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Epidemiology and natural history of hepatitis C virus infection among children and young people

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Keywords: Child, Chronic hepatitis, Hepatocellular carcinoma, Liver cirrhosis, Viral hepatitis

Electronic word count: 5458

Figures: 4. Tables: 4.

Contributor's Statements:

Study conception and design:	AA, WLI, DAK
Data collection:	AA, BW, WLI, JB, CL, DAK
Data analysis:	LM, WLI, DAK
Draft Manuscript preparation:	LM
Final manuscript:	All co-authors

All authors had full access to all of the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Financial Support: Funding to support HCV Research UK was provided by a grant from the Medical Research Foundation, the independent charity of the UK Medical Research Council (award no: C0365).

Abbreviations:

DAAs	Direct acting antivirals
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCV R UK	HCV Research UK
INF	Interferon
IVD	Intravenous drug
LTx	Liver transplantation
SVR	Sustained virological response
UK	United Kingdom

Abstract

Background: Chronic hepatitis C virus (HCV) infection is a global health burden. Although HCV infection rarely contributes to morbidity during childhood, the majority of HCV infected children develop chronic HCV with a lifetime risk of liver disease. Little is known about the development of long-term liver disease and treatment effect in patients infected with HCV in childhood.

Method: Retrospective review of patients infected with HCV in childhood enrolled in HCV Research UK.

Results: 1049 patients were identified. The main routes of infection were intravenous drug use (53%); blood product exposure (24%); perinatal infection (11%). Liver disease developed in 32% of patients at a median of 33 years irrespective of mode of infection. Therefore, patients with perinatal exposure developed cirrhosis at an earlier age than the rest of the risk groups. Incidence of hepatocellular carcinoma (HCC) was 5%, liver transplant 4% and death occurred in 3%. Overall, 663 patients were treated (interferon/Peg interferon; 55% or direct acting antivirals; 40%). Sustained virological response (SVR) was achieved in 406 (75%). There was higher mortality among patients without SVR vs SVR (5% vs 1%, $p=0.003$). Treatment was more effective in those without cirrhosis and disease progression was less (13%), compared to those patients with cirrhosis at the time of therapy (28%) $p<0.001$, who were more likely to develop HCC, require liver transplantation, or die.

Conclusion: HCV infection in young people causes significant liver disease, which can now be prevented with antiviral therapy. Early treatment, especially before development of cirrhosis is essential. Detection of HCV should be aimed

at relevant risk groups and anti-viral therapy should be made available in childhood to prevent long-term liver disease and spread of HCV.

Lay summary

Chronic HCV infection is a global health problem, which can now be treated with potent directly acting antiviral drugs. This study demonstrates (i) HCV infection in childhood causes serious liver disease in 32% of patients at a median of 33 years, irrespective of age, mode and route of infection (ii), the commonest routes of infection in those under 18 years of age in the UK are intravenous drug use (53%), via blood or blood products (24%) and via perinatal transmission (11%); (iii) disease outcome was better in patients treated before the development of advanced liver disease. Anti -viral therapy should be made available in childhood to prevent long-term liver disease and spread of HCV.

Introduction

Chronic hepatitis C virus (HCV) infection is a global health burden with an estimated prevalence varying between 0.6%-10% dependent on geographical location and an estimated 71 million people worldwide with chronic infection (1-3). In Western Europe, the estimated prevalence is 1.5%-3.5%, but in the UK it is 0.5%. Chronic HCV is associated with increased morbidity and mortality and is a leading cause of end stage liver disease, cirrhosis and liver cancer worldwide (3-6). Although HCV infection rarely contributes to morbidity during childhood, the majority of HCV infected children develop chronic HCV with a lifetime risk of serious liver disease (7). Furthermore, some studies indicate that HCV affects childhood quality of life and behaviour, as cognitive function has been shown to be affected and families report increased stress which affects family dynamics and wellbeing (7, 8).

Several factors have been associated with accelerated disease progression but it is not clear whether or not infection in early life carries a different risk of progressive disease than infection in adulthood (9, 10). Since the mode of infection and genotype differs between countries and regions, knowledge of epidemiology at a local level is important in order to effectively plan prevention, surveillance, and prioritise treatment (11). Currently, there are little data on mode of infection, genotype and development of long term liver disease in patients infected with HCV in childhood in the UK.

Currently, access to clinical trials of DAAs in childhood is limited which denies timely access to effective therapies for young infected children. HCV Research UK is a UK database and biobank which established a cohort of HCV infected

children and adults to address gaps in knowledge of epidemiology, treatment, disease progression, and prognosis (12, 13).

The aim of this study was to describe the epidemiology and natural history of HCV in a UK cohort of patients who were infected during childhood.

Patients and methods

Retrospective, descriptive study of patients infected with HCV in childhood in the UK.

The HCV Research UK database and Biobank

HCV Research UK (HCV R UK) is a national, clinical, multicentre research database and biobank set up in 2012 to collect information about adults and children infected with HCV in the UK (12, 13). All highly populated areas of the UK are represented in the cohort and only patients who were in prison at time of clinic appointments or patients who were unable to give written informed consent were excluded from recruitment. More than 10,000 patients with past or current infection have been enrolled from 51 specialist adult and 7 paediatric HCV centres. Written informed consent was obtained at time of enrolment. For children under 16 years, this was supplied by parents or legal guardians. The HCV R UK database holds anonymised information including demographic data, risk factors for HCV infection including date of first exposure to risk, past and current alcohol intake, virology data, laboratory data, biopsy and imaging results(13). The baseline data at enrolment of each participant is collected through a detailed, standardised questionnaire while follow-up data is collected

through assessment of medical notes. In addition, prospective clinical data on risk behaviours, physical characteristics, HCV virology, comorbidities, liver disease status, treatment, and mortality are collected biennially for all patients in the cohort.

Diagnosis of cirrhosis was made at the discretion of the local physician by histology, imaging studies, serum markers or clinical diagnosis with accompanying clinical signs (ascites, portal hypertension, and/or variceal bleed).

Patients

Clinical and epidemiological data from patients enrolled in the HCV R UK clinical database and biobank was requested in October 2016 and the data updated in March 2017. Patients were included if age at first infection was estimated (based on first exposure to risk) to be between 0-18 years or if age between 0-18 years was recorded at the time of first positive HCV test, the time of first attendance or at the time of consent.

Statistical analysis

Statistical analyses were performed using STATA 13 (StataCorp LP, Texas). Clinical characteristics were analysed in a descriptive way and reported as mean ± standard deviation (SD) or median and range where assumptions of normal distribution were not met. For pairwise comparison, chi square test was used for binary outcome variables and Fisher exact test was used for small samples.

The unpaired t-test and multivariate logistic regression with indicator variable was used for continuous numerical outcome variables and Wilcoxon rank-sum test was used for non-normally distributed data.

Statistical significance was defined as $p<0.05$.

Results

Demographic data

In total, 1086 patients infected with HCV in childhood were identified from the HCV R UK database of whom 37 patients were excluded due to discrepancies between date of birth, date of infection and possible infection route leaving 1049 patients for data analysis. Estimated time of first infection between 0 and 18 years was given in 984/1049 (94%) of patients, while the remaining 65 patients were included based on age <18yrs at their first positive HCV test (n=64) or their age at consent <18yrs (n=1). Baseline characteristics of the cohort are shown in table 1.

HCV genotypes, tested in 938 patients (89%), were G1: 531 (57%); G2: 50 (5%); G3: 328 (35%), G4: 27 (3%), G5: 1 (0.1%) and mixed type: 1 (0.1%). Forty-four (4%) patients were co-infected with HIV of whom 41 (93%) were treated with antiretrovirals; 363 (35%) had a history of heavy alcohol use – 301/759 (40%) males and 62/287 (22%) females, $p<0.001$. Spontaneous clearance of infection was seen in 3% (36/1049), of whom 26 (72%) were males.

Route of infection

Patient characteristics by mode of infection are shown in table 2. The most prevalent route of infection was intravenous drug use (IVD group): 560 (53%), followed by receipt of blood products (blood group): 251 (24%), including 85 with coagulation bleeding disorders; perinatal exposure (perinatal group): 119 (11%) and unknown or other route of infection (unknown group): 119 (11%). There were less male patients in the perinatal group (35%) compared to the IVD blood and other infection route groups (78%, 77% and 73% respectively, p<0.001). The genotype distribution shows fewer genotype 3 infections in the blood group (18%) compared to the other 3 groups (35%) (p<0.001).
Median age at first infection was 16yrs (range 10-18) in the IVD group, 11yrs (range 0-17yrs) in the blood group and at birth (0yrs) in the perinatal group (figure 1). The gap between infection and diagnosis was a median 19 to 24yrs in the IVD group, blood group and unknown risk group and 2yrs in the perinatal group.

Development of liver disease

In total, 334/1049 (32%) of patients had a diagnosis of cirrhosis at the time of data analysis. Cirrhosis was diagnosed by liver biopsy (110, 33%), imaging studies including transient elastography (85, 25%), endoscopy or clinical signs of cirrhosis (101, 30%), serum markers (7, 2%) and unknown/missing (31, 9%). By multivariate regression analysis, significant risk factors for the development of cirrhosis were male gender (p=0.003, OR 1.6 [95%CI 1.2-2.2]) and heavy alcohol use (p<0.001, OR 1.6 [95%CI 1.2-2.8]) while HIV co-infection was not significant (p=0.88, OR 0.95 [95%CI -0.2-0.5]). The time to cirrhosis and age at

development of liver disease between the different risk groups is presented in figure 2 and shows that the rate of liver disease progression appears to be similar across all patient groups.

The median time to develop cirrhosis was 33yrs (range 12-53yrs) which was estimated in 281/334 (84%) patients. There was no significant difference between any of the groups (IVD group: 33yrs; blood group: 32yrs; perinatal group 36yrs; unknown group: 36yrs), ($p=0.76$). Thus, patients with perinatal infection developed cirrhosis earlier at a median age of 36yrs (range 17-53yrs) compared to 48yrs (range 33-68yrs), 46yrs (range 12-61yrs), and 51.5yrs (range 12-65yrs) in the IVD, blood, and unknown groups, respectively ($p<0.001$).

There were less patients with cirrhosis in the perinatal group (8%, 10/119) compared to the IVD, blood and unknown groups (37%, 205/560; 32%, 79/250; 34%, 40/119) ($p<0.001$). However, 101 (85%) of patients with perinatal infection were younger than 33yrs of age at the time of data analysis and so may not have had time to develop cirrhosis, whilst 7 of the 18 (38%) above the age of 33yrs had developed cirrhosis, suggesting a similar pattern of development of cirrhosis irrespective of infection route. Cirrhosis developed in the perinatal group despite the low prevalence of associated risk factors (male gender, heavy alcohol use) compared to the IVD group (table 2).

HCC was diagnosed in 55/1049 (5%) of the patients. Of these 55 patients 38/55 (70%) were from the IVD group, 11/55 (20%) in the blood product group, and 6/55 (10%) of the patients in the unknown group. 44 of the 55 patients with HCC (80%) had cirrhosis prior to the diagnosis of HCC. There was no

difference in heavy alcohol use between patients with (23/44, 52%) or without cirrhosis (6/11, 55%), p=0.9 prior to diagnosis of HCC. Overall, median time to development of HCC was 39yrs (range 23-53 years) while median age at diagnosis of HCC was 55yrs (range 37-68yrs), figure 3.

46 (4%) of patients had received a liver transplant (LTx). Of these, 33 were cirrhotic and 17 had HCC at the time of transplant. Median time to LTx from first infection was 34yrs (range 16-50yrs) while median age at time of LTx was 49yrs (range 27-66yrs), figure 4. There was no significant effect of mode of transmission (p=0.90; p=0.18) respectively). There was no difference between those who required LTx and those who did not with regard to HIV co-infection (2/47 (4%) vs. 42/1002 (4%), p=0.2) or history of heavy alcohol use (21/47 (44%) vs. 342/1002 (34%), p=0.1). Renal failure was reported more frequently in patients who had LTx (4/47 (9%) vs. 7/1002 (0.7%), p=0.001).

The overall mortality in the cohort was 3% (28/1049). In multivariate analysis the presence of cirrhosis (p<0.001, OR 6.2 [95%CI 2.6-14.7]) was the only significant risk factor. Heavy alcohol use (p=0.3, OR 1.5 [95%CI 0.7-3.3]), HCC (p=0.8, OR 1.2 [95%CI 0.4-3.9]), gender (p=0.8, OR 1.6 [95%CI 0.5-3.3]) and LTx (p=0.9, OR 1.0 [95%CI 0.3-3.7]) were not associated with mortality.

Treatment

In total 663 (63%) patients in the cohort had received treatment, 133 and 46 of whom received 2 and 3 separate treatment regimens, respectively. Treatment outcome was missing for 122 individuals. Of the 541 patients whose treatment outcome was known, for 292 (54%) the last treatment was an interferon (INF)

based treatment regimen + ribavirin (RBV); only 6 patients (1%) had INF alone;95 (18%) had INF in combination with direct acting antivirals (DAAs). 119 (22%) received DAAs alone. In 29 (5%) patients, the treatment regimen was unknown, mostly because they had taken part in clinical trials. Overall, sustained virological response (SVR) was achieved in 406 (75%) patients while 135 (25%) patients were non-responders or responder-relapsers. Treatment outcomes stratified by the last regimen received and liver disease status are shown in table 3. There was no difference in the overall SVR rates between non-cirrhotic and cirrhotic patients (265/360 [74%] vs 111/142 [78%], p=0.29), although this is confounded by the fact that 314/360 (87%) of the former group received an INF-containing regimen, whilst 67/142 (47%) of the latter group received all DAA regimens. The apparently higher SVR rate in cirrhotic patients treated with an interferon-based regimen (32/46, 70%) as compared to non-cirrhotic patients (162/238, 68%) is probably because in the former group the predominant genotype was GT3 (28/46, 61%), who generally have a better response to IFN therapies, whereas in the latter group it was GT1 (115/238, 48%), with only 97 (40%) GT3 infections.

Progression of liver disease

502 patients underwent treatment with complete data (i.e. the treatment regimen, outcome and liver disease status were known 142 with cirrhosis and 360 patients without. Progression of liver disease according to treatment outcome in patients treated with and without cirrhosis is shown in table 4.

Disease progression occurred in 87/502 (17%); 47/360 (13%) events were recorded in those without cirrhosis, compared to 40/142 (28%) in patients with cirrhosis (p<0.001). Progression to cirrhosis was seen in 24/265 (9%) patients, who achieved SVR, compared to 15/95 (16%) who failed to achieve SVR (p = 0.07). Progression to HCC, liver transplant or death was seen almost exclusively in those patients who were cirrhotic at treatment onset. Although HCC developed in 16 cirrhotic patients post-SVR, in 12 of these patients, the HCC was diagnosed in the same year that SVR was recorded. It is highly likely, therefore, that many, if not all of these tumours did not arise *de novo* post SVR in a non-infected liver, but were present during the period of therapy and follow-up to assessment of treatment outcome.

The median length of follow-up for the cirrhotic patients, without further liver disease at time of data analysis was 3 years for those with SVR (range 0-20 years) and 3 years (range 1-13 years) for non-SVR patients. For the non-cirrhotic patients the follow-up time was 5 years (range 1-24 years) for SVR patients and 6 years (range 1-22 years) for non-SVR patients.

Significantly more patients with SVR treated with cirrhosis compared to patients treated before diagnosis of cirrhosis progressed to HCC (16 [14%] vs. 2 [1%], p<0.001), or required LTx (7 [6%] vs. 3 [1%], p=0.005) or died (5 [4%] vs. 0 [0%], p=0.001 (table 4). Furthermore, mortality amongst cirrhotic patients who achieved SVR (5/111, 4%) was significantly less than for those who did not achieve SVR (7/31, 23%, p = 0.004).

Discussion

This is the first study to describe the epidemiological characteristics and development of long term liver disease in a UK cohort of patients infected with HCV in childhood. The main route of infection was IV drug use in adolescents in the UK. Serious long term liver disease developed in one third of the patients and treatment was more effective in those who were treated before cirrhosis developed, as those treated with cirrhosis were more likely to develop HCC, require liver transplantation, or die.

Studies of the development of liver disease in adult patients with chronic HCV prior to treatment have found that alcohol intake and severity of portal fibrosis are correlated with future disease progression and development of cancer (14). There are few studies describing disease progression in adulthood in patients who were infected with HCV during childhood. Many studies are in heterogeneous populations with insufficient long term follow-up to provide clear outcomes. (14-17). Previous studies have reported that HCV infection in children differs from adults in some ways such as modes of transmission, rates of clearance, progression of fibrosis, and the duration of potential chronic infection when acquired at birth (18, 19). A risk of the development of hepatic fibrosis whilst in childhood of less than 2% has been reported , but this is much higher in patients with longer follow-up and duration of infection, indicating disease progression is more likely 10 years after the onset of infection (20-23). Other paediatric studies have demonstrated that the degree of hepatic fibrosis correlates with age and duration of infection and suggest that progression occurs at a slower pace in young children compared to those infected late in

life (16, 24-27). Disease may progress more rapidly in older patients due to the presence of multiple additional risk factors such as alcohol consumption and co-infection with HIV, and therefore it is important to distinguish between disease development in those infected as neonates and young people versus disease development in young adults (18, 28-30).

The proportion of HCV-infected children who may develop serious long-term liver disease is not clear from the current literature. In this study 33% of patients infected with HCV in childhood developed long term liver disease including cirrhosis, HCC or a requirement for LTx. A critical finding in our analysis was that the long-term development of progressive liver disease is independent of the age or route of acquisition, with a median time to diagnosis of 32-36 years. Other studies have suggested that vertically infected children may develop liver disease more frequently than children infected by blood products (31-33). However, most of these studies do not have data beyond 10yrs of follow-up of children infected with HCV and are likely to underestimate the proportion of HCV-infected children who will develop long-term liver disease. Cirrhosis was less frequent in perinatally infected patients compared to the other risk groups in our cohort. However, perinatally infected patients older than 33 years in our cohort had the same frequency of cirrhosis as the other risk groups, even though heavy alcohol use was much less frequent in this subgroup.

The rate of disease progression is influenced by a variety of host, viral, and environmental factors, most notably alcohol abuse and coinfection with HBV and HIV (2, 34). Such associations were not evident in our cohort, most likely

because of the relatively low frequency of these risk factors in those children infected at an early age.

There was more than a 20 year delay between suspected time of infection and diagnosis of HCV in this chort, except in the perinatally infected patients, probably because of lack of HCV testing in relevant paediatric risk groups (9). As all blood donors are now screened for all blood borne viruses, vertical transmission of HCV via mother-to-child transmission is now reported to be the leading cause of paediatric infection globally while risk factors for HCV infection in adults include IVD use, blood transfusion before 1992 and HIV-infection (35-38).

In this cohort, in contrast to other paediatric studies, more than half of the infected patients reported IV drug use in adolescence as the main route of infection, followed by blood product exposure, while vertical transmission only accounted for 11% of the cases (39, 40). These data reflect the long term follow up of this cohort infected with HCV prior to screening of blood products and modern management of IV drug abuse (41, 42). These data may be an under-estimate of the actual number of UK children infected with HCV as it is likely that many are not identified and hence are not receiving appropriate treatment and counselling. Healthcare workers at primary and secondary healthcare levels should encourage testing of relevant risk groups, such as young adolescents who participate in IV drug use and the children of such individuals.

75% of the treated patients in this cohort achieved SVR. Life-threatening complications of end stage liver disease were much less frequent in patients treated before they became cirrhotic (see Table 4) as reported previously in the literature (43, 44).

We have not attempted a more detailed interpretation of the treatment data in this cohort since the data were collected during a period when there were rapid changes in HCV treatment regimens,and there are a number of possible confounders. For instance, many of the patients treated with DAAs will be those who had failed earlier treatment regimens, and will thus have been a "difficult-to-treat" group, with potentially more severe liver disease at time of initiation of treatment. Nevertheless, our data provide a clear indication of the need to start treatment as early as possible before the development of established liver disease. We have confirmed previous reports that achievement of SVR in patients with cirrhosis reduces, but does not eliminate, the risk of HCC development. (32, 33, 45).

Some limitations should be taken into account when interpreting the results. The duration of infection was estimated on the assumption that patients were infected at time of first exposure to risk. For the IVD group, this is a simplification since it is possible that actual infection occurred sometime later in life. Calculations based on the risk of infection in IVD users suggests that around 50% of all IVD users who acquire HCV infection do so within 3 years of onset of injecting behaviour (46). Thus, our quoted estimate of time to cirrhosis for this group may be a slight overestimate.

Treatment data from this cohort reflects historical practice as INF based treatment regimens are no longer recommended in adult guidelines and DAAs are the preferred treatment with high SVR rates and few side-effects. However, only two DAAS are licensed in children over 12 years of age (sofosbuvir with ribavirin and sofosbuvir/ledipasvir) . Although clinical trials of DAA's are ongoing in children under 12 years, there will be a delay until they are licensed (11).

It is likely that we have not enrolled all children with HCV infection in the UK and so there may be selection bias in recruitment of patients who attended specialist clinics, who may have had more severe liver disease (47). However, we believe the cohort is representative of patients with HCV infection attending specialist treatment centres and therefore an assessment of the long-term outcome of HCV infection in this population. The strengths and limitations of the HCV Research UK cohort are described in more detail elsewhere (13).

In conclusion, HCV infection in childhood causes serious long-term liver disease which is an important and ongoing problem in in the UK which can now be prevented with antiviral therapy. Early treatment, especially before development of cirrhosis, significantly decreases morbidity and mortality associated with HCV infection. We recommend that healthcare workers are aware of the prevalence of HCV in childhood, particularly in young adolescents, and that testing according to NICE guidelines are implemented and treatment is made available. Pharmacological treatment of chronic HCV in childhood should be provided to children by health authorities based on the present evidence of increased risk of serious liver disease in adulthood.

Acknowledgements

HCV Research UK investigators are as follows: Agarwal K. (Kings College Hospital, London), Aldersley M. (St James's University Hospital, Leeds), Ala A. (Frimley Park Hospital), Alexander G. (Addenbrookes Hospital, Cambridge), Aspinall R. (Queen Alexandra Hospital, Portsmouth), Barclay S. (Glasgow Royal Infirmary), Barnes E. (John Radcliffe Hospital, Oxford), Bansal S. (King's College Hospital Paediatrics), Bassendine M. (Freeman Hospital, Newcastle), Benselin J. (University of Nottingham), Brown A. (St Mary's Hospital, London), Butterworth J. (Royal Shrewsbury Hospital), Ch'ng C. (Singleton Hospital, Swansea), Cooke G. (St Mary's Hospital, London), Corless L. (Hull Royal Infirmary), Cramp M. (Derriford Hospital, Plymouth), Datta S. (Southern General Hospital & Glasgow Victoria Hospital), Davison S. (Leeds Children's Hospital), Dillon J. (Ninewells Hospital, Dundee), Forton D. (St George's Hospital, London), Foster G. (The London Hospital), Foxton M. (Chelsea & Westminster), Fraser A. (Aberdeen Royal Infirmary), Gelson W. (Addenbrookes Hospital, Cambridge), Gera A. (Queen Elizabeth Hospital, Woolwich), Geretti A. M. (Royal Liverpool University Hospital), Goldberg D. (Health Protection Scotland), Gorard D. (Wycombe Hospital), Gordon F. (Bristol Royal Infirmary), Gore C. (Hepatitis C Trust), Harris H. (Public Health England), Hayes P. (Royal Infirmary of Edinburgh), Heydtmann M. (Royal Alexandra Hospital, Glasgow), Higham A. (Royal Lancaster Infirmary), Holtham E. (University of Nottingham), Hubscher . (Queen Elizabeth Hospital, Birmingham), Hutchinson S. (Glasgow Caledonian University), Irving W. L. (University of Nottingham), Jenkins N. (Birmingham Heartlands Hospital), Kelly D. (Birmingham Children's Hospital),

Kennedy N. (Monklands Hospital), Khakoo S. (Southampton General Hospital), Knowles J. (James Cook University Hospital, Middlesbrough), Langford A. (British Liver Trust), Lawson A. (Royal Derby Hospital), Leen C. (Western General Hospital, Edinburgh), Loganathan S. (Royal Aberdeen Childrens Hospital & Tayside Childrens Hospital, Dundee), McDonald S. E. (University of Glasgow), McLauchlan J. (University of Glasgow), McPherson S. (Freeman Hospital, Newcastle), Mills P. (Gartnavel General Hospital, Glasgow), Moreea S. (Bradford Teaching Hospitals NHS Foundation Trust), Mutimer D. (Queen Elizabeth Hospital, Birmingham), Nastouli E. (Great Ormond Street), Neal K. (Public Health England), Patel A. (University of Glasgow), Priest M. (Gartnavel General Hospital), Prince M. (Manchester Royal Infirmary), Quinlan P. (Advanced Data Analysis Centre, University of Nottingham), Reddy Y. (Royal Blackburn Hospital), Richardson P. (Royal Liverpool University Hospital), Rosenberg W. (Royal Free Hospital & University College Hospital), Ryder S. (Queen's Medical Centre, Nottingham), Shields P. (Royal Preston Hospital), Shorrock C. (Blackpool Victoria Hospital), Singhal S. (Sandwell & City Hospitals, Birmingham), Sreedharan A. (Lincoln County Hospital), Srirajaskanthan R. (University Hospital Lewisham), Stone B. (Royal Hallamshire Hospital, Sheffield), Thursz M. (St Mary's Hospital, London), Tudor-Williams G. (St Mary's Hospitals Paediatrics), Ustianowski A. (North Manchester General Hospital), Verma S. (Royal Sussex County Hospital, Brighton), Wilkes B. (University of Nottingham), Wiselka M. (Leicester Royal Infirmary). We acknowledge the tremendous support received from nurses and data entry clerks at all participating sites. We are also grateful to HCV

Research UK, in particular Jennifer Benselin for collecting and collating data. Most of all, we acknowledge the participants themselves for agreeing to enrol in the cohort.

Tables

Table 1 Patient characteristics of 1049 patients enrolled in the HCV Research UK project between March 2012 and October 2016.

Demographic variable	Result	n
Male	759 (72.3)	1046[1]
Age at infection, median (range)	15 (0-18)	1049
Age at first positive HCV test, median (range)	33 (0-65)	1049
Current age, median (range)	50 (3-77)	1049
Ethnicity		
White	945 (90.9)	1040[2]
Asian	52 (5.0)	1040[2]
African	12 (1.2)	1040[2]
Arabic	8 (0.8)	1040[2]
Other	23 (2.2)	1040[2]
Infection route		
Intravenous drug use	560 (53.4)	1049
Transfusion of blood/blood products	251 (23.9)	1049
Vertical transmission	119 (11.4)	1049
Other or unknown transmission route[3]	119 (11.4)	1049
Genotype		
1	531 (56.6)	938[4]
2	50 (5.3)	938[4]
3	328 (35)	938[4]
4	27 (2.9)	938[4]
5	1 (0.1)	938[4]
Mixed	1 (0.1)	938[4]
Risk factor for infection		
Coagulation bleeding disorder[5]	85 (8.2)	1032[5]
Co-factors for disease progression		
HIV co-infection	44 (4.4)	998[6]
History of heavy alcohol use	363 (35.3)	1029[7]

Data in the table are presented as n (%), unless otherwise specified. HCV: Hepatitis C virus, HIV: Human immunodeficiency virus

[1]Missing: 3, [2]Missing: 9, [3]Including tattoos, dental work, born abroad, surgery, and unknown, [4]Missing/unknown: 111, [5]Haemophilia, idiopathic thrombocytopenic purpura, Von Willebrands, thalassemia, missing: 17, [6]Missing/not tested: 51, [7]Missing: 20

Table 2 Patient characteristics and development of liver disease in 1049 patients diagnosed with hepatitis C in childhood by mode of infection.

Demographic variable	Infection route			
	Perinatal group (n=119)	Blood group (n=251)	IV group (n=560)[1]	Unknown group (n=119)
Male	42 (35)	194 (77)	434 (78)	87 (73)
Age at first infection, years, median (range)	0 (0-1)	11 (0-17)	16 (10-18)	15 (0-18)
Age at first positive HCV test, years, median (range)	2 (0-53)[2]	29 (0-64)	38 (12-65)	37 (3-65)
Years between first infection and diagnosis, years, median (range)	2 (0-53)	19 (0-52)	22 (0-51)	24 (0-50)
Current age years, median (range)	14 (3-55)	48 (21-73)	52 (21-77)	52 (10-72)
Follow-up time, years, median (range)	13 (3-55)	36 (8-59)	37 (5-61)	37 (4-57)
Genotype				
1	59 (50)	159 (64)	257 (46)	56 (47)
2	1 (1)	9 (4)	34 (6)	6 (5)
3	42 (35)	46 (18)	198 (35)	42 (35)
4 and 5	6 (5)	9 (4)	10 (2)	3 (3)
Mixed type	-	-	-	1 (1)
Unknown	11 (9)	28 (10)	61 (11)	11 (9)
Risk factors for disease progression				
History of heavy alcohol use	2 (2)	39 (16)	279 (50)	43 (36)
IV drug use within the last 6 months	-	-	45 (8)	1[2] (0.8)
Development of liver disease				
Cirrhosis	10 (8)	79 (32)	205 (37)	40 (34)
Age at cirrhosis, years, median (range)	36 (17-53)	46 (23-61)	48 (33-68)	52 (12-65)
Years between first infection to cirrhosis diagnosis, years, median (range)	36 (17-53)	32 (12-53)	33 (17-51)	36 (1-50)
Hepatocellular carcinoma	-	11 (4)	38 (7)	6 (5)
Age at time of hepatocellular carcinoma, years, median (range)	-	55 (37-63)	56 (48-68)	54 (52-54
Years from first infection to hepatocellular carcinoma, years, median (range)	-	42 (23-53)	40 (32-51)	38 (35-39)
Liver transplant[4]	-	13 (5)	28 (5)	5[3] (4)
Age at time of liver transplant, years, median (range)	-	46 (27-63)	50 (36-66)	51 (4-54)
Years from first infection to liver transplant, years, median (range)	-	37 (16-49)	33 (20-50)	36 (28-39)
Death	-	6 (2)	19 (3)	7 (6)

Data in the table are presented as n (%), unless otherwise specified. HCV: Hepatitis C virus, HIV: Human immunodeficiency virus.

[1]One patient was registered in the database with other route of infection (born abroad) and no other risk factor for infection but having IV drug use within the last 6 months.

[2]One patient born in Lithuania was registered in the database with an age of 53 at time of first positive HCV test corresponding to the same year the patient was enrolled in HCV Research UK.

[3]Year 2017 was used to calculate current age when data retrieval was conducted.

[4]One patient has been excluded from transplant data analysis due to transplant on the basis of biliary atresia before the diagnosis of HCV.

Table 3. Treatment outcome according to disease status at onset of therapy and treatment regimen in patients infected with HCV in childhood in whom treatment outcome is known.

Treatment regimen	Non-cirrhotic[1]			Cirrhotic[2]			Cirrhosis status unknown[3]		
	N	**SVR**	**Non-SVR**	**N**	**SVR**	**Non-SVR**	**N**	**SVR**	**Non-SVR**
INF (n=6)	4 (67%)	2 (50%)	2 (50%)	2 (33%)	2 (100%)	-	-	-	-
INF+RBV (n=292)	238 (81%)	162 (68%)	76 (32%)	46 (16%)	32 (70%)	14 (30%)	8 (3%)	6 (75%)	2 (25%)
INF+DAA (n=95)	72 (76%)	61 (85%)	11 (15%)	19 (20%)	14 (74%)	5 (26%)	4 (6%)	3 (75%)	1 (25%)
DAA (n=119)	25 (21%)	22 (88%)	3 (12%)	67 (56%)	56 (84%)	11 (16%)	27 (23%)	21 (78%)	6 (22%)
Unknown (n=29)	21 (72%)	18 (86%)	3 (14%)	8 (28%)	7 (88%)	1 (12%)	0	0	0
Total (n=541)	**360 (67%)**	**265 (74%)**	**95 (26%)**	**142 (26%)**	**111 (78%)**	**31 (22%)**	**39 (7%)**	**30 (77%)**	**9 (23%)**

Data is presented as n (%). DAA: Direct acting antiviral; INF: Interferon based treatment regimen; RBV: Ribavirin; SVR: Sustained virological response.

Table 4. Disease progression according to disease status at onset of therapy and treatment outcome for patients infected with HCV in childhood.

Event	TOTAL (n=502)	Non-cirrhotic		Cirrhotic	
		SVR (n=265)	Non-SVR (n=95)	SVR (n=111)	Non-SVR (n=31)
Cirrhosis	39[1] (11%)	24 (9%)	15 (16%)	NA	NA
HCC	23 (5%)	2[2] (1%)	1 (1%)	16[3] (14%)	4 (13%)
LTx	11 (2%)	3 (1%)	0	7 (6%)	1 (3%)
Death	14 (3%)	0	2[4] (2%)	5[5] (5%)	7[6] (23%)

Data is presented as n (%). HCC: Hepatocellular carcinoma; LTx: Liver transplantation; SVR: Sustained virological response.

[1]This outcome only applies to patients who were non-cirrhotic before therapy, the denominator is 360.

[2]One patient also had a liver transplant.

[3]Six patients also had a liver transplant.

[4]No record of cause of death.

[5]One patient had a liver transplant + HCC before death. Two patients had other cancers, one patient with no record of cause of death.

[6]One patient had a liver transplant and one patient died with HCC, one patient with no record of cause of death.

Figure legends

Fig. 1. Patient age at infection by risk group in patients infected with HCV in childhood.

Fig. 2. Time between first infection and diagnosis of cirrhosis and real age in patients infected with HCV in childhood. HCC: hepatocellular carcinoma; LTx: liver transplantation.

Fig. 3. Time between first infection and diagnosis of hepatocellular carcinoma and real age in patients infected with HCV in childhood. HCC: hepatocellular carcinoma; LTx: liver transplantation.

Fig. 4. Time between first infection and time of liver transplantation and real age in patients infected with HCV in childhood. HCC: hepatocellular carcinoma; LTx: liver transplantation.

Fig. 1

Figures

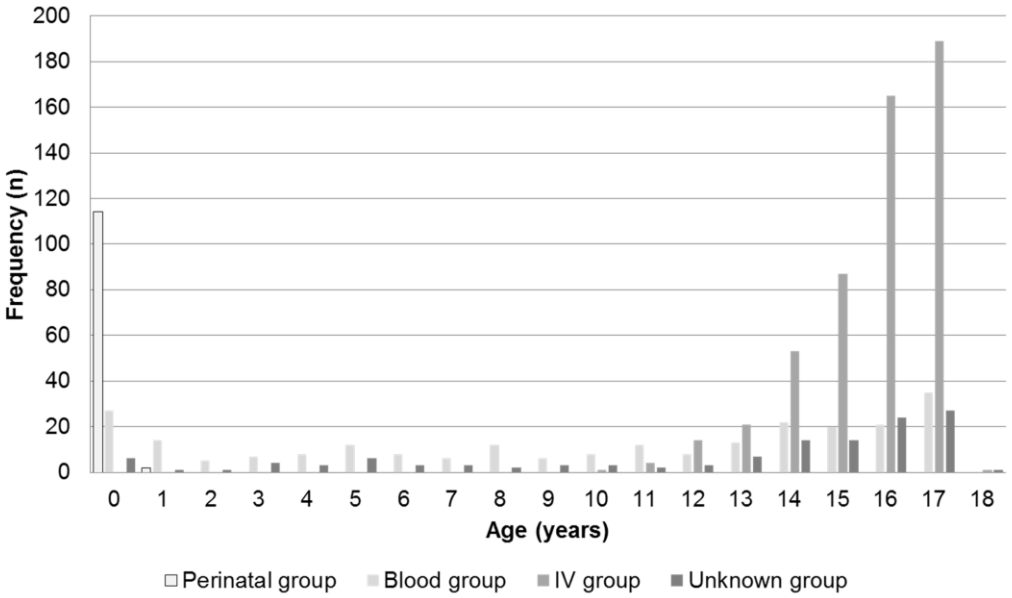
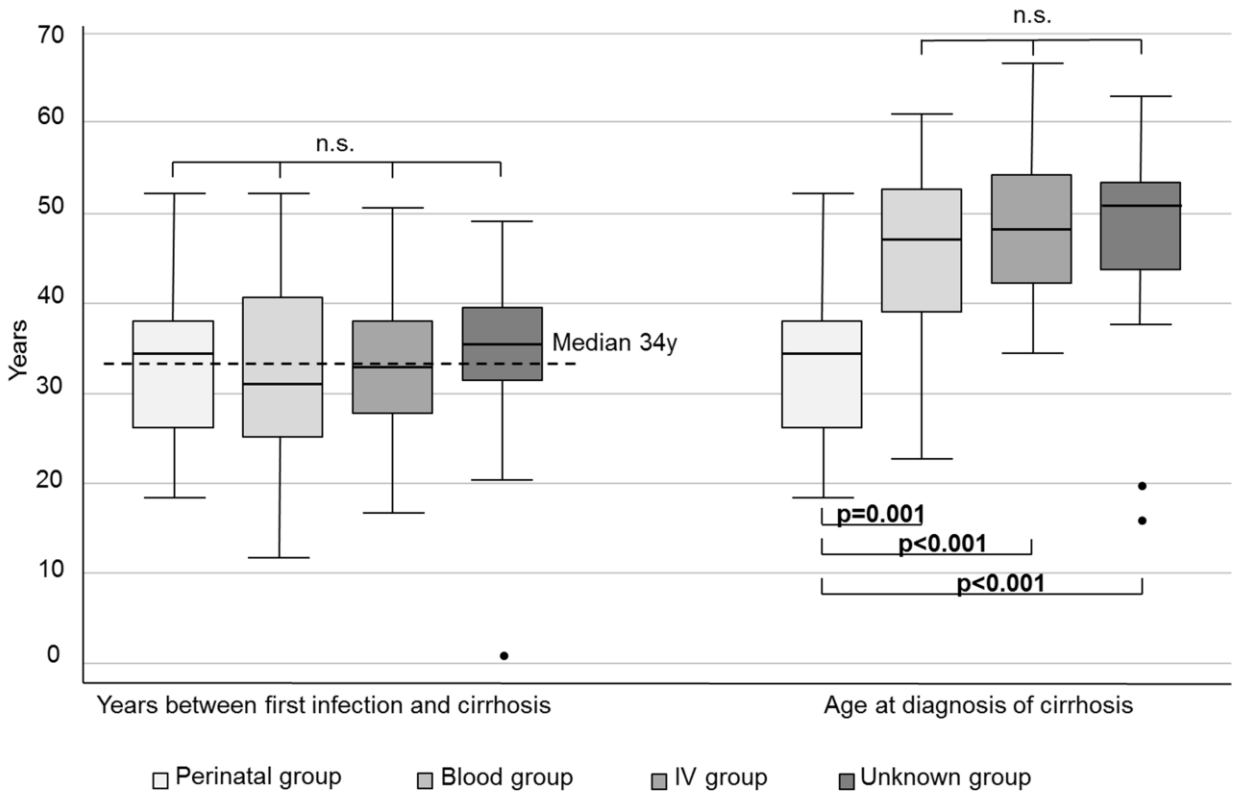


Fig. 2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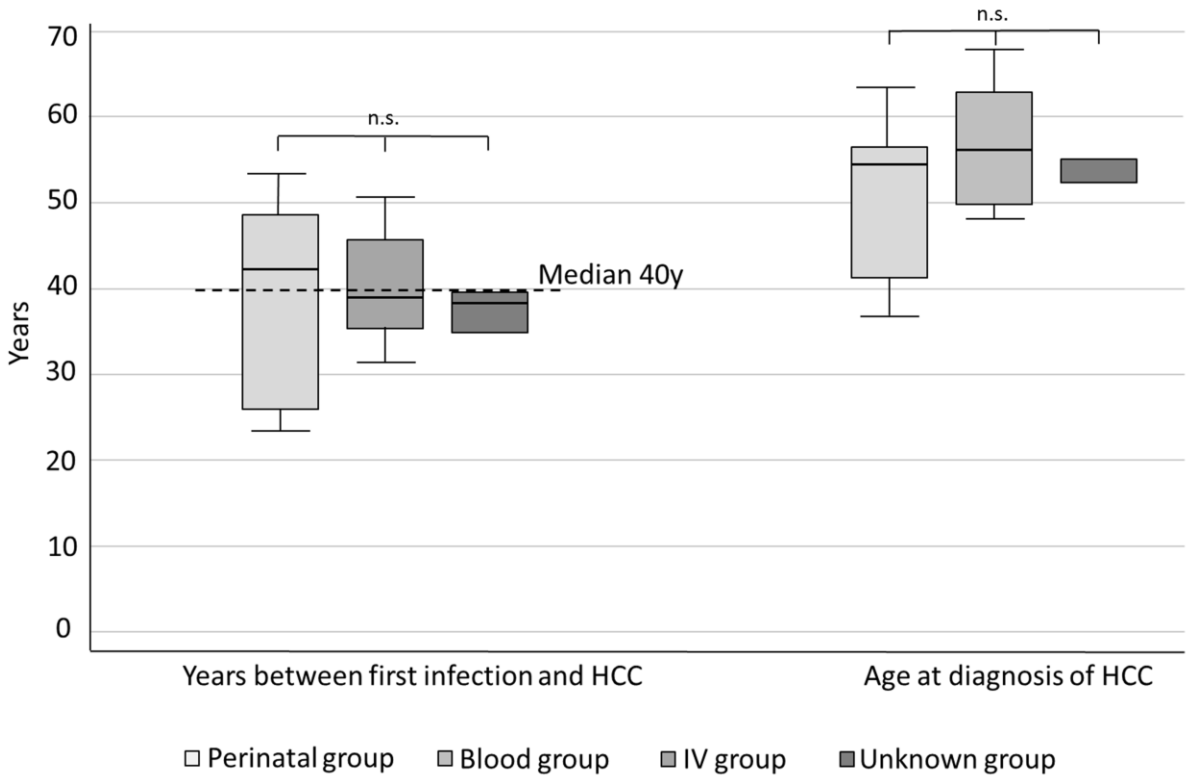
Median 34y
p=0.001
p<0.001
p<0.001
Years between first infection and cirrhosis
Age at diagnosis of cirrhosis
Perinatal group
Blood group
IV group
Unknown group

Fig. 3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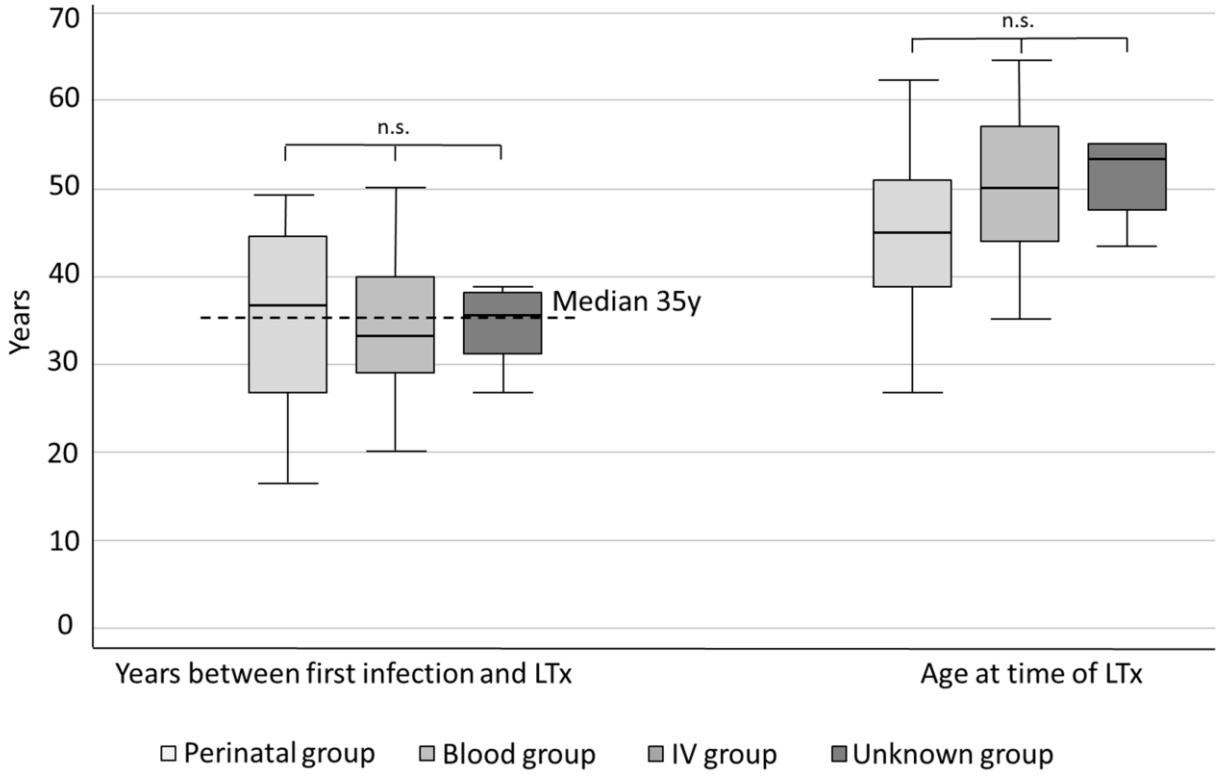
Years between first infection and HCC
Age at diagnosis of HCC
Perinatal group
Blood group
IV group
Unknown group

Fig. 4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Median 35y
Years between first infection and LTx
Age at time of LTx
Perinatal group
Blood group
IV group
Unknown group

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