Frequent loss to follow-up after diagnosis of hepatitis C virus infection: A barrier towards the elimination of hepatitis C virus

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Abstract

Background: Previous studies on hepatitis C cascade of care have been mainly focused on diagnosis and treatment rate, while less attention has been given to patients lost to follow-up (LTFU) after diagnosis. Analyses of this latter issue on population level are missing.

Aims: In this nationwide study of people with HCV, we aimed to estimate the proportion LTFU after HCV diagnosis, characterize them, and analyze their other healthcare contacts.

Methods: Patients diagnosed with chronic HCV in the Swedish National Patient Register during 2001-2011 and still alive December 31, 2013, were included. The number of cured patients without need of follow-up was estimated. Visits to HCV specialist care during 2012-2013 were analysed. For those LTFU, other specialist care contacts were studied.

Results: In total 29 217 patients were included, with 24 733 with need of HCV care. 61% (n = 15 007) of them were LTFU from HCV care in 2012-2013 and 58% did not attend HCV care during the second year after HCV diagnosis. The departments of surgery/orthopaedic or psychiatry/dependency were the most common other non-primary healthcare contacts. Predictors for LTFU were young age, male sex, low education, presence of psychiatric/dependency diagnosis, unmarried and longer duration since diagnosis of HCV.

Conclusions: This study showed that almost two-thirds of patients were LTFU after HCV diagnosis, with frequent occurrence early after diagnosis. Efforts to link patients back to HCV care, in combination with early and easy access to HCV treatment and harm reduction, are necessary to reach the HCV elimination goal.

KEYWORDS
cascade, HCV, healthcare contacts, lost to follow-up

Abbreviations: CI, confidence interval; DAA, direct-acting antivirals; DR, Cause of Death Register; GH, Department of Gastroenterology and Hepatology; GH, gastroenterology and hepatology; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; ICD, International Classification of Diseases; ID, Department of Infectious Diseases; ID, infectious diseases; IFN, interferon; LISA, Longitudinal Integration Database for Health Insurance and Labour Market Studies; LTFU, lost to follow-up; NPR, National Patient Register; OR, odds ratio; PDR, Prescribed Drug Register; PWID, people who inject drugs; TPR, Total Population Register; WHO, World Health Organization.

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1 | INTRODUCTION

Chronic hepatitis C virus (HCV) infection is a major cause of liver-related morbidity and mortality around the world, with an estimated 71 million people infected. The major route of transmission in industrialized countries is injection drug use. Therapy for chronic HCV has substantially improved with the introduction of interferon (IFN)-free direct-acting antivirals (DAAs) in 2014, enabling treatment with high cure rates, shorter duration and few side effects.

With new effective therapies, the World Health Organization (WHO) has launched a plan to eliminate HCV and HBV infections by the year 2030. Elimination of HCV was defined as a reduction of new infections by 90% and a reduction of HCV-related mortality by 65% compared with the situation in 2015. To accomplish this goal, several factors must be in place for the HCV cascade of care, such as a high diagnosis rate of HCV infection, effective linkage to care, maintenance of patients in care, structure for scaling up treatment, and harm reduction to prevent reinfection and new infections.

Previous studies have shown that only a small proportion of persons infected with HCV reach the stage of antiviral treatment in the HCV cascade of care. Much of the focus of HCV treatment has been the diagnosis of HCV, which can be challenging with different diagnosis rates between countries. Another focus has been the low rate of treated patients among those diagnosed. Less attention has been paid to the challenge of maintaining patients in HCV care after diagnosis or how to link the patients who were lost to follow-up (LTFU) back to HCV care. Some studies of mainly small cohorts in different countries have shown that a high proportion of patients with diagnosed HCV infection are LTFU, likely because of the slow, asymptomatic and silent progression of the disease, in combination with the previous IFN-based treatment with substantial side effects and low chance of cure. Retrieval of those LTFU back into the HCV cascade of care is therefore an important step on the road towards HCV elimination. Studies that address these issues are scarce, and analyses on a population level are missing.

In Sweden, the diagnosis rate of HCV infections is high compared with most other countries, but the treatment uptake has, until recently, nevertheless been low. To implement the WHO elimination plan, there is a need to characterize the patients who were LTFU after diagnosis and to identify possibilities to retrieve them back to HCV care (eg, through other healthcare contacts). By using the unique Swedish personal identification numbers and the national registers with high coverage, a nationwide population-based study of people with HCV diagnosis and their healthcare contacts is possible. The aim of this nationwide study of people with HCV infection was to estimate the prevalence of those LTFU after diagnosis, to characterize them, and to analyze their non-primary healthcare contacts.

Key points

- We showed in this nation-wide study that as high as two-thirds of patients with hepatitis C diagnosis were lost to follow-up from hepatitis C care after diagnosis in Sweden.
- The departments of surgery/orthopaedic or psychiatry/dependency were the most common other non-primary healthcare contacts for patients lost to follow-up from hepatitis C care.

2 | MATERIALS AND METHODS

2.1 | Study population

This is a retrospective study of a national cohort of people with chronic HCV infection diagnosis in Sweden using prospectively collected data from the following national registers. These are the National Patient Register (NPR), the Cause of Death Register (DR), and the Prescribed Drug Register (PDR) at the Swedish National Board of Health and Welfare and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA) and the Total Population Register (TPR) at Statistics Sweden. The Swedish unique personal identification number (social security number) was used to link individuals between registers.

The NPR contains information on inpatient care in Sweden from 1964 (complete coverage from 1987), day surgery from 1997, and non-primary outpatient care (defined as visits to hospital-based medical specialists and will be referred to as specialist care) from 2001. The register contains many variables related to the patient visit (eg department/clinic, date, main and contributory diagnoses based on the International Classification of Diseases [ICD; ICD-9, 1987–1996; ICD-10; from 1997]). Information regarding death was retrieved from the DR. The TPR covers the entire Swedish population and includes information on year of birth, sex and place of residence, as well as emigration status. The highest attained education was retrieved from the LISA database.

We have previously used NPR to identify all inpatients and outpatients with an HCV infection diagnosis with ICD-10 code B18.2 from 1997 to 2013 who were alive as of 31 December 2013 (n = 34 633) (Figure 1). In the present study, persons aged <18 years (year 2012) were excluded, leaving 34 456 with a chronic HCV infection diagnosis. Only patients with a minimum of 1 visit with chronic HCV infection diagnosis registered in the NPR during 2001-2011 and alive in 31 December 2013, were included. Those with HCV care visits only before 2001 (n = 1007) and patients with a first HCV diagnosis in 2012 or 2013 (n = 4231) were excluded because the data from outpatient care are available only from 2001, and we aimed to examine LTFU during 2012-2013. In total, 29 217 fulfilled these criteria and constituted the study population (Figure 1).

Information on county of residence at diagnosis, highest attained education (≤9 years, 10-12 years, or > 12 years), marital status (married vs unmarried, divorced or widowed) at diagnosis, country of origin (Sweden, Europe or Non-European countries), and emigration/immigration was added from the TPR and LISA registers.
The patients with HCV infection were followed from the first visit during 2001-2011 until the end of 2013 to identify and study adult patients who were LTFU (defined as no medical visits with chronic HCV diagnosis at HCV care departments during 2012-2013). All recorded inpatient and non-primary specialist care outpatient visits during 2012-2013 were analyzed. For patients who emigrated and then immigrated back during the study period, the first visit after last immigration was regarded as the first visit in the present study.

2.2 | HCV treatments

The PDR contains data of all prescribed drugs in Sweden from July 2005, including dates of prescription and dispensation, using the Anatomic Therapeutic Chemical codes. The first full year included in the register was 2006. The register is complete for prescriptions in ambulatory care; however, in-hospital use of drugs is not recorded. Of note, HCV drugs are only prescribed in ambulatory care in Sweden. The number of prescriptions was evenly distributed over the years except for a lower number in 2013—the year before the introduction of the first DAAs in Sweden.

According to the PDR, the number of patients who initiated treatment for HCV infection during 2006-2010 was 4484, and the mean number of treatment initiations was 897 per year. Since treatment practices were similar without major changes during the study period, this mean annual number was used to extrapolate the estimated number of treatment initiations in 2001-2005. A total of 8968 persons were estimated to have initiated treatment during 2001-2010 (patient initiating therapy in 2011 was not included in this estimate because those patients most likely visited an HCV specialist in 2012 for either a treatment visit or a follow-up visit). Based on previous studies of pegylated IFN and ribavirin combination therapy, a cure rate of 50% was assumed, suggesting that 4484 persons had achieved virologic cure and did not need follow-up visits in 2012 or 2013.17-19

2.3 | Specialist care visits

In Sweden, most patients with diagnosed HCV infection will be referred to the Department of Infectious Diseases (ID), except those with decompensated liver disease that usually are referred to the Department of Gastroenterology and Hepatology (GH). Both ID and GH are specialized hospital settings (ie non-primary care) and the only departments/clinics that treated patients with HCV during the IFN-era, as well as being the only departments/clinics allowed to prescribe DAA treatment from 2014 to December 2017, hence limiting patients’ access to HCV treatment to these departments/clinics. The departments of ID can be considered as secondary healthcare and not tertiary, since the patients are referred from diagnosing departments as primary care or other health care departments directly to these departments. As of January 2018, physicians at other departments were allowed to prescribe DAAs, but with the stipulation that this should be in collaboration with a physician at an ID or GH department. In this study, the ID and GH departments are therefore referred to as “HCV care departments.”

The inpatient and outpatient visits from 2001 to 2013 were analyzed using data from NPR. For patients who never attended HCV care during 2012-2013, other specialist departments/clinics were analyzed. These include all healthcare visits to specialized care in Sweden but do not include primary care. We analyzed the data in total and by each department. The non-HCV specialized care was divided into the following groups: Internal Medicine, Psychiatry/Dependency, Surgery/Orthopaedics, Emergency department, ID/GH contacts for other reasons than HCV infection (ie without ICD code for HCV), Dermatology/Venereology, Obstetrics/Gynaecology, Geriatrics and Other (Table S1).

2.4 | Statistical analyses

A univariate regression analysis was used to calculate the odds ratio for a follow-up visit at a HCV care department. Parameters
of sex, birth year with 5-year increments starting with 1949, living in a large city (Stockholm, Gothenburg, or Malmö) or not, education (<9 years, 9-12 years, or >12 years), psychiatric disease except diagnosis of substance dependence (F-diagnosis except F10-F19), diagnosis of substance dependence (F10-F19), country of origin, marital status (married or not married [single, widowed or divorced] at diagnosis of HCV infection), and duration after HCV diagnosis (duration from the first visit with HCV diagnosis during the study period to 31 December 2013) were tested in a univariate analysis. A stepwise multivariate regression model was used to assess for factors that were independently associated with a follow-up visit at HCV care departments. All P values are two-sided and \( P < .05 \) was considered statistically significant. Data handling and analyses were performed using SAS (version 9.4, SAS Institute Inc), and SPSS (version 24, IBM Corp) software, respectively. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden.

3 | RESULTS

3.1 | The study population

In total 29 217 individuals with chronic HCV diagnosis in 2001-2011 were included for analyses (Table 1). Sixty-three percent were men, and the most common birth years were 1950-1969 (59%). Most patients were of Swedish origin (81%), and 40% had a diagnosis of dependence registered in the NPR. The highest numbers of first visits

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**TABLE 1** Demographics and characteristics of patients with chronic hepatitis C virus (HCV) diagnosed during 2001–2011 in Sweden, attending or not attending HCV care (departments of infectious diseases or gastroenterology and hepatology) during 2012–2013, and still alive on 31 December 2013

| Characteristic                  | All\(^d\) | Patients attending HCV care\(^a\) | Patients not attending HCV care\(^a\) |
|--------------------------------|-----------|----------------------------------|-------------------------------------|
| Total, n (%)                   | 29 217 (100) | 9726 (33)                        | 19 491 (67)                        |
| Sex, n (%)                     |           |                                  |                                     |
| Men                            | 18 432 (63) | 5983 (32)                        | 12 449 (68)                        |
| Women                          | 10 785 (37) | 3743 (35)                        | 7042 (65)                          |
| Birth years (%)                |           |                                  |                                     |
| <1950                          | 3577 (12)  | 1296 (36)                        | 2281 (64)                          |
| 1950–1969                      | 17 131 (59)| 5775 (34)                        | 11 356 (66)                        |
| 1970–1989                      | 8246 (28)  | 2539 (31)                        | 5707 (69)                          |
| ≥1990                          | 263 (1)    | 116 (44)                         | 147 (56)                           |
| Living in large city, n (%)    | 11 222 (38)| 3779 (39)                        | 7443 (38)                          |
| Education\(^a\), n (%)         |           |                                  |                                     |
| ≤9 y                           | 10 454 (36)| 3266 (31)                        | 7188 (69)                          |
| 10–12 y                        | 15 243 (52)| 5146 (34)                        | 10 097 (66)                        |
| >10 y                          | 3161 (11)  | 1181 (37)                        | 1980 (63)                          |
| Country of origin, n (%)       |           |                                  |                                     |
| Sweden                         | 23 589 (81)| 7735 (33)                        | 15 854 (67)                        |
| Europe                         | 3113 (11)  | 1130 (36)                        | 1983 (64)                          |
| Non-Europe                     | 2515 (7)   | 861 (34)                         | 1654 (66)                          |
| Married, n (%)                 | 6123 (21)  | 2306 (24)                        | 3817 (20)                          |
| Diagnosis of substance dependence\(^b\), n (%) | 11 784 (40) | 3705 (31) | 8079 (69) |
| Psychiatric diagnosis, except dependence\(^c\), n (%) | 3418 (12) | 1253 (37) | 2165 (63) |
| Hepatitis B co-infection, n (%) | 2370 (8)   | 740 (8)                          | 1990 (10)                          |
| HIV co-infection, n (%)        | 588 (2)    | 316 (3)                          | 272 (1)                            |

Abbreviations: HCV, hepatitis C virus; HIV, human immunodeficiency virus.

\(^a\)Data on 28 858 persons (1% missing).

\(^b\)Identified in the National Patient Register for ever having ICD-10 F10-F19.

\(^c\)Identified in the National Patient Register for ever having ICD-10 F00-F09 or F20-F99 after inclusion.

\(^d\)Percent in relation to all.

\(^e\)Percent in relation to the proportion of patients in each category.
During the study period were in years 2001 and 2002, when both newly diagnosed patients and those diagnosed before 2001 (with follow-up visits in 2001 and 2002) were included. In the following years, approximately 2000-2500 persons annually attended their first visit recorded in the NPR. The mean follow-up time after HCV diagnosis was 8.2 years, with 239,094 person-years in total.

**FIGURE 2.** Estimated number and percentage of patients LTFU with chronic HCV infection after diagnosis. (A) Left bar: All patients and the estimated percentage of cured* patients. Right bar: Percentage of patients LTFU after exclusion of the estimated percentage of cured* patients. (B) Left bar: Percentages of patients in HCV care, LTFU, and cured* without need for follow-up. Right bar: Percentages of patients LTFU and cured* with or without a specialist visit (other than HCV care) in 2012 or 2013. (C) Specialist care departments visited by patients LTFU or cured* during 2012 or 2013. *Estimate of patients cured of HCV. GH, gastroenterology and hepatology; HCV, hepatitis C virus; ID, infectious diseases; LTFU, lost to follow-up.
3.2 | Patients lost to follow-up after diagnosis of HCV

An estimated 4484 of total infected patients (15%) had achieved virologic cure and did not need follow-up during 2012-2013. These patients were excluded from the total population for the calculation of proportion LTFU, leaving an estimated 24,733 patients in need of HCV care during 2012-2013. There were 9726 (39%) who attended HCV specialist care in 2012-2013, while 15,007 patients did not (Figure 2A). Thus, 61% of the patients with estimated need of HCV care were LTFU during 2012-2013.

When studying LTFU in different regions (by county), the estimates of LTFU varied from 49% to 65% (Table S2). These percentages were after implementing the general assumption that 15% already had been cured and did not need HCV care (applied equally in all Swedish regions).

The characteristics of patients attending HCV care (n = 9726) and those who did not attend HCV care (LTFU and cured; n = 19,491) are shown in Table 1. Since we could not identify the cured patients on an individual level, these patients were included in the group who did not attend HCV care when characterizing other specialist care contacts.

3.3 | Other specialist care contacts

Among the 19,491 who did not visit any HCV care department during 2012-2013, there were 15,467 (79%) who had ≥1 visit to another specialist care department, while 4024 (21%) did not visit any specialist care provider at all (Figure 2B). The most common other contacts for patients LTFU in 2012-2013 were Surgery/Orthopaedic departments (n = 7610; 39%), Psychiatry/Dependency departments (n = 7031; 36%), Internal Medicine (n = 6676; 34%), Emergency Department (n = 3495; 18%), ID/GH departments for reasons other than HCV diagnosis (n = 2063; 11%), Obstetrics/Gynaecology (n = 1812; 9%), Dermatology/Venereology (n = 1244; 6%), and Geriatrics (n = 245; 1%) (Figure 2C). Other department contacts (n = 4909; 25%) constituted mostly of “Unknown” (n = 1561), Ophthalmology (n = 1355), and Otolaryngology (n = 1151).

The percentages of visits to different departments by the LTFU patients that attended specialist care in 2012-2013, grouped by birth year and sex, are shown in Figure S1. Visits to Psychiatry/Dependency departments were less common in the elderly population (both men and women), and visits to ID/GH for reasons other than HCV infection were more common in the youngest population. Internal Medicine and Surgery/Orthopaedic visits increased with age, whereas the percentage of Emergency Department visits was stable regardless of birth year and sex. The visits to Obstetrics/Gynaecology decreased by age (Figure S1).

3.4 | Predictors for LTFU and the effect of follow-up time

Male sex, younger age, lower education, psychiatric disease or dependency diagnosis, unmarried, HCV treatment and longer duration since HCV diagnosis were found to be significant risk factors for LTFU in the univariate analyses (Table 2). Living in a large city and country of origin (Sweden/Europe/Non-Europe) did not influence the risk for LTFU. All the significant factors in the univariate analyses remained significant in the multivariate analyses (Table 2).

Among the total study population, 58% (n = 16,889) did not see an ID or GH specialist for their HCV during the second year after diagnosis. Among the three quarters of patients (n = 21,924) diagnosed at ID/GH departments, 48% (n = 10,414) did not visit a HCV care department during the second year after diagnosis. This percentage was 89% (n = 6,475) for patients diagnosed elsewhere.

### Table 2

| Risk Factor                        | Univariate analysis | Multivariate analysis |
|-----------------------------------|---------------------|-----------------------|
|                                   | OR  | 95% CI  | P value* | OR  | 95% CI  | P value* |
| Male sex                          | 1.09 | 1.04–1.15 | .01      | 1.10 | 1.04–1.15 | .001     |
| Birth year (5-y increments)       | 0.96 | 0.95–0.97  | <.001    | 0.96 | 0.95–0.97  | <.001    |
| Education (≤9 y, 10–12 y, >12 y)  | 1.13 | 1.08–1.17  | <.001    | 1.13 | 1.08–1.17  | <.001    |
| Psychiatric disease exclusive of dependency diagnosis (no vs yes) | 1.21 | 1.12–1.31 | <.001    | 1.21 | 1.12–1.31 | <.001    |
| Only dependency diagnosis (no vs yes) | 0.98 | 0.94–1.00 | .02      | 0.97 | 0.94–1.00 | .02      |
| Living in big cities              | 1.03 | 0.98–1.08  | .3       |      |          |          |
| Country of origin (Sweden/Europe/Non-Europe) | 0.99 | 0.96–1.04 | 1.0     |      |          |          |
| Marital status (unmarried vs married) | 1.20 | 1.12–1.28 | <.001    | 1.20 | 1.12–1.27 | <.001    |
| Treated 2005–2010 (no vs yes)     | 0.82 | 0.77–0.88  | <.001    | 0.82 | 0.77–0.88  | <.001    |
| Observation time, y               | 0.94 | 0.93–0.94  | <.001    | 0.94 | 0.93–0.94  | <.001    |

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; OR, odds ratio; y, years.

*P < .05 was considered to be statistically significant.
In addition, we did a longitudinal aggregated annual analysis examining the proportion of patients that (a) visited HCV care departments, (b) only visited other specialist care or (c) did not have any specialist care visit at all after the first HCV visit. Patients were categorized in two groups: those attending HCV care and those LTFU in 2012-2013. Most patients in HCV care (85%; n = 8262) had ≥1 visit to an HCV care department during the first year after diagnosis. This percentage was 60% (n = 5831) during the second year after HCV diagnosis (Figure S2A). Among the patients LTFU, 70% (n = 13 662) attended an HCV care department during the first year after diagnosis, but this percentage dropped to 33% (n = 6497) during the second year after HCV diagnosis (Figure S2B). Furthermore, the annual percentage of patients in HCV care attending an HCV care department never went below 50%. Conversely, the percentage of patients LTFU visiting an HCV care department continuously decreased to 5% over the years after HCV diagnosis. The percentage of patients not attending any other specialist care was between 7% and 17% for patients in HCV care and between 25% and 36% for those LTFU.

4 | DISCUSSION

This nationwide study of >25 000 Swedish patients with chronic HCV infection shows that two-thirds of patients were LTFU after HCV diagnosis without access to antiviral treatment and cure, which is a significant barrier to achieve HCV elimination. Many patients were LTFU early after HCV diagnosis. We found that a substantial proportion of patients LTFU had attended Surgery/Orthopaedic, Psychiatry/Dependency, or Internal Medicine departments, which could serve as units to link the patients back to HCV care.

To our knowledge, this is the first published nationwide study of patients with LTFU after diagnosis that also includes analyses of their other healthcare contacts. Most previous studies have looked at small cohorts, although one larger study in the United States by Viner et al showed that only 6% of persons with HCV were receiving HCV care and 3% underwent antiviral treatment.9,10 The high percentage of patients LTFU in our study is somewhat unexpected, given that Sweden has public healthcare for all inhabitants, with healthcare visits and medication for HCV infection free of charge. The reason for the high rate of patients LTFU after HCV diagnosis could be multifactorial. The most common route of transmission of HCV is intravenous drug use in the Western world, with frequent drug dependency or psychiatric co-morbidity in this population.20 A chaotic social situation with high unemployment, homelessness, criminalization, or fear of stigma may affect the compliance to subsequent clinical visits.21

So far, most studies, including ours, have investigated patients LTFU during the IFN era, before the introduction of modern DAA therapies. The IFN-based therapies were associated with substantial side effects and low cure rates, and some patients were treated several times without cure. These side effects and low cure rates have probably reduced the patients’ interest in remaining in the HCV care continuum. Another important factor could be the long asymptomatic phase in combination with low awareness or knowledge of the risk for serious liver complications, leading to poor motivation to stay in the HCV care continuum. Besides missing the opportunity of cure from the infection, patients who are LTFU will not be monitored for liver disease. Therefore, they will miss the opportunity to be diagnosed for potential progressive liver disease and the subsequent prevention of liver-related death by surveillance for hepatocellular carcinoma or oesophageal varices with bleeding risks. We have previously shown the high risk of liver-related deaths in a nationwide study of patients with HCV in Sweden, emphasizing the importance of prevention of such mortality.20 Liver biopsy, which is an invasive method with pain as the most common complication, has been previously used to assess the stage of liver fibrosis, and fear of such procedure has been identified as one of the patient-identified barriers to HCV care.21 Nowadays, simplified tools for HCV care are available with the use of non-invasive methods such as transient elastography or algorithms based on blood markers to assess liver fibrosis, which together with the DAAs enable the monitoring and treatment for even hard-to-reach populations.

The HCV prevalence in Sweden is approximately 0.4%, with higher prevalence seen among men in the birth cohort born 1950-1969 and lower in older or younger age groups. However, transmission of HCV infection is still ongoing, and each year about 700 infections have been diagnosed in age groups of 15-29 years.11 The drug abuse diagnoses were only found in 40% of the patients in this study, which is a low rate but this probably reflects that many past or current PWID are not in contact with health care for their drug abuse, and other arenas to reach the patients are needed. It has been estimated that up to 85% of HCV infections in Sweden are diagnosed and reported to the Communicable Disease Register. The diagnosis rate is a remarkably high proportion compared with most other countries.12 This study shows that even in countries with a high rate of diagnosis, the treatment uptake can be low because of other obstacles in HCV continuum, such as the frequent LTFU.

This study showed that about two-thirds of patients did not attend HCV care as early as the second year after HCV diagnosis, emphasizing the need of early intervention after diagnosis to provide cure and reach the elimination goal. The predictors for patients LTFU in this study were young age, male sex, low education, presence of psychiatric or dependency diagnosis, unmarried, and longer duration since diagnosis of HCV. Young age may be associated with on-going drug use or lower motivation for follow-up because of the slow progression of the disease. Our findings emphasize the importance of providing easy and early access to HCV treatment for especially young patients or those with psychiatric or dependency diagnosis. Point-of-care HCV testing with a one-step screening and diagnosis visit could simplify and facilitate the linkage of patients to treatment to prevent the frequent and early LTFU as seen in our study.22

There are different pathways to link the patients who were LTFU back to HCV care. An effort to retrieve patients LTFU back to HCV care are currently ongoing by local authorities for Communicable Diseases in Sweden, using data from the Communicable Disease Register to identify and contact these individuals by letters. Other initiatives of linkage to care include public information through advertising, information in media, social media and reaching high-risk groups at needle exchange programs, dependency clinics, homeless shelters or...
prisons. Since the most common other health care contacts for those LTFU from HCV care departments were Surgery/Orthopaedic departments, Psychiatry/Dependency departments, Internal Medicine and Emergency Department, collaboration between these departments and HCV care departments should take place to link the patients back to HCV care. Increased awareness of HCV infection at these mentioned departments, with increased testing for HCV or electronic medical record alert of those with known HCV diagnosis could lead to increased linkage and access to HCV care for those LTFU.

Although cost-effective, the current DAA prices could constitute an obstacle to the access to treatment after diagnosis, despite decreasing prices, compared with the beginning of the DAA era. The restricted access to DAAs based on fibrosis stages was removed in January 2018 in Sweden, enabling treatment for patients irrespective of stage of fibrosis. Although unrestricted access to universal coverage of DAAs is currently present in several countries (eg Australia, Brazil, Egypt, Georgia, Iceland and Mongolia), it is still limited in many countries around the world.23 One strategy to increase the uptake of treatment in countries with unrestricted access is to open up the availability of DAAs to psychiatry/dependency departments or primary care settings. The treatment rate has increased in 2018 in Sweden, probably because of the removal of liver disease-based restrictions for reimbursement of DAA therapies and the recent efforts to contact patients LTFU, but treatment is still offered primarily in contact with HCV specialists at hospital settings. Recent studies have shown good results when providing HCV treatment in non-specialized healthcare settings.24,25 Since treatment has become easier with DAAs, with higher safety and efficacy compared with the IFN-based regimens, expanding HCV treatment to non-specialized settings could provide a great opportunity to treat those LTFU or difficult-to-reach populations, such as persons who inject drugs (PWID) or otherwise marginalized populations. Australia is one of the countries on track to reach the WHO HCV elimination goal, through universally funded and rapid DAA treatment uptake that includes non-specialized prescribing.26 Treatment in a variety of locations near the patient, with availability in all appropriate Drug Use services, is part of the Scottish national elimination strategy.27 This convenience of treatment locations is supported by our data with frequent healthcare contacts for non-HCV care among people LTFU. Harm reduction is an important part of HCV care for PWID, besides the antiviral treatment to prevent reinfections and new infections. Reduction in incidence and prevalence of HCV among PWID with opioid dependency has been shown when combining antiviral therapy with opioid substitution therapy and needle and syringe exchange programs (ie treatment as prevention).8,28

The strength of the study is the nationwide coverage with large numbers of included patients and a long-term follow-up. Linkage of different national registers were possible with the use of the unique personal identification number of each resident in Sweden, which enabled this study with such coverage and follow-up time, with evaluation of certain risk factors for LTFU, and a possibility to identify specialist care contacts. Previous studies describing patients with HCV who are LTFU have mainly included smaller cohorts from tertiary centres, with limited possibility to analyse other health contacts for these patients. Our study may provide knowledge needed for linkage to care in nationwide strategies to achieve the WHO elimination goal, especially in Western countries.

One drawback of this study is the lack of data for visits to primary care. However, treatment with DAA is currently not available in primary care settings in Sweden, like in many other countries.23 These departments could constitute a targeted unit for linkage of patients back to HCV care or become facilities for HCV treatment, as is the current situation in Australia. Another drawback is the lack of information of cure after treatment, without the possibility to identify those who are cured at an individual level. However, by making an estimation by calculating the number of patients treated, we could still conclude that the proportion of patients LTFU was high, with approximately two-thirds of patients without immediate access to cure. The lack of data on cure on individual level could potentially introduce some bias when analysing other healthcare contacts, including for both patients with a chronic infection and the smaller proportion of patients with a cured infection. However, the healthcare contacts for departments of Surgery, Orthopaedics, Internal Medicine, Psychiatry, and other non-HCV care departments will probably not differ significantly when comparing before and after cure, since these contacts probably were less connected to the HCV infection per se and associated more with the patient characteristics. This study was evaluating those LTFU in the IFN-era and not the situation in the DAA era. The intention was to estimate the number of patients LTFU once DAAs became available, to estimate what efforts would be necessary to reach and treat most of these patients. Therefore, we analyzed healthcare contacts just 2 years before the DAA introduction. Evaluation of LTFU after DAA introduction was not performed in this study, but could be further evaluated in future studies. In Sweden, we are currently at the stage in which we have now treated the warehoused patients with DAA at the treating clinics, and need to reach the patients LTFU, in order to accomplish the elimination goal. Our data from pre-DAA era are therefore still of relevance, to point out the necessity to proactively perform reach out programs from treating clinics to different arenas for linkage, and to identify important health care units for such actions. Also, high risk populations as persons at opioid substitution treatment (OST) clinics, needle exchange programs, prisons or homeless persons, are important to reach and link to HCV care. Effort to educate health care workers at all these arenas should be made to raise the awareness and knowledge of HCV, in order to recruit the patients back to HCV care.

To conclude, this study showed that a high proportion of patients with HCV infection were LTFU early after HCV diagnosis, highlighting a significant barrier toward the WHO goal of HCV elimination. Other major healthcare contacts for those LTFU were the departments of Surgery/Orthopaedics and Psychiatry/Dependency. Efforts to link patients LTFU back to HCV care, in combination with early and easy access to HCV treatment and harm reduction for all patients, are necessary to reach the HCV elimination goal.

CONFLICT OF INTEREST
SA has received honoraria for lectures/advisory boards from AbbVie, BMS, Gilead and MSD, and received research grants from AbbVie
and Gilead. JS, JK and KB are employees of AbbVie and may hold AbbVie stocks or stock options. ASD has received honoraria for lectures/consultancies from AbbVie, BMS, Gilead and MSD.

AUTHORS CONTRIBUTIONS
SA and AD conceived the study design, contributed to planning of the study and interpretation of data, and were the main authors of the manuscript. JS contributed to study design, planning of the study, data collection, interpretation of data, performed all the statistical analyses, and revised the manuscript critically. KB and JK contributed to study design, planning of the study, interpretation of data and revised the manuscript critically.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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