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COHORT PROFILE

Cohort Profile: The Swiss Hepatitis C Cohort Study (SCCS)

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How did the study come about?

The hepatitis C virus, formerly classified as 'non-A non-B' hepatitis virus, was identified in 1989.[1] This blood-borne virus is endemic worldwide, with an estimated 170 million persons chronically infected, representing approximately 3% of the world population.[2] Long-term morbidity associated with persistent hepatitis C virus infection includes the development of cirrhosis and primary liver cancer.

The Swiss Hepatitis C Cohort Study (SCCS) is a joint effort between the Swiss Group of Experts in Viral Hepatitis and the Swiss Association for the Study of the Liver. The SCCS was established because large population-based cohort studies are the only way to confirm or refute working hypotheses on the natural course of chronic hepatitis C and on hepatitis C virus pathology, and partly because experience with a similar collaborative effort of specialized treatment centres had already been successfully established for a human immunodeficiency virus cohort in Switzerland.[3–9] Therefore, the aims of the SCCS were to set up an infrastructure and investigative network fostering clinical and biomedical research on the natural history of hepatitis C virus infection and to optimize and standardize the management and treatment of hepatitis C virus-infected patients. The cohort is expected to add information on factors that shape progression of hepatitis C virus infection, thus informing future therapeutic decisions and predictions of the burden of hepatitis C virus-related diseases at the population level, as well as supplementing epidemiological data collected by the mandatory national surveillance system at the Swiss Federal Office of Public Health. Ethical approval for data collection was obtained from each hospital's ethics committee.

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Recruitment for the SCCS began in September 2000, with initial funding from the Swiss Group of Experts in Viral Hepatitis. Since April 2001, funding of the core structure has been largely provided by the Swiss National Science Foundation. Additional sources of funding, for both the core structure and the scientific nested projects, have been provided over the years by several public and private institutions, including the Swiss Office for Education and Science and the European Commission.

What does it cover?

The SCCS collects standardized prospective information on adults with confirmed hepatitis C virus infection through questionnaires, clinical examination and laboratory investigations conducted at eight centres providing specialist treatment across Switzerland. Since its inception, the SCCS has evolved to include nested scientific projects to answer a range of questions such as the correlation of expression levels of PP2Ac (protein phosphatase 2, catalytic subunit, alpha isoform) in the liver and pattern of response to interferon-alpha-based therapy, or the significance of connective tissue growth factor in the progression of disease in patients with chronic hepatitis C.

Who is in the sample?

Adult patients aged 18 years and over, who were confirmed hepatitis C virus antibody positive by immunoblot, with no exclusion criteria other than age less than 18 years. From 1 September 2000, the start of recruitment, until 31 December 2005, a total of 2452 persons had been enrolled into the cohort, contributing a total of 4239 person years of follow-up (to 30 June 2006).

The eight centres cover all regions of the country and include all five university teaching hospitals in Switzerland (Basel, Bern, Geneva, Lausanne, Zurich) and three major cantonal hospitals (Lugano, Neuchâtel and St.Gallen). A number of satellite centres (smaller regional hospitals) or investigators (practising physicians; mostly gastroenterologists) are

associated with each of the eight main centres, thus forming a second level of local networks.

Patient characteristics

Table 1 shows selected characteristics of participants at enrolment. The median age at enrolment was 42 years (inter-quartile range, 35–50 years; Table 1). Fifty-eight per cent were in the 25–44 year age-group, similar to the proportion observed in the mandatory reporting system (61%, based on cumulative figures from 1988 to 2005). The median time since diagnosis of hepatitis C virus infection was 3.7 years (inter-quartile range, 0.9–7.8), with 58% having been diagnosed 0–5 years prior to enrolment.

Most participants in the SCCS were males (63%), whites (95%) and of Swiss nationality (75%). The majority were educated to apprenticeship/high-school level (51%) and were in paid or unpaid employment (64%). The most commonly reported hepatitis C virus risk factor (more than one could be reported per person) was a history of injection drug use (57%), with time of starting injecting drugs being on average 17 years (inter-quartile range, 12–23 years) before enrolment. Only 231 participants (9.4%) had no risk factor recorded. Cross-tabulation of the risk factors showed that injection drug use and transfusion were also mentioned in 28% and 54%, respectively, of those reporting an invasive medical procedure.

Infection with hepatitis C virus genotype 1 was the most common (46%), followed by genotype 3 (27%). Thirty-nine per cent had ever been infected with hepatitis B virus of whom 4.8% (45/946) were hepatitis B surface antigen positive; 8% were co-infected with human immunodeficiency virus. About two-thirds (64%) of the SCCS participants were hepatitis C virus ribonucleic acid positive at enrolment, and a raised alanine transaminase was found in 1498 persons (61%). Overall, 38% had an alanine transaminase ratio in the range of >1.0–2.5 times the upper end of normal.

How often have they been followed up?

Participants have been followed up at 6–12 monthly intervals at which time standardized follow-up information is collected covering events and behaviours since the last visit. If a patient did not return for the scheduled follow-up visit, then his/her treating physician sent the patient at least two further written invitations to attend before they were considered lost to follow-up. A 'Stop Form' was completed, when the patient was either lost to follow-up or had died. Cause of death was coded according to the ICD 10 classification.[10]

What has been measured?

At enrolment

A standardized enrolment questionnaire was completed by patients' physicians or a study nurse. The information was largely taken from medical notes but for some questions, e.g. concerning quality of life, it was obtained by a face-to-face interview. Other items of information collected included ethnicity, drinking habits, employment, income, history of certain pre-specified hepatitis C virus infection risk events or

Table 1 Selected baseline (enrolment) characteristics of all SCCS participants compared with those who were cirrhotic: 1 September 2000–31 December 2005

Variable description	Total number (%) ($n=2452$)	Cirrhotics (%) ($n=339$)
Age at enrolment (years)		
Median (inter-quartile range)	42 (35–50)	50 (44–59)
Age at diagnosis (years)*		
Median (inter-quartile range)	37 (30–46)	45 (38–54)
Gender		
Male	1555 (63)	247 (73)
Ethnic group		
White	2323 (95)	323 (95)
Nationality		
Swiss	1830 (75)	239 (71)
Education(highest completed)		
No higher/short term professional	803 (33)	109 (32)
Apprenticeship/matura	1251 (51)	167 (49)
Higher including university	366 (15)	59 (17)
Missing	32 (1.3)	4 (1.2)
Employment status		
Employment (paid or unpaid)	1570 (64)	195 (58)
Unemployed	254 (10)	19 (5.6)
Retired or other situation	613 (25)	124 (37)
Missing	15 (0.6)	1 (0.29)
Income per year (in CHF)		
<40 000	758 (31)	93 (27)
40 000–79 999	743 (30)	110 (32)
80 000–120 000	308 (13)	48 (14)
>120 000	114 (4.6)	25 (7.4)
Missing	529 (22)	63 (19)
Body Mass Index (kg/m^2)		
Underweight<18.5	93 (3.8)	10 (2.9)
Normal 18.5–25	1446 (59)	169 (50)
Overweight 25–30	680 (28)	120 (35)
Obese and morbidly obese ⩾30	228 (9.3)	40 (12)
Missing	5 (0.2)	none
Positive history of hepatitis C virus risk factors (more than one could be mentioned)		
Injection drug use	1386 (57)	134 (40)
Invasive medical procedure[a]	858 (35)	134 (40)
Transfusion[b]	559 (23)	92 (27)
Reported hepatitis C virus positive sexual partner	321 (13)	28 (8.3)
Accidental needlestick	256 (10)	25 (7.4)
Professional exposure to blood	186 (7.6)	24 (7.1)
Living with hepatitis C virus positive person (not a sexual partner)	123 (5.0)	11 (3.2)
None recorded	231 (9.4)	63 (19)
Alcohol consumption (ever having drunk this quantity)		
⩽20 g alcohol per day	1382 (56)	158 (47)
>20–40 g alcohol per day	357 (15)	40 (12)
>40 g alcohol per day	679 (28)	131 (39)
Missing	34 (1.4)	10 (2.9)
Comorbidity		
Diabetes	94 (3.8)	33 (9.7)

(continued)

Table 1 Continued

Variable description	Total number (%) ($n = 2452$)	Cirrhotics (%) ($n = 339$)
Presence of other infection markers[c]		
Hepatitis A virus antibody positive	1026 (42)	153 (45)
Missing	599 (24)	77 (23)
Ever infected with hepatitis B virus[d]	946 (39)	132 (39)
Missing	76 (3.1)	15 (4.4)
Ever infected with hepatitis B virus who were also hepatitis B surface antigen positive	45 (1.8)	12 (3.5)
Human immunodeficiency virus antibody positive	190 (7.8)	22 (6.5)
Missing	637 (26)	103 (30)
Information on hepatitis C virus infection		
Hepatitis C virus ribonucleic acid positive**	1565 (64)	191 (56)
Hepatitis C virus genotype		
1	1128 (46)	171 (50)
2	206 (8.4)	27 (8)
3	654 (27)	81 (24)
4	213 (8.7)	28 (8.3)
5	3 (0.1)	0
6	3 (0.1)	1 (0.3)
Missing	242 (10)	31 (9.1)
Information at enrolment on hepatitis C virus associated disease		
Ever had a liver biopsy	1235 (50)	257 (76)
Cirrhosis documented (clinical or histological diagnosis)	339 (14)	All cirrhotic
Missing	29 (1.2)	NA
Primary liver cancer (hepatocellular)	25 (1.0)	24 (7.1)
Alanine transaminase ratio (ratio of laboratory value to upper end of normal range)**		
$\leqslant 1.0$	824 (34)	80 (24)
>1.0–2.5	930 (38)	129 (38)
$\geqslant 2.5$	568 (23)	110 (32)
Missing	130 (5.3)	20 (5.9)
History of hepatitis C virus related treatment		
Ever on drug treatment for hepatitis C virus	752 (31)	173 (51)
Missing	220 (9)	27 (8)
Ever complementary medicine	173 (7.1)	36 (11)

[a]Includes acupuncture, autotransfusion, injection and dental treatment.

[b]Includes haemophilia and dialysis.

[c]Window of up to 180 days after enrolment date.

[d]Positive for $\geqslant 1$ of the following: antibodies to hepatitis B core antigen, hepatitis B surface antigen, hepatitis B e antigen, antibodies to hepatitis B e antigen, hepatitis B virus deoxyribonucleic acid, antibodies to hepatitis D virus. Excluded if positive for antibodies to hepatitis B surface antigen only.

*anamnestic or documented.

**window of 90 days either side of enrolment date.

Table 2 SCCS: summary of main variables collected via questionnaires at enrolment and follow-up

Variable	Source	Enrolment	Follow-up
Sociodemographic			
Nationality	SR	X	
Canton of residence	SR	X	
Ethnicity	SR	X	
Educational level attained	SR	X	
Income (household)	SR	X	
Occupational			
Employment status	SR	X	X
Health			
Anthropometry (weight and height)		X	X
Hospital admission in preceding 6 months	SR	X	X
Specific diseases	SR	X	X
Parameters of liver disease progression	SR and documented	X	X
Previous and ongoing treatments for hepatitis C virus infection	SR and documented	X	X
Other blood test results	Laboratory report	X	X
Peripheral blood mononuclear cells	Frozen for future genetic studies	X	X
Health behaviours			
Risk factors for hepatitis C virus acquisition	SR	X	
Injection drug use		X*	X[a]
Alcohol consumption	SR	X	X
Psychosocial			
Quality of life	SR	X	X

[a]Time frame: since last visit.

*Time frame: ever

SR, self-reported; X, data collected.

Note: questions at enrolment and follow-up are not necessarily identical.

behaviours and whether or not the patient had had previous hepatitis C virus treatment (Table 2).

Patients also had a physical examination, which could lead to a liver biopsy being performed. The results of a clinically indicated liver biopsy were documented and graded as activity of chronic hepatitis (none, minimal, mild, moderate, severe) and fibrosis (none, portal fibrosis, portal fibrosis with rare septa, bridging fibrosis, probable or definite cirrhosis).

Completed questionnaires and other information-gathering forms were collected and kept centrally, at the Centre Hospitalier Universitaire Vaudois in Lausanne, where they were checked for completeness and correctness. If inconsistencies were found or corrections were thought to be necessary, then the form/s were sent back to the physician for amendment. Finally, data were entered onto a computer database by a person with paramedical training.

Laboratory procedures

Each treating physician was responsible for collecting clinical and laboratory data as well as taking blood specimens from their patients. Blood tests performed at enrolment covered aspects of general health, e.g. haemoglobin, parameters of the hepatitis C virus infection (serum hepatitis C virus ribonucleic acid levels), of hepatitis C virus-related liver disease (levels of the liver enzyme alanine transaminase) and markers indicating other past or current infections, e.g. hepatitis A and B viruses and human immunodeficiency virus infection. Other laboratory tests, e.g. liver function tests such as alanine transaminase were done according to the laboratory's standard protocols in use at the time. We calculated raised alanine transaminase ratios based on denominators that were the upper end of the quoted normal range for the laboratory concerned. All laboratories performed regular quality controls to assure validity of their results.

Follow-up

At each follow-up visit, a separate questionnaire was completed, which differed slightly from that at enrolment (Table 2).

What is attrition like?

In addition to participants who moved away or retracted their consent to be in the study, we considered participants as lost to follow-up if s/he was not reported as dead and had not been seen at a follow-up visit for more then 2.5 years. To apply this definition correctly, we restricted this analysis to participants who were registered before 1 January 2004 (total of 1679) and used available follow-up information until 30 June 2006.

Of the 1679 persons registered by the 1 January 2004, we classified 522 as losses to follow-up (31%). When compared with all those enrolled in the cohort, participants lost to follow-up were more likely to have been younger (median 39; inter-quartile range, 29–42 years) and to have had injection drug use as a reported risk factor. Regarding some of the clinical features, 11% were cirrhotic and 25% had an alanine transaminase level 2.5 times the upper limit of normal or higher. They did not differ substantially regarding other socio-demographic factors such as sex, ethnicity, nationality, education and employment status.

What has it found? Key findings

In the near future, the SCCS is expected to provide more substantive results addressing its aims and objectives. In this baseline report, we were able to compare our findings to other published international cohort studies of hepatitis C virus infected persons.

Patient characteristics

Overall, our cohort is similar to other international cohorts based on hospital patients. The mean age in the SCCS was 43 years, similar to a prospective cohort from France, where the mean age was 45.3 years.[11] The median age at diagnosis (37, inter-quartile range, 30–46 years; Table 1) was similar to the median age at reporting in the Swiss national surveillance data (36, inter-quartile range, 29–46 years; based on cumulative figures 1988–2005; Table 3).

Table 3 Hepatitis C cases reported to the Swiss Federal Office of Public Health: physician reports 1988–2005*

Variable description	Physician reports 1988–2005 ($n = 28\,941$)	(%)
Age at reporting (years)		
Median (inter-quartile range)	36 (29–46)	–
Missing	39	0.13
Gender		
Male	17601	61
Missing	38	0.13
Nationality		
Swiss	18459	64
Missing	4114	14
Positive history of hepatitis C virus risk factors (more than one could be mentioned)		
Injection drug use	13116	45
Transfusion	2213	7.6
Dialysis	140	0.48
Contact with hepatitis C virus positive person	1757	6.1
Sexual contact with hepatitis C virus positive person	2896	10
Health care professional (including accidental needlestick)	515	1.8
Other[a]	1032	3.6
Unknown/none identified	5039	17
Missing	6189	21

[a]Includes acupuncture, tattoo, piercing, surgery, endoscopy, injection, dentist, professional exposure other than healthcare and 'exposure abroad'.
* Based on data to 24 August 2006.

Injection drug use was the most frequently reported risk factor in the SCCS (57%), which compared with a hospital-based British cohort that reported 64.5% injection drug use.[12] In the Swiss Federal Office of Public Health data, the most commonly reported risk factor was also injection drug use (58% of those who were not completely missing risk factor information).

Most participants in the SCCS were males (63%), whites (95%) and of Swiss nationality (75%). This was also in accordance with data from the Swiss Federal Office of Public Health, where the majority reported were males (61%) and Swiss Nationals (73% of those with a given nationality). Other health-care based cohort studies of hepatitis C virus infected persons have shown a preponderance of males over females. For example, studies by Mohsen, in the UK, had 68% males;[12] Roudot-Thoraval in France had 59% males[11] and Niederau in Germany had 52% males.[13]

The genotype most commonly associated with injection drug use is genotype 3.[14] However, in our cohort the commonest was genotype 1 (46%). This is interesting because, although the

majority reported injection drug use as a risk factor, many also reported an invasive medical procedure and transfusion as risk factors as well. Therefore, it may be through these other exposures that the infections arose. It also has cost implications for treatment because genotype 1 infections have a lower success rate with pegylated interferon and ribavirin dual therapy, with a 40–50% sustained viral response after a longer period (48 weeks) of treatment, than genotypes 2 or 3 (80% sustained viral response after 24 weeks).[15]

Amongst those documented as cirrhotic at enrolment (339 or 14% of all participants), a higher percentage reported ever having drunk >40 g of alcohol per day (39% of cirrhotics versus 28% of all participants). Of those who were cirrhotic at enrolment, 24 (7%; 1% of all participants) already had a diagnosis of a primary hepatocellular cancer. Other cohorts, based on hospital patients with known hepatitis C virus infection, have shown a range of 8.3–21.4% for cirrhotics and 1–3.6% for those with primary hepatocellular cancer within which our proportions fall.[11–13]

Time to event analysis

We performed time-to-event analysis for a combined endpoint of a new diagnosis of primary liver cancer or death from liver cancer (ICD-10: C22). We used the reported date of the first positive hepatitis C virus test as time zero, with participant observation beginning at the date of enrolment (staggered entry into the time-to-event analysis). Time of observation ended with date of the event, the most recent date of a follow-up visit, or the date of death; whichever came first. We then calculated the rate for the combined endpoint by dividing the total number of events by the total person-years of observation in the SCCS and calculated 95% confidence intervals assuming a Poisson distribution. This analysis was performed for all participants and stratified for those with or without cirrhosis at enrolment.

A total of 54 cases of a new primary hepatocellular cancer or death due to liver cancer occurred since registration (to 30 June 2006), resulting in a crude event rate of 1.3/100 person-years [95% confidence interval (CI) 0.98–1.7/100 person-years]. When stratified by whether or not patients were cirrhotic at enrolment, the crude death rate was 4.0/100 person years (95% CI 2.7–5.9/100 person-years) for cirrhotics, which was 4.8 times higher (95% CI 2.8–8.2) than for non-cirrhotics. When using the date of the first known anti-hepatitis C virus positive test as time zero, we obtained a cumulative event risk, of primary hepatocellular cancer or death from liver cancer, at 15 years of 19% (95% CI 14–26%).

Pathology of hepatitis C virus

There has been one publication to date, which has shown that insulin resistance may play a role in fibrogenesis in patients with chronic hepatitis C infected with genotypes other than genotype 3.[16]

What are the main strengths and weaknesses?

The SCCS study group is composed of an experienced team in clinical, laboratory and epidemiological areas, who are well placed to undertake the scientific agenda of the cohort and who continuously review progress in terms of its aims and objectives. The participants enrolled in the SCCS study came from across Switzerland and had, at enrolment, a broad range of demographic and clinical characteristics as shown by the distribution of age at diagnosis, education, income, employment and clinical features, e.g. hepatitis C virus genotype, alanine transaminase levels and the presence of other infection markers. When comparing the cohort with the Swiss national surveillance data, the sample seemed similar in terms of age at diagnosis, sex, nationality and the most frequently reported risk factor is for hepatitis C virus infection. Therefore, its main strengths are that it should provide generalizable results on the progression of hepatitis C virus infection as well as facilitate the conduct of targeted nested studies including those investigating new treatment approaches. As the SCCS is a 'purpose-built' cohort, data collection has been standardized and is directly comparable between centres as well as being available from a single centralized database. International collaboration is already happening and will strengthen findings by providing a broader diversity of patients and opportunity for combining datasets for analysis.

In the 4–6 years of operating, the number of participants classified as lost to follow-up was substantial, especially among individuals with a history of injection drug use. This might bias findings if attrition is linked to disease severity and/or death. To address this possible source of bias the recruitment centres, together with the central data centre, will increase their efforts to actively identify those who have not been seen for more than 2 years and encourage them to attend a follow-up visit.

The SCCS also appeared to enrol individuals with more severe disease, probably because the majority came from secondary and tertiary health care services. Despite this, the cohort should still provide generalizable results, although efforts are being made to recruit more patients from local networks. Finally, the study is only in adults aged 18 years and over, so will not provide information on infants and children.

Can I get hold of the data? Where can I find out more?

The data and clinical samples are, in principle, available to all researchers independently of their association with the SCCS. All scientific projects intending to use data and/or clinical samples from the SCCS must firstly be submitted as a 'Letter of Intent', to the Scientific Committee (see subsequently) to be evaluated. If deemed feasible and of sufficient scientific merit, the author/s will be invited to submit a full proposal and access to the data is granted after approval of the project. Since May 1 2004, the SCCS has been involved in the ViRgil (vigilance against viral resistance) Network of Excellence, funded by the European commission over 4 years (www.virgil-net.org). Thus, external collaborations are positively encouraged, particularly with other cohort studies, with ownership of data remaining with the individual cohorts involved. Indeed, the ViRgil network consists of 66 research groups throughout Europe looking at how and why resistance to anti-viral drugs develops

in viruses in general, but initially focusing on three major infectious diseases: hepatitis C virus, hepatitis B and influenza.

Scientific projects must be submitted in the form of a Letter of Intent, with an estimate of resources required, to both the Chairman of the Scientific Committee (Prof. D. Moradpour) and to the SCCS Chairman (Prof. F. Negro). For the addresses, please see Appendix.

At present there is no dedicated website for the SCCS, although this is currently under discussion.

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Conflict of interest: None declared.

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Appendix

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