron-Kaczmarska A, Radkowski M. Natural history of acute symptomatic hepatitis type C. Infection. 2004;32(3):138-43.
37. Quinn PG, Jamal MM, Carey JD, Arora S, Harris T, Johnston DE, et al. A case-control study of the factors associated with spontaneous resolution of hepatitis C viremia. American Journal of Gastroenterology. 1999;94(3):668-73.
38. Zhang M, Rosenberg PS, Brown DL, Preiss L, Konkle BA, Eyster ME, et al. Correlates of spontaneous clearance of hepatitis C virus among people with hemophilia. Blood. 2006;107(3):892-7.
39. Oda K, Uto H, Kumagai K, Ido A, Kusumoto K, Shimoda K, et al. Impact of a single nucleotide polymorphism upstream of the IL28B gene in patients positive for anti-HCV antibody in an HCV hyperendemic area in Japan. Journal of Medical Virology. 2014;86(11):1877-85.
40. Keating S, Coughlan S, Connell J, Sweeney B, Keenan E. Hepatitis C viral clearance in an intravenous drug-using cohort in the Dublin area. Irish Journal of Medical Science. 2005;174(1):37-41.
41. Bakr I, Rekacewicz C, El Hosseiny M, Ismail S, El Daly M, El-Kafrawy S, et al. Higher clearance of hepatitis C virus infection in females compared with males. Gut. 2006;55(8):1183-7.
42. Rao HY, Sun DG, Jiang D, Yang RF, Guo F, Wang JH, et al. IL28B genetic variants and gender are associated with spontaneous clearance of hepatitis C virus infection. Journal of Viral Hepatitis. 2012;19(3):173-81.
43. Rao HY, Sun DG, Yang RF, Liu F, Wang J, Feng B, et al. Outcome of hepatitis C virus infection in Chinese paid plasma donors: a 12-19-year cohort study. Journal of Gastroenterology & Hepatology. 2012;27(3):526-32.

44. Alric L, Fort M, Izopet J, Vinel JP, Bureau C, Sandre K, et al. Study of host- and virus-related factors associated with spontaneous hepatitis C virus clearance. Tissue Antigens. 2000;56(2):154-8.

45. Poustchi H, Esmaili S, Mohamadkhani A, Nikmahzar A, Pourshams A, Sepanlou SG, et al. The impact of illicit drug use on spontaneous hepatitis C clearance: experience from a large cohort population study. PLoS ONE [Electronic Resource]. 2011;6(8):e23830.

46. El-Attar MM, Ahmed MAH, Shehata Hasan M, Aly MA, Nasr AM. Spontaneous viral clearance of chronic HCV infection in Upper Egypt: A community-based study with a 10year follow-up. Arab Journal of Gastroenterology. 2010;11(4):197-201.

47. Kamal SM, Kassim SK, Ahmed AI, Mahmoud S, Bahnasy KA, Hafez TA, et al. Host and viral determinants of the outcome of exposure to HCV infection genotype 4: A large longitudinal study. American Journal of Gastroenterology. 2014;109(2):199-211.

48. Esmat G, Hashem M, El-Raziky M, El-Akel W, El-Naghy S, El-Koofy N, et al. Risk factors for hepatitis C virus acquisition and predictors of persistence among Egyptian children. Liver International. 2012;32(3):449-56.

49. Garten RJ, Lai SH, Zhang JB, Liu W, Chen J, Yu XF. Factors influencing a low rate of hepatitis C viral RNA clearance in heroin users from Southern China. World Journal of Gastroenterology. 2008;14(12):1878-84.

50. Piasecki BA, Lewis JD, Reddy KR, Bellamy SL, Porter SB, Weinrieb RM, et al. Influence of alcohol use, race, and viral coinfections on spontaneous HCV clearance in a US veteran population. Hepatology. 2004;40(4):892-9.

51. Yu MLD, C. Y.;Huang, C. F.;Lee, J. J.;Yeh, M. L.;Yeh, S. M.;Kuo, H. T.;Huang, J. F.;Chang, J. M.;Chen, H. C.;Juo, S. H.;Hwang, S. J.;Chuang, W. L. High hepatitis B virus surface antigen levels and favorable interleukin 28B genotype predict spontaneous hepatitis C virus clearance in uremic patients. J Hepatol. 2014;60(2):253-9.

52. Spada E, Amoroso P, Taliani G, Zuccaro O, Chiriaco P, Maio P, et al. Role of IL28B gene polymorphism and cell-mediated immunity in spontaneous resolution of acute hepatitis C. Clinical Infectious Diseases. 2013;57(6):803-11.
53. Mehta SH, Cox A, Hoover DR, Wang X-H, Mao Q, Ray S, et al. Protection against persistence of hepatitis C. The Lancet. 2002;359(9316):1478-83.
54. Crebely J, Raffa JD, Lai C, Krajden M, Conway B, Tyndall MW. Factors associated with spontaneous clearance of hepatitis C virus among illicit drug users. Canadian Journal of Gastroenterology. 2007;21(7):447-51.
55. Kim A, Schulze Zur Wiesch J, Allen T, Gandhi R, Davis B, Jones A, et al., editors. Virus-specific T-cell responses and loss of spontaneous control of HCV in HIV+ individuals. 13th Conference on Retroviruses and Opportunistic Infections; 2006.
56. Grebely J, Prins M, Hellard M, Cox AL, Osburn WO, Lauer G, et al. Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: Towards a vaccine. The Lancet Infectious Diseases. 2012;12(5):408-14.
57. Lontok E, Harrington P, Howe A, Kieffer T, Lennerstrand J, Lenz O, et al. Hepatitis C virus drug resistance–associated substitutions: State of the art summary. Hepatology. 2015;62(5):1623-32.
58. Pawlotsky J-M. Hepatitis C Virus Resistance to Direct-Acting Antiviral Drugs in Interferon-Free Regimens. Gastroenterology. 2016.
59. Focaccia R, Ferreira R, de Mello PSM. Management of Hepatitis C Infection with Direct Action Antiviral Drugs (DAA).
60. Bouman A, Heineman MJ, Faas MM. Sex hormones and the immune response in humans. Human reproduction update. 2005;11(4):411-23.
61. Klein MB, Thorpe J, Saeed S, Cohen J, Conway B, Cooper C, et al. A portrait of HIV-hepatitis C CO-infected persons in care in Canada: The canadian CO-infection cohort study (CCC; CTN 222). Canadian Journal of Infectious Diseases and Medical Microbiology. 2010;SB):48B.

62. Tang S, Yue M, Su J, Yu R, Zhou D, Xu K, et al. Association of genetic variants in estrogen receptor alpha with HCV infection susceptibility and viral clearance in a high-risk Chinese population. European Journal of Clinical Microbiology and Infectious Diseases. 2014;33(6):999-1010.
63. Guidotti LG, Chisari FV. Noncytolytic control of viral infections by the innate and adaptive immune response. Annual review of immunology. 2001;19(1):65-91.
64. Chung RT. Acute hepatitis C virus infection. Clinical infectious diseases. 2005;41(Supplement 1):S14-S7.
65. Busch MP, Shafer KAP. Acute-phase hepatitis C virus infection: implications for research, diagnosis, and treatment. Clinical Infectious Diseases. 2005;40(7):959-61.
66. Manns MP, McHutchison JG, Gordon SC, Rustgi VK, Shiffman M, Reindollar R, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. The Lancet. 2001;358(9286):958-65.
67. McHutchison JG, Lawitz EJ, Shiffman ML, Muir AJ, Galler GW, McCone J, et al. Peginterferon alfa-2b or alfa-2a with ribavirin for treatment of hepatitis C infection. New England Journal of Medicine. 2009;361(6):580-93.
68. Hadziyannis SJ, Sette H, Morgan TR, Balan V, Diago M, Marcellin P, et al. Peginterferon-α2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Annals of internal medicine. 2004;140(5):346-55.
69. Pianko S, Flamm SL, Shiffman ML, Kumar S, Strasser SI, Dore GJ, et al., editors. High efficacy of treatment with sofosbuvir+ GS-5816+/-ribavirin for 12 weeks in treatment experienced patients with genotype 1 or 3 HCV infection. Hepatology; 2014: WILEY-BLACKWELL 111 RIVER ST, HOBOKEN 07030-5774, NJ USA.
70. Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. New England Journal of Medicine. 2015;373(27):2608-17.

71. Gomez CR, Boehmer ED, Kovacs EJ. The aging innate immune system. Current opinion in immunology. 2005;17(5):457-62.
72. Safdar K, Schiff ER, editors. Alcohol and hepatitis C. Seminars in liver disease; 2004.
73. Jamal MM, Saadi Z, Morgan TR. Alcohol and hepatitis C. Digestive Diseases. 2006;23(3-4):285-96.
74. Encke J, Wands J. Ethanol inhibition: the humoral and cellular immune response to hepatitis C virus NS5 protein after genetic immunization. Alcoholism: Clinical and Experimental Research. 2000;24(7):1063-7.
75. Geissler M, Gesien A, Wands JR. Inhibitory effects of chronic ethanol consumption on cellular immune responses to hepatitis C virus core protein are reversed by genetic immunizations augmented with cytokine-expressing plasmids. The Journal of Immunology. 1997;159(10):5107-13.
76. Golden-Mason L, Stone AE, Bambha KM, Cheng L, Rosen HR. Race-and gender-related variation in natural killer p46 expression associated with differential anti-hepatitis c virus immunity. Hepatology. 2012;56(4):1214-22.
77. Rosen HR, Weston SJ, Im K, Yang H, Burton JR, Erlich H, et al. Selective decrease in hepatitis C virus–specific immunity among African Americans and outcome of antiviral therapy. Hepatology. 2007;46(2):350-8.
78. Zheng MH, Li Y, Xiao DD, Shi KQ, Fan YC, Chen LL, et al. Interleukin-28B rs12979860C/T and rs8099917T/G contribute to spontaneous clearance of hepatitis C virus in Caucasians. Gene. 2013;518(2):479-82.
79. Jimenez-Sousa MA, Fernandez-Rodriguez A, Guzman-Fulgencio M, Garcia-Alvarez M, Resino S. Meta-analysis: Implications of interleukin-28B polymorphisms in spontaneous and treatment-related clearance for patients with hepatitis C. BMC Medicine. 2013;11(1).
80. Ge D, Fellay J, Thompson AJ, Simon JS, Shianna KV, Urban TJ, et al. Genetic variation in IL28B predicts hepatitis C treatment-induced viral clearance. Nature. 2009;461(7262):399-401.

81. Rauch A, Kutalik Z, Descombes P, Cai T, Di Iulio J, Mueller T, et al. Genetic Variation in IL28B Is Associated With Chronic Hepatitis C and Treatment Failure: A Genome-Wide Association Study. Gastroenterology. 2010;138(4):1338-45.e7.

82. Liver EAftSot. EASL Recommendations on Treatment of Hepatitis C 2016. Journal of Hepatology. 2016.

Figure Legend

Figure 1. Articles Screening following PRISMA Diagram

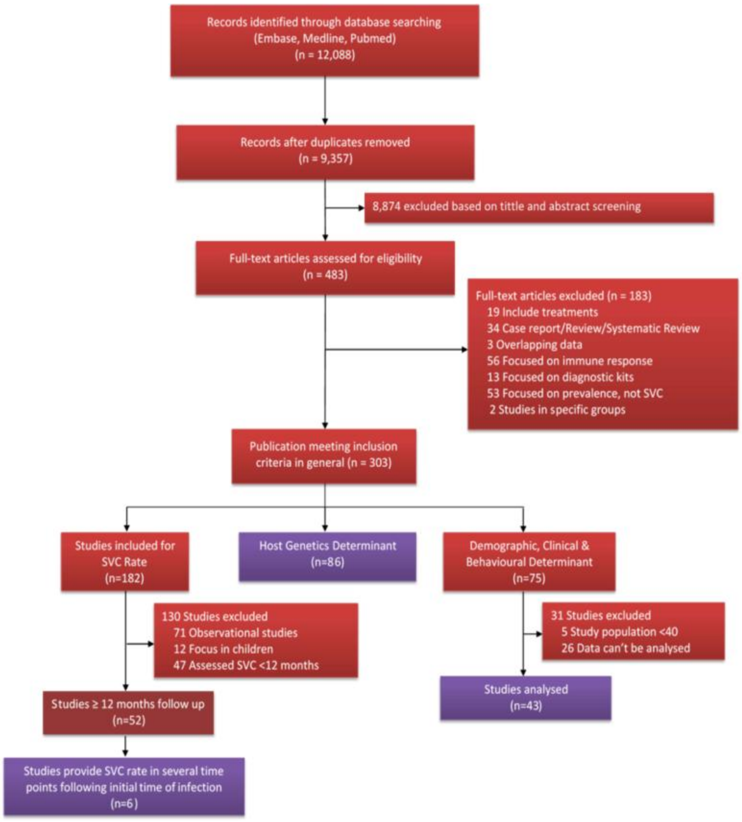
Figure 2. Rate of spontaneous Clearance within 3, 6, 12, and 24 months after infection

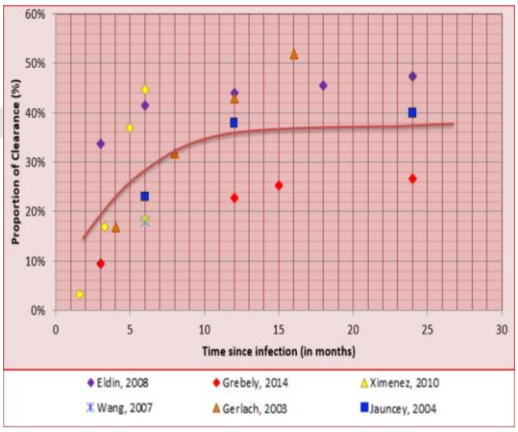
Figure 3. Forest Plot Assessing Demographic Factors Associated with HCV Clearance

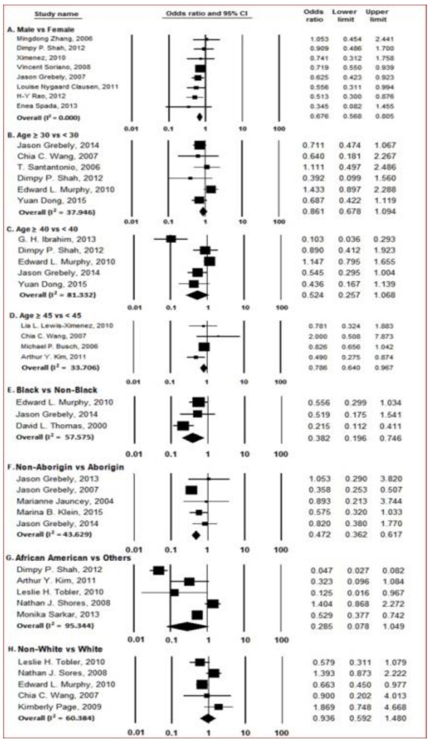
Figure 4. Forest Plot Assessing Clinical Factors Associated with HCV Clearance

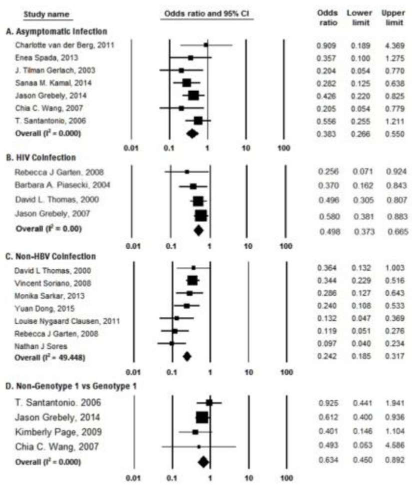
Figure 5. Forest Plot Assessing Behaviour Factors Associated with HCV Clearance

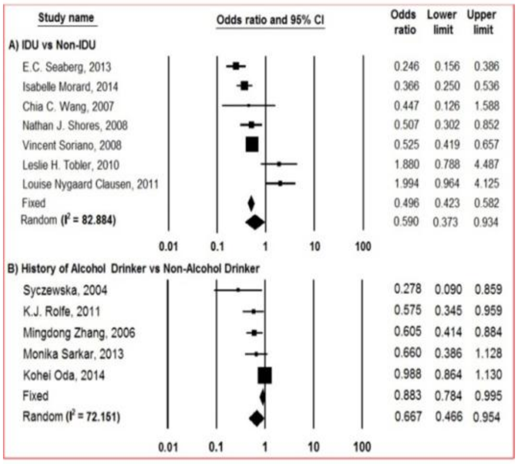
Figure 6. Odd Ratio of HCV Spontaneous Clearance in relation to Allele Frequency

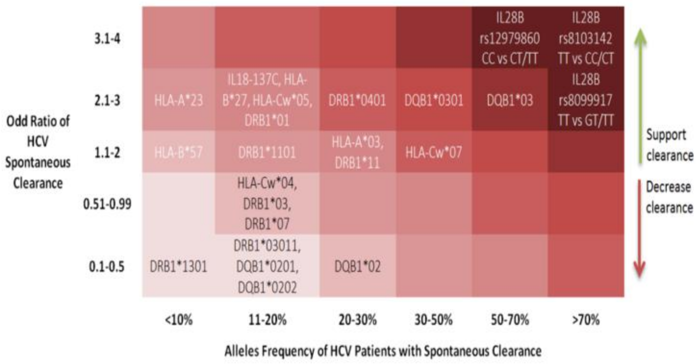

Records identified through database searching
(Embase, Medline, Pubmed)
(n = 12,088)
Records after duplicates removed
(n = 9,357)
8,874 excluded based on tittle and abstract screening
Full-text articles assessed for eligibility
(n = 483)
Full-text articles excluded (n = 183)
19 Include treatments
34 Case report/Review/Systematic Review
3 Overlapping data
56 Focused on immune response
13 Focused on diagnostic kits
53 Focused on prevalence, not SVC
2 Studies in specific groups
Publication meeting inclusion
criteria in general (n = 303)
Studies included for
SVC Rate
(n=182)
Host Genetics Determinant
(n=86)
Demographic, Clinical &
Behavioural Determinant
(n=75)
130 Studies excluded
71 Observational studies
12 Focus in children
47 Assessed SVC <12 months
31 Studies excluded
5 Study population <40
26 Data can't be analysed
Studies ≥ 12 months follow up
(n=52)
Studies analysed
(n=43)
Studies provide SVC rate in several time
points following initial time of infection
(n=6)


Proportion of Clearance (%)
60%
50%
40%
30%
20%
10%
0%
0
5
10
15
20
25
30
Time since infection (in months)
Eldin, 2008
Grebely, 2014
Ximenez, 2010
Wang, 2007
Gerlach, 2003
Jauncey, 2004


Study name
Odds ratio and 95% CI
Odds ratio Lower limit Upper limit
A. Male vs Female
Mingdong Zhang, 2006 1.053 0.454 2.441
Dimpy P. Shah, 2012 0.909 0.486 1.700
Ximenez, 2010 0.741 0.312 1.758
Vincent Soriano, 2008 0.719 0.550 0.939
Jason Grebely, 2007 0.625 0.423 0.923
Louise Nygaard Clausen, 2011 0.556 0.311 0.994
H-Y Rao, 2012 0.513 0.300 0.876
Enea Spada, 2013 0.345 0.082 1.455
Overall (I² = 0.000) 0.676 0.568 0.805
0.01 0.1 1 10 100
B. Age ≥ 30 vs < 30
Jason Grebely, 2014 0.711 0.474 1.067
Chia C. Wang, 2007 0.640 0.181 2.267
T. Santantonio, 2006 1.111 0.497 2.486
Dimpy P. Shah, 2012 0.392 0.099 1.560
Edward L. Murphy, 2010 1.433 0.897 2.288
Yuan Dong, 2015 0.687 0.422 1.119
Overall (I² = 37.946) 0.861 0.678 1.094
0.01 0.1 1 10 100
C. Age ≥ 40 vs < 40
G. H. Ibrahim, 2013 0.103 0.036 0.293
Dimpy P. Shah, 2012 0.890 0.412 1.923
Edward L. Murphy, 2010 1.147 0.795 1.655
Jason Grebely, 2014 0.545 0.295 1.004
Yuan Dong, 2015 0.436 0.167 1.139
Overall (I² = 81.332) 0.524 0.257 1.068
0.01 0.1 1 10 100
D. Age ≥ 45 vs < 45
Lia L. Lewis-Ximenez, 2010 0.781 0.324 1.883
Chia C. Wang, 2007 2.000 0.508 7.873
Michael P. Busch, 2006 0.826 0.656 1.042
Arthur Y. Kim, 2011 0.490 0.275 0.874
Overall (I² = 33.706) 0.786 0.640 0.967
0.01 0.1 1 10 100
E. Black vs Non-Black
Edward L. Murphy, 2010 0.556 0.299 1.034
Jason Grebely, 2014 0.519 0.175 1.541
David L. Thomas, 2000 0.215 0.112 0.411
Overall (I² = 57.575) 0.382 0.196 0.746
0.01 0.1 1 10 100
F. Non-Aborigin vs Aborigin
Jason Grebely, 2013 1.053 0.290 3.820
Jason Grebely, 2007 0.358 0.253 0.507
Marianne Jauncey, 2004 0.893 0.213 3.744
Marina B. Klein, 2015 0.575 0.320 1.033
Jason Grebely, 2014 0.820 0.380 1.770
Overall (I² = 43.629) 0.472 0.362 0.617
0.01 0.1 1 10 100
G. African American vs Others
Dimpy P. Shah, 2012 0.047 0.027 0.082
Arthur Y. Kim, 2011 0.323 0.096 1.084
Leslie H. Tobler, 2010 0.125 0.016 0.967
Nathan J. Shores, 2008 1.404 0.868 2.272
Monika Sarkar, 2013 0.529 0.377 0.742
Overall (I² = 95.344) 0.285 0.078 1.049
0.01 0.1 1 10 100
H. Non-White vs White
Leslie H. Tobler, 2010 0.579 0.311 1.079
Nathan J. Sores, 2008 1.393 0.873 2.222
Edward L. Murphy, 2010 0.663 0.450 0.977
Chia C. Wang, 2007 0.900 0.202 4.013
Kimberly Page, 2009 1.869 0.748 4.668
Overall (I² = 60.384) 0.936 0.592 1.480
0.01 0.1 1 10 100


Study name
Odds ratio and 95% CI
Odds ratio Lower limit Upper limit
A. Asymptomatic Infection
Charlotte van der Berg, 2011 0.909 0.189 4.369
Enea Spada, 2013 0.357 0.100 1.275
J. Tilman Gerlach, 2003 0.204 0.054 0.770
Sanaa M. Kamal, 2014 0.282 0.125 0.638
Jason Grebely, 2014 0.426 0.220 0.825
Chia C. Wang, 2007 0.205 0.054 0.779
T. Santantonio, 2006 0.556 0.255 1.211
Overall (I² = 0.000) 0.383 0.266 0.550
0.01 0.1 1 10 100
B. HIV Coinfection
Rebecca J Garten, 2008 0.256 0.071 0.924
Barbara A. Piasecki, 2004 0.370 0.162 0.843
David L. Thomas, 2000 0.496 0.305 0.807
Jason Grebely, 2007 0.580 0.381 0.883
Overall (I² = 0.00) 0.498 0.373 0.665
0.01 0.1 1 10 100
C. Non-HBV Coinfection
David L Thomas, 2000 0.364 0.132 1.003
Vincent Soriano, 2008 0.344 0.229 0.516
Monika Sarkar, 2013 0.286 0.127 0.643
Yuan Dong, 2015 0.240 0.108 0.533
Louise Nygaard Clausen, 2011 0.132 0.047 0.369
Rebecca J Garten, 2008 0.119 0.051 0.276
Nathan J Sores 0.097 0.040 0.234
Overall (I² = 49.448) 0.242 0.185 0.317
0.01 0.1 1 10 100
D. Non-Genotype 1 vs Genotype 1
T. Santantonio, 2006 0.925 0.441 1.941
Jason Grebely, 2014 0.612 0.400 0.936
Kimberly Page, 2009 0.401 0.146 1.104
Chia C. Wang, 2007 0.493 0.053 4.586
Overall (I² = 0.000) 0.634 0.450 0.892
0.01 0.1 1 10 100


Study name
Odds ratio and 95% CI
Odds ratio
Lower limit
Upper limit
A) IDU vs Non-IDU
E.C. Seaberg, 2013 0.246 0.156 0.386
Isabelle Morard, 2014 0.366 0.250 0.536
Chia C. Wang, 2007 0.447 0.126 1.588
Nathan J. Shores, 2008 0.507 0.302 0.852
Vincent Soriano, 2008 0.525 0.419 0.657
Leslie H. Tobler, 2010 1.880 0.788 4.487
Louise Nygaard Clausen, 2011 1.994 0.964 4.125
Fixed 0.496 0.423 0.582
Random (I^2 = 82.884) 0.590 0.373 0.934
0.01 0.1 1 10 100
B) History of Alcohol Drinker vs Non-Alcohol Drinker
Syczewska, 2004 0.278 0.090 0.859
K.J. Rolfe, 2011 0.575 0.345 0.959
Mingdong Zhang, 2006 0.605 0.414 0.884
Monika Sarkar, 2013 0.660 0.386 1.128
Kohei Oda, 2014 0.988 0.864 1.130
Fixed 0.883 0.784 0.995
Random (I^2 = 72.151) 0.667 0.466 0.954
0.01 0.1 1 10 100


Odd Ratio of HCV Spontaneous Clearance
3.1-4
2.1-3
1.1-2
0.51-0.99
0.1-0.5
IL28B rs12979860 CC vs CT/TT
IL28B rs8103142 TT vs CC/CT
HLA-A*23
IL18-137C, HLA-B*27, HLA-Cw*05, DRB1*01
DRB1*0401
DQB1*0301
DQB1*03
IL28B rs8099917 TT vs GT/TT
HLA-B*57
DRB1*1101
HLA-A*03, DRB1*11
HLA-Cw*07
HLA-Cw*04, DRB1*03, DRB1*07
DRB1*1301
DRB1*03011, DQB1*0201, DQB1*0202
DQB1*02
Support clearance
Decrease clearance
<10%
11-20%
20-30%
30-50%
50-70%
>70%
Alleles Frequency of HCV Patients with Spontaneous Clearance

Appendix 1

Table 1. Characteristic of studies included in HCV Spontaneous Viral Clearance Rate (SVC) Analysis

First Author	Country	Year	Study Population	M/F	Age*	Σ HCV (+)	Σ Clearance	Proportion	95% CI
Noha Sharaf Eldin	Egypt	2008	HCV infected patients	69/48		117	51	43.59	34.55-53.06
Marianne Jauncey	Australia	2004	IDU	27/30		57	24	42.11	29.4-55.88
Ximenez	Brazil	2010	HCV infected patients	25/40	45.7±12.4 (Range 20-77)	65	29	44.62	33.1-56.8
Jason Grebely	Australia, Canada, Netherland, USA	2014	HCV infected patients	404/228		632	173	27.4	24.0-31.0
Chia C. Wang	USA	2007	HCV infected patients	35/32	Median 31 (Range 17-82)	67	15	22.39	13.47-33.90
J. Tilman Gerlach	Germany	2003	HCV infected patients	25/35		60	24	44.4	31.90-57.80

*Mean of age, otherwise stated in the table

Table 2. Characteristic of Studies Included Assessing Demographic, Clinical and Behavioural Factors Associated with HCV Spontaneous Clearance

First Author	Country	Year	Study Population	M/F	Age*	Σ of HCV (+)	∑ of Clearance	∑ of Chronic HCV	Proportion
E.C. Seaberg	USA	2013	IDU	528/0	Median 33.5 (Range 17-70)	528	118	410	22.35
Isabelle Morard	Switzerland	2014	HCV infected patients	886/564		1450	160	1290	11.03
Chia C. Wang	USA	2007	HCV infected patients	35/32	Median 31 (Range 17-82)	67	15	52	22.39
Nathan J. Shores	USA, Spain, Italy	2008	HIV (+)	572/197	Median 41 (Range 37-45)	769	102	667	13.26
Vincent Soriano	Europe, Israel & Argentina	2008	HIV (+)	1348/592	Median 37.2	1940	444	1496	22.89
Leslie H. Tobler	USA	2010	Blood donors			302	100	202	33.11
Louise Nygaard Clausen	Denmark	2011	HIV (+)	215/112	Median 36 (Range 30-41)	327	76	251	23.24
K.J. Rolfe	UK	2011	HCV infected patients	202/119		321	102	219	31.78
Charlotte H.B.S. van der Berg	Netherland	2011	IDU	62/44	Median 28.5	106	35	71	33.02
Jason Grebely	Australia, Canada, USA, Netherland	2014	HCV infected patients	404/228		632	173	459	27.37
Edward L. Murphy	USA	2010	Blood donors	415/279		695	179	516	25.76
Kimberly Page	USA	2009	IDU	61/34		95	20	75	21.05
Jason Grebely	Canada	2007	HCV infected patients			762	179	583	23.49

Marianne Jauncey	Australia	2004	IDU	27/30		57	24	33	42.11
Nasheed Moqueet	Canada	2015	HIV (+)	367/174		541	79	462	14.60
Dimpy P. Shah	USA	2012	IDU	337/83		420	62	358	14.76
Arthur Y. Kim	USA	2011	HCV infected patients	131/215		346	66	280	19.08
Monika Sarkar	USA	2013	HCV infected patients	0/897	39.5±6.5	897	168	729	18.73
David L. Thomas	USA	2000	IDU		Median 34 (Range 29.8-38.4)	919	90	829	9.79
G.H. Ibrahim	Egypt	2013	HCV infected patients			115	22	93	19.13
Yuan Dong	China	2015	HIV (+)		Median 34	432	97	335	22.45
Michael P. Busch	USA	2006	Blood donors	1261/794		2055	402	1653	19.56
Lia L. Lewis-Ximenez	Brazil	2010	HCV infected patients	25/40	45.7±12.4 (Range 20-77)	65	29	36	44.62
Syczewska	Poland	2004	HCV infected patients	41/36		77	23	54	29.87
Patrick G. Quinn	USA	1999	HCV infected patients	155/103		258	44	214	17.05
Mingdong Zhang	USA	2006	Transfusion Dependent patients	671/41		712	192	520	26.97
Kohei Oda	Japan	2014	HCV infected patients	167/335	73 (Range 37-97)	502	149	353	29.68
T. Santantonio	Italy	2006	HCV infected patients	134/69	37.5 (Range 17-83)	203	73	130	35.96
S Keating	Ireland	2005	IDU	342/154	28.75 ±6.35	496	191	305	38.51
I Bakr	Egypt	2006	Sero incident cases	511/399		910	350	560	38.46
Hui-Ying Rao	China	2012	Blood donors	156/192	53.7±7.4	348	74	274	21.26
L. Alric	France	2000	HCV infected patients	171/174		345	63	282	18.26
Hossein Poustchi	Iran	2011	Sero incident cases	162/85		247	95	152	38.46

Madiha Mohamed El-Attar	Egypt	2010	HCV infected patients	115/85	46.5±13.6 (Range 12-75)	200	35	165	17.50
Sanaa M. Kamal	Egypt	2014	HCV infected patients	69/67		136	48	88	35.29
Gamal Esmat	Egypt	2011	HCV infected patients	53/43	5.9±2.4	96	31	65	32.29
J. Tilman Gerlach	Germany	2003	HCV infected patients	25/35	Range 17-63	60	24	36	40.00
Rebecca J Garten	China	2008	IDU	334/13	27.4±5.6	347	30	317	8.65
Enea Spada	Italy	2013	HCV infected patients	39/17	Median 31 (Range 19-78)	56	18	38	32.14
Noha Sharaf Eldin	Egypt	2008	HCV infected patients	69/48		117	51	66	43.59
H-Y Rao	China	2012	Blood donors	163/213	53.2±8	376	80	296	21.28
Barbara A. Piasecki	USA	2004	HCV infected patients	496/0		496	203	293	40.93
Ming-Lung Yu	Taiwan	2014	Transfusion Dependent patients	115/172	62±11.6	287	73	214	25.44

*Mean of age, otherwise stated in the table

Table 3. Characteristic of Studies Included Assessing Immunological Factors Associated with HCV Spontaneous Clearance

First Author	Country	Year	Study Population	M/F	Age*	∑ of HCV (+)	∑ of Clearance	∑ of Chronic HCV	∑ of Control
C. Goulding	Ireland	2005	Transfusion Dependent patients	0/283		283	87	196	120
Elizabeth J. Minton	UK	2005	HCV infected patients	404/202		606	190	416	
Ming-Lung Yu	Taiwan	2014	Transfusion Dependent patients	115/172	62±11.6	287	73	214	
Matthew E. Cramp	UK	1998	HCV infected patients	61/43	SVC 15.5, Range (3-42) CHC 14.2, Range (2-40)	104	49	55	134
Qian Cui	China	2010	HCV infected patients	249/113	SVC 32.43±6.15; CHC 32.63±6.18	362	189	173	225
B.S. de Almeida	Brazil	2010	HCV infected patients	42/93	SVC 53 ± 12; CHC 51 ± 11	135	45	90	
Julia di Iulio	Switzerland	2011	HIV (+)			460	227	233	
Priya Duggal	International study	2013	HCV infected patients	1492/909		2401	919	1482	
Franziska S. Hoffmann	Germany	2015	HCV infected patients	355/439		794	285	509	520
Peng Huang	China	2014	Blood donors	159/566	SVC 57.32±7.93; CHC 57.73±8.05	725	193	532	482
Peng Huang	China	2015	HCV infected patients	312/152	SVC 39.10 ±12.17; CHC 40.47 ± 12.33	464	246	218	773
G.H. Ibrahim	Egypt	2013	HCV infected patients	59/34	Range 23-65	93	22	71	70
Leila Ksiaa	Tunisia	2007	HCV infected patients	48/51	Overall 56.7±12.4	99	24	75	

First Author	Country	Year	Study Population	M/F	Age*	∑ of HCV (+)	∑ of Clearance	∑ of Chronic HCV	∑ of Control
Cheikrouhou					SVC 55.5; CHC 58				
Marco Antonio Montes-Cano	Spain	2005	HCV infected patients	109/87		196	65	131	
Nasheed Moqueet	Canada	2015	HIV (+)	367/174	44±8.2	541	79	462	
Isabelle Morard	Switzerland	2014	HCV infected patients	886/564	Median SVC 38; Median CHC 20	1450	160	1290	
Jacob Natterman	Germany	2011	HCV infected patients	0/396	24.7±4	396	119	277	105
Khadija Rebbani	Morocco	2014	HCV infected patients	85/88	SVC 60.2 ± 12.3; CHC 63.5 ± 10.5	173	54	119	
Heidar Sharafi	Iran	2014	HCV infected patients	333/17	SVC 39.2±11.1; CHC 39.8±10.1	350	91	259	
Haibo Sun	China	2015	General population	363/259	SVC 48.2±8.7; CHC 52±9.2	622	544	78	215
Shaidi Tang	China	2014	Blood donors	433/876	SVC 55.4±8.8; CHC 56.2±8.0	1309	429	880	1174
Chloe L. Thio	USA	2002	HCV infected patients	581/94	SVC 25.1; CHC 27.3	675	231	444	
David L. Thomas	USA	2009	HCV infected patients	802/206	SVC 33.9; CHC 32.0	1008	388	620	
Hans L. Tillman	Germany	2010	HCV infected patients	0/190	24.6±4	190	67	123	
Xing-xin Xue	China	2015	HCV infected patients	456/720		1176	444	732	1107
Ming Yue	China	2013	General population	372/180	SVC 41.68±12.24; CHC 42.96±2.39	552	293	259	784
Valli De Re	Italy	2014	HCV infected patients			2931	397	2534	1366

First Author	Country	Year	Study Population	M/F	Age*	∑ of HCV (+)	∑ of Clearance	∑ of Chronic HCV	∑ of Control
S. Ezzikouri	Morocco	2013	HCV infected patients	78/135	SVC 59.81±12.81; CHC 63.09±12.06	213	63	150	109
Ming Yue	China	2014	HCV infected patients	382/353	SVC 44.99 ± 13.84; CHC 45.91 ± 13.76	735	317	418	989
Yu Liu	China	2013	Blood donors	42/58	SVC 30.0±10.7; CHC 31.8±10.3	100	24	76	111
Sayeh Ezzikouri	UK	2013	HCV infected patients	132/168	SVC 57.77±15.64; CHC 63.66±12.26	300	68	232	138
Juliene Antonio Ramos	Brazil	2012	HCV infected patients	88/91	SVC 44.4, range (21–73); CHC 52.4, range (24–74)	179	18	161	
M. Bes	Spain	2012	Blood donors	43/26	SVC 46, range (27–61); CHC 43, range (23–63)	69	21	48	30
Xiaodong Shi	China	2012	General population	441/284	SVC 51.7±9.4; CHC 50.6±9.1	725	196	529	171
Fatma M. Shebl	USA	2011	IDU	825/384		1209	326	883	
Qian Cui	China	2011	HCV infected patients	372/180	SVC 39.10±12.26; CHC 39.23±12.6	552	293	259	421
Fuad Kurbanov	Egypt	2011	HCV infected patients	126/153	Median 38	279	130	149	
L. N. Clausen	Denmark	2011	HIV (+)	128/78	SVC 33, range (29–40); CHC 36, range (31–42)	206	47	159	
Jane H Wang	USA	2009	HCV infected patients	62/43	SVC 26.0, range (19-33);	105	49	56	

First Author	Country	Year	Study Population	M/F	Age*	∑ of HCV (+)	∑ of Clearance	∑ of Chronic HCV	∑ of Control
					CHC 25.6 range (19-32)				
Ping An	USA	2008	HCV infected patients	536/95		658	241	417	
Rebecca A. Harris	USA	2008	HCV infected patients	87/6	Median SVC 46; Median CHC 52	93	23	70	
Viviana Romero	USA	2008	IDU	119/41	SVC 37.8; CHC 39.9	160	39	121	
J. P. Pandey	Spain	2007	HCV infected patients	72/45		117	50	67	
Branwen J. Hennig	UK	2007	HCV infected patients	345/282		631	112	519	
Kazunori Kusumoto	Japan	2006	HCV infected patients	162/298	SVC 67.9 ± 11.3; CHC 63.4 ± 9.6	460	114	346	
D A Price	UK	2006	HCV infected patients			420	108	312	
TK Oleksyk	USA	2005	HCV infected patients			274	91	183	
Liam J. Fanning	Ireland	2004	HCV infected patients	39/186		225	86	139	
Janardan P. Pandey	USA	2004	HCV infected patients		Median SVC 36 (22-62); Median CHC 36 (23-54)	298	100	198	
S. Barret	Ireland	2003	HCV infected patients	0/158	SVC 45.3±7.3; CHC 44.7±8.5	158	66	92	
Jose Azocar	USA	2003	HCV infected patients	87/25	SVC 37.9; CHC 39.2	112	40	72	
Chloe L. Thio	USA	2001	HCV infected patients	476/98	SVC 25.7; CHC 24.8	574	200	374	
L. Alric	France	2000	HCV infected patients	171/174	SVC 42.1±15.4; CHC 46±12.3	345	63	282	800
Liam J. Fanning	Ireland	2000	HCV infected patients	0/156		156	84	72	
Alessandra Mangia	Italy	1999	HCV infected patients			184	35	149	200

First Author	Country	Year	Study Population	M/F	Age*	∑ of HCV (+)	∑ of Clearance	∑ of Chronic HCV	∑ of Control
Laurent Alric	France	1997	HCV infected patients	67/61	SVC 40.6 ± 15.7; CHC 45.4 ± 12.4;	128	25	103	800
Sandra Beinhardt	Austria	2012	HCV infected patients	64/56	37±16	120	59	61	96
Li Cai	China	2014	HCV infected patients	469/823	SVC 49.95±13.52; CHC 50.26±13.52	1292	479	813	1051
Jeny R. Cursino-Santos	Brazil	2007	HCV infected patients	79/25	Median SVC 40 (27-56); Median CHC 42 (24-71)	104	29	75	166
Vito di Marco	Italy	2012	HCV infected patients	124/121	SVC 18.6±8; CHC 18.7±6.5	245	98	147	
Karen Fitzmaurice	Ireland & Swiss	2014	HCV infected patients			780	332	448	
Charlotte H.B.S. van der Berg	Netherland	2011	IDU	62/44	Median 28.5	106	35	71	
Jason Grebely	Australia, Canada, Netherland, USA	2014	HCV infected patients	404/228		632	173	459	
Arthur Y. Kim	USA	2011	HCV infected patients	131/215		346	66	280	
Alessandra Mangia	Italy	2011	HCV infected patients	59/58	SVC 34.1±6.3; CHC 35.8±5.7	117	49	68	130
Susan M. McKiernan	Ireland	2004	HCV infected patients	0/243	27.35±5.52	243	95	148	
Susan M. McKiernan	Ireland	2000	HCV infected patients	0/243	SVC 48.75; CHC 47.86	243	95	148	1910
E.J. Minton	UK	1998	HCV infected patients	106/67	SVC 37.9, range (17-70); CHC 37.2, range (20-77)	173	35	138	
Alessandra Mangia	Italy	2014	HCV infected patients	408/313	SVC 35.9±15; CHC 53.6±12.7	721	100	621	178
Serkan Ocal	Turkey	2014	HCV infected patients	130/59	Median 27, range (17-56)	189	57	129	199

First Author	Country	Year	Study Population	M/F	Age*	∑ of HCV (+)	∑ of Clearance	∑ of Chronic HCV	∑ of Control
Kohei Oda	Japan	2014	HCV infected patients	167/335	73, range (37-97)	502	149	353	
H-Y Rao	China	2012	HCV infected patients	163/213	53.2±8	376	80	296	
Maria Concetta Renda	Italy	2011	HCV infected patients	16/26	44.68±12.09	42	20	22	
E.C. Seaberg	USA	2013	HCV infected patients	528/0	Median 33.5, range (17-70)	528	118	410	
Enea Spada	Italy	2013	HCV infected patients	39/17	Median 31, range (19-78)	56	18	38	
CL Thio	USA	2004	HCV infected patients	469/98		567	192	375	
Sanaa M. Kamal	Egypt	2014	HCV infected patients	69/67	SVC 36.48 ± 7.64; CHC 37.17 ± 6.2	136	48	88	20
S Barret	Ireland	2001	HCV infected patients	0/155	SVC 45.8±4.9; CHC 45.7±6.0	155	68	87	
Leila Ksiaa Cheikrouhou	Tunisia	2011	Transfussion Dependent patients	48/52	SVC 55.5±11.71; CHC 58±13.08	100	24	76	
Maria Elisa Mancuso	Italy	2014	HCV infected patients	329/13	Median SVC 39.6 (34.8–55.3); Median CHC 47.2 (40.8–56.9)	342	59	283	
Peter V. Aka	USA	2014	HCV infected patients			1075	185	890	
Vagner Ricardo Lunge	Brazil	2011	HIV (+)	86/52	SVC 42.7±9.5; CHC 41.4±9.5	138	34	104	
Melissa Laird	France	2014	HCV infected patients	22/11		33	19	14	
Yin Huang	USA	2007	IDU			251	85	166	
Wen Xiao	China	2015	HCV infected patients	231/588	SVC 57.1±7.9; CHC 56.2±7.6	819	219	600	375
Alessandra Mangia	Italy	2004	HCV infected patients	134/140	Range 20-79	220	50	170	
Patricia K. Constantini	UK	2002	HCV infected patients	93/57	38.8, range (16-68)	150	57	93	

*Mean of age, otherwise stated in the table

Appendix 2

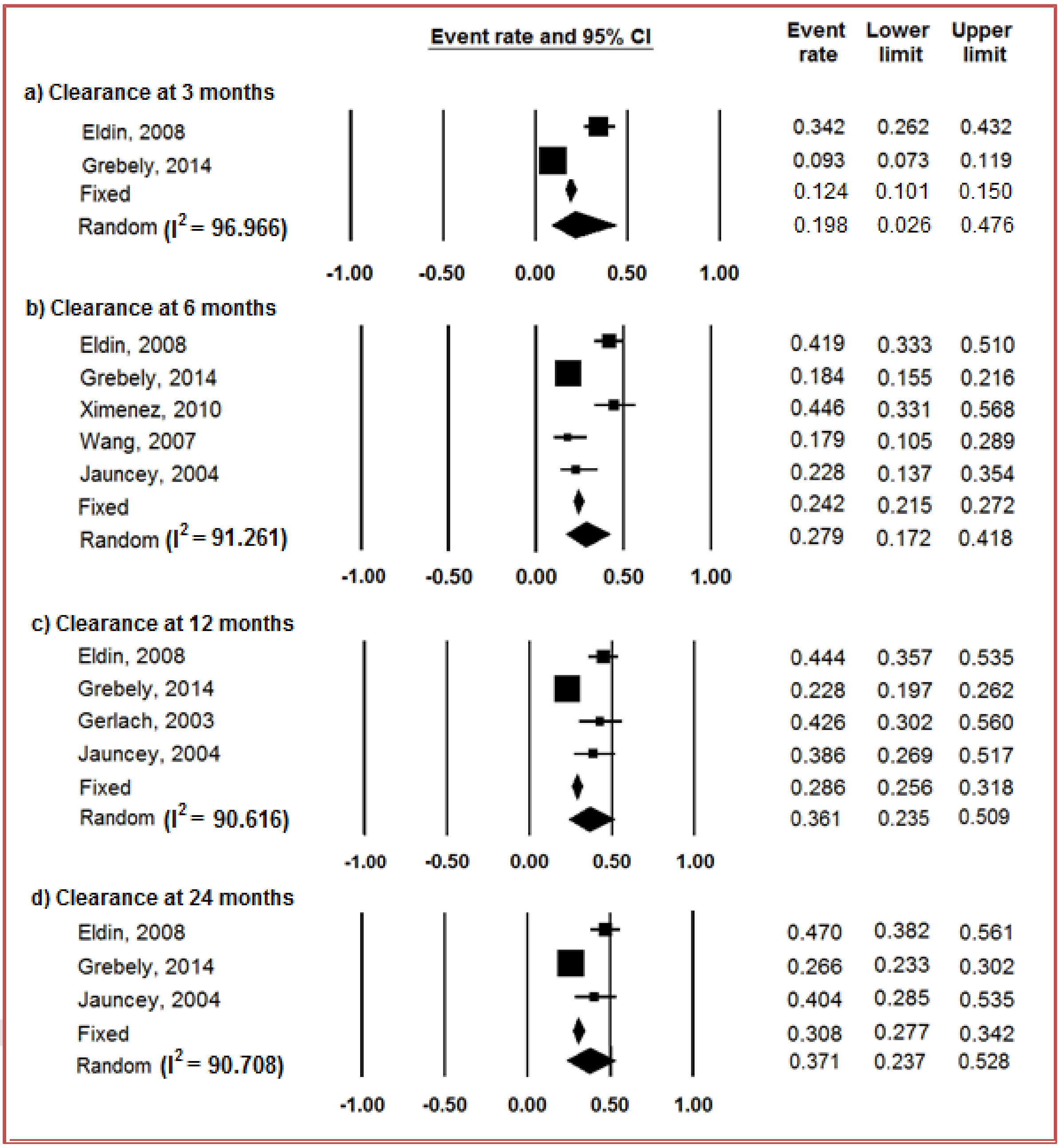


Figure 1. Rate of Spontaneous Clearance in Several Time Points

Appendix 3

Table 1. Result of Meta-Analysis Examining Demographic, Clinical, and Behaviour Factors Associated with HCV Spontaneous Clearance

Determinants	All Studies					>12 months study				
	∑ study	I^2	OR	Lower CI	Upper CI	∑ study	I^2	OR	Lower CI	Upper CI
Demographic Determinants										
Male vs Female[‡]	8	0·00	0·68	0·57	0·81	6	0·00	0·61	0·48	0·78
Age ≥ 30 yo vs <30 yo	6	37·96	0·86	0·68	1·09	3	0·00	0·77	0·54	1·09
Age ≥ 40 yo vs <40 yo	5	81·33	0·52	0·26	1·07	1	NA	NA	NA	NA
Age ≥ 45 yo vs <45 yo	4	33·71	0·79	0·64	0·97	2	21·87	1·03	0·49	2·16
Black vs Non-Black	3	57·58	0·38	0·20	0·75	2	46·19	0·30	0·13	0·69
Non-Aborigin vs Aborigin	5	43·63	0·47	0·36	0·62	3	58·07	0·55	0·28	1·07
African American vs Non-African American	5	95·33	0·29	0·08	1·05	0	NA	NA	NA	NA
White vs Others	5	60·38	0·94	0·53	1·48	2	0·00	1·53	0·70	3·34
Clinical Determinants										
Asymptomatic Infection	7	0·00	0·38	0·27	0·56	6	0·00	0·41	0·28	0·62
HIV Co-infection[‡]	4	0·00	0·50	0·37	0·66	2	0·00	0·54	0·40	0·75
Non HBV co-infection[‡]	7	49·45	0·21	0·14	0·32	2	47·68	0·22	0·11	0·45

Non Genotype 1 vs Genotype 1	4	0·00	0·63	0·45	0·89	4	0·00	0·63	0·45	0·89
Behaviour Determinants										
IDU vs Non-IDU	7	82·88	0·59	0·37	0·93	2	75·14	1·04	0·24	4·44
Alcohol*	5	72·15	0·67	0·47	0·95	2	38·99	0·50	0·26	0·96

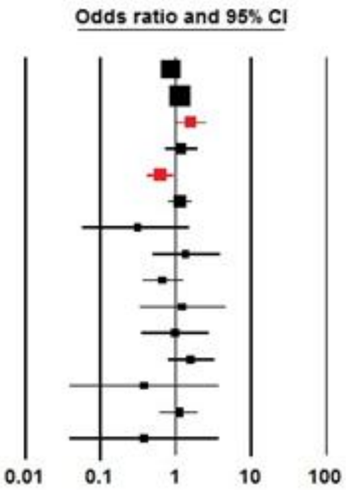
‡Multivariate analysis

*Alcohol drinker or had history of drinking excess alcohol

Appendix 4

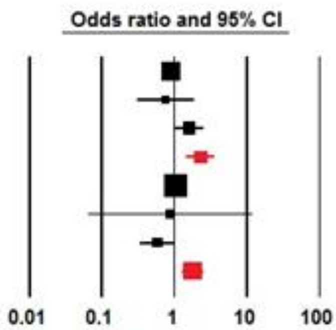
HLA Class I – A

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
A*01	0.855	0.647	1.130	-1.101	0.271
A*02	1.145	0.896	1.464	1.081	0.280
A*03	1.577	1.010	2.462	2.004	0.045
A*11	1.182	0.726	1.925	0.672	0.502
A*23	0.606	0.402	0.914	-2.390	0.017
A*24	1.130	0.769	1.660	0.623	0.534
A*25	0.310	0.064	1.504	-1.453	0.146
A*26	1.351	0.479	3.810	0.569	0.570
A*29	0.671	0.355	1.268	-1.229	0.219
A*30	1.223	0.332	4.503	0.303	0.762
A*31	0.968	0.344	2.724	-0.062	0.951
A*32	1.581	0.778	3.214	1.265	0.206
A*33	0.375	0.038	3.681	-0.842	0.400
A*68	1.100	0.617	1.961	0.323	0.747
A*74	0.375	0.038	3.681	-0.842	0.400



HLA Class I – B

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
B*07	0.889	0.647	1.221	-0.727	0.467
B*08	0.762	0.308	1.885	-0.588	0.556
B*15	1.590	0.993	2.547	1.929	0.054
B*27	2.291	1.446	3.629	3.532	0.000
B*35	1.038	0.803	1.342	0.285	0.776
B*38	0.858	0.063	11.648	-0.115	0.908
B*5301	0.577	0.326	1.022	-1.887	0.059
B*57	1.781	1.286	2.466	3.475	0.001



HLA Class I – C

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Cw*01	1.597	0.639	3.992	1.001	0.317
Cw*02	0.935	0.470	1.860	-0.192	0.848
Cw*03	0.838	0.537	1.307	-0.779	0.436
Cw*04	0.601	0.463	0.780	-3.827	0.000
Cw*05	1.844	1.146	2.968	2.520	0.012
Cw*06	1.555	0.835	2.895	1.392	0.164
Cw*07	1.995	1.362	2.923	3.544	0.000
Cw*08	0.873	0.434	1.756	-0.381	0.703
Cw*12	1.271	0.515	3.136	0.520	0.603
Cw*15	0.895	0.245	3.273	-0.168	0.867
Cw*16	0.998	0.647	1.540	-0.009	0.993

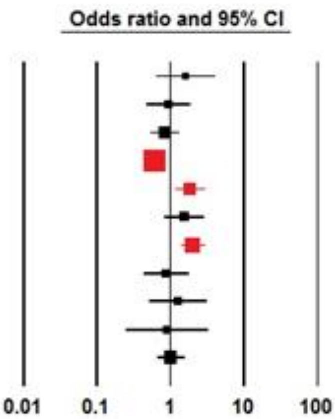
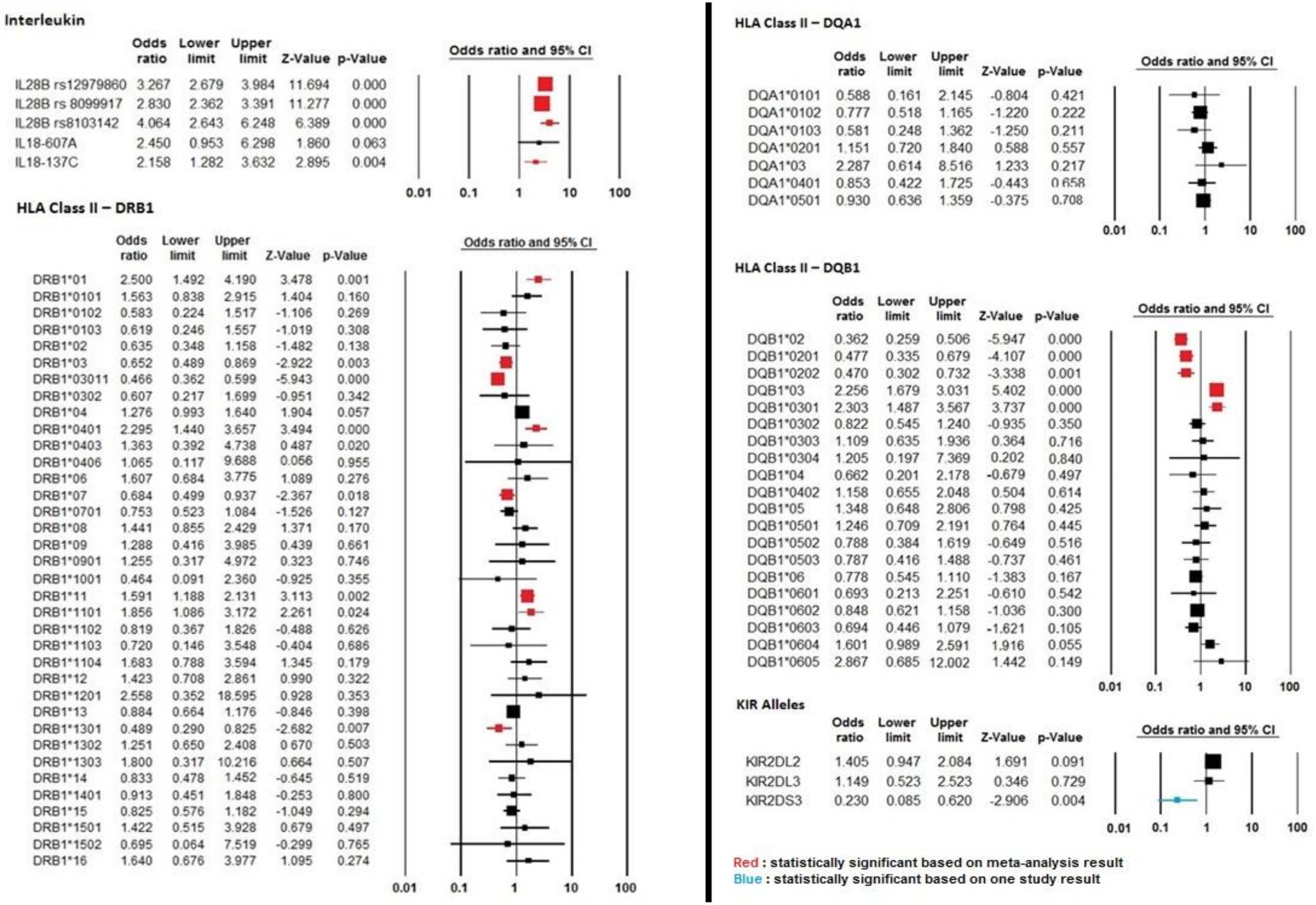


Figure 1. Forest Plot Assessing HLA Class I Associated with HCV Spontaneous Clearance



Interleukin

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
IL28B rs12979860	3.267	2.679	3.984	11.694	0.000
IL28B rs 8099917	2.830	2.362	3.391	11.277	0.000
IL28B rs8103142	4.064	2.643	6.248	6.389	0.000
IL18-607A	2.450	0.953	6.298	1.860	0.063
IL18-137C	2.158	1.282	3.632	2.895	0.004

HLA Class II – DRB1

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
DRB1*01	2.500	1.492	4.190	3.478	0.001
DRB1*0101	1.563	0.838	2.915	1.404	0.160
DRB1*0102	0.583	0.224	1.517	-1.106	0.269
DRB1*0103	0.619	0.246	1.557	-1.019	0.308
DRB1*02	0.635	0.348	1.158	-1.482	0.138
DRB1*03	0.652	0.489	0.869	-2.922	0.003
DRB1*03011	0.466	0.362	0.599	-5.943	0.000
DRB1*0302	0.607	0.217	1.699	-0.951	0.342
DRB1*04	1.276	0.993	1.640	1.904	0.057
DRB1*0401	2.295	1.440	3.657	3.494	0.000
DRB1*0403	1.363	0.392	4.738	0.487	0.020
DRB1*0406	1.065	0.117	9.688	0.056	0.955
DRB1*06	1.607	0.684	3.775	1.089	0.276
DRB1*07	0.684	0.499	0.937	-2.367	0.018
DRB1*0701	0.753	0.523	1.084	-1.526	0.127
DRB1*08	1.441	0.855	2.429	1.371	0.170
DRB1*09	1.288	0.416	3.985	0.439	0.661
DRB1*0901	1.255	0.317	4.972	0.323	0.746
DRB1*1001	0.464	0.091	2.360	-0.925	0.355
DRB1*11	1.591	1.188	2.131	3.113	0.002
DRB1*1101	1.856	1.086	3.172	2.261	0.024
DRB1*1102	0.819	0.367	1.826	-0.488	0.626
DRB1*1103	0.720	0.146	3.548	-0.404	0.686
DRB1*1104	1.683	0.788	3.594	1.345	0.179
DRB1*12	1.423	0.708	2.861	0.990	0.322
DRB1*1201	2.558	0.352	18.595	0.928	0.353
DRB1*13	0.884	0.664	1.176	-0.846	0.398
DRB1*1301	0.489	0.290	0.825	-2.682	0.007
DRB1*1302	1.251	0.650	2.408	0.670	0.503
DRB1*1303	1.800	0.317	10.216	0.664	0.507
DRB1*14	0.833	0.478	1.452	-0.645	0.519
DRB1*1401	0.913	0.451	1.848	-0.253	0.800
DRB1*15	0.825	0.576	1.182	-1.049	0.294
DRB1*1501	1.422	0.515	3.928	0.679	0.497
DRB1*1502	0.695	0.064	7.519	-0.299	0.765
DRB1*16	1.640	0.676	3.977	1.095	0.274

HLA Class II – DQA1

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
DQA1*0101	0.588	0.161	2.145	-0.804	0.421
DQA1*0102	0.777	0.518	1.165	-1.220	0.222
DQA1*0103	0.581	0.248	1.362	-1.250	0.211
DQA1*0201	1.151	0.720	1.840	0.588	0.557
DQA1*03	2.287	0.614	8.516	1.233	0.217
DQA1*0401	0.853	0.422	1.725	-0.443	0.658
DQA1*0501	0.930	0.636	1.359	-0.375	0.708

HLA Class II – DQB1

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
DQB1*02	0.362	0.259	0.506	-5.947	0.000
DQB1*0201	0.477	0.335	0.679	-4.107	0.000
DQB1*0202	0.470	0.302	0.732	-3.338	0.001
DQB1*03	2.256	1.679	3.031	5.402	0.000
DQB1*0301	2.303	1.487	3.567	3.737	0.000
DQB1*0302	0.822	0.545	1.240	-0.935	0.350
DQB1*0303	1.109	0.635	1.936	0.364	0.716
DQB1*0304	1.205	0.197	7.369	0.202	0.840
DQB1*04	0.662	0.201	2.178	-0.679	0.497
DQB1*0402	1.158	0.655	2.048	0.504	0.614
DQB1*05	1.348	0.648	2.806	0.798	0.425
DQB1*0501	1.246	0.709	2.191	0.764	0.445
DQB1*0502	0.788	0.384	1.619	-0.649	0.516
DQB1*0503	0.787	0.416	1.488	-0.737	0.461
DQB1*06	0.778	0.545	1.110	-1.383	0.167
DQB1*0601	0.693	0.213	2.251	-0.610	0.542
DQB1*0602	0.848	0.621	1.158	-1.036	0.300
DQB1*0603	0.694	0.446	1.079	-1.621	0.105
DQB1*0604	1.601	0.989	2.591	1.916	0.055
DQB1*0605	2.867	0.685	12.002	1.442	0.149

KIR Alleles

	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
KIR2DL2	1.405	0.947	2.084	1.691	0.091
KIR2DL3	1.149	0.523	2.523	0.346	0.729
KIR2DS3	0.230	0.085	0.620	-2.906	0.004

Figure 2. Forest Plot Assessing Interleukin, KIR Alleles and HLA Class II Associated with HCV Spontaneous Clearance