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ORIGINAL ARTICLE

Socio-economic factors associated with loss to follow-up among individuals with HCV: A Dutch nationwide cross-sectional study

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Abstract

Background and Aims: The path to hepatitis C virus (HCV) elimination is complicated by individuals who become lost to follow-up (LTFU) during care, particularly before receiving effective HCV treatment. We aimed to determine factors contributing to LTFU and whether LTFU is associated with mortality.

Methods: In this secondary analysis, we constructed a database including individuals with HCV who were either LTFU (data from the nationwide HCV retrieval project, CELINE) or treated with directly acting antivirals (DAA) (data from Statistics Netherlands) between 2012 and 2019. This database was linked to mortality data from Statistics Netherlands. Determinants associated with being LTFU versus DAA-treated were assessed using logistic regression, and mortality rates were compared between groups using exponential survival models. These analyses were additionally stratified on calendar periods: 2012–2014, 2015–2017 and 2018–2019.

Results: About 254 individuals, LTFU and 5547 DAA-treated were included. Being institutionalized (OR = 5.02, 95% confidence interval (CI) = 3.29–7.65), household income below the social minimum (OR = 1.96, 95% CI = 1.25–3.06), receiving benefits (OR = 1.74, 95% CI = 1.20–2.52) and psychiatric comorbidity (OR = 1.51, 95% CI = 1.09–2.10) were associated with LTFU. Mortality rates were significantly higher in individuals LTFU compared to those DAA-treated (2.99 vs. 1.15/100 person-years

Abbreviations: ATC, Anatomical Therapeutic Chemical; CI, confidence interval; DAA, direct-acting antivirals; DTC, diagnosis treatment combination; GP, general practitioner; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; ICD, International Classification of Diseases and Related Health Problems; IQR, interquartile range; LTFU, lost to follow-up; OR, odds ratio; PY, person-years; WHO, World Health Organization.

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(PY), $p < .0001$), while in those DAA-treated, mortality rates slowly increased between 2012–2014 (.22/100PY) and 2018–2019 (2.25/100PY).

Conclusion: In the Netherlands, individuals who are incarcerated/institutionalized, with low household income, or with psychiatric comorbidities are prone to being LTFU, which is associated with higher mortality. HCV care needs to be adapted for these vulnerable individuals.

KEYWORDS
hepatitis C, lost to follow-up, mortality, socio-economic status

1 | INTRODUCTION

The introduction of highly effective direct-acting antiviral (DAA) agents has accelerated efforts to eliminate hepatitis C virus (HCV) infection. In 2016, the World Health Organization (WHO) adopted a Global Health Sector Strategy on viral hepatitis, aiming to reach global elimination of viral hepatitis as a public health threat by 2030.[1] One potential threat for HCV elimination, in particular, is that individuals with HCV become lost to follow-up (LTFU) before initiating DAA treatment. Studies conducted in various settings have found that 23%–88% of individuals previously in care are indeed LTFU.[2] Therefore, re-linkage to care and treatment of these individuals should be a pivotal part of the micro-elimination strategy. In the Netherlands, the nationwide project CELINE has demonstrated that retrieval of individuals with HCV who were LTFU is feasible and can contribute to HCV elimination.[3]

To further understand the populations needing more focused retrieval, which could thereby assist in reducing the number of people discontinuing HCV care, it is crucial to identify the underlying determinants of LTFU. During the nationwide project CELINE, we identified a large cohort of individuals who were LTFU in the Netherlands.[3] We hypothesized that individuals with lower socio-economic status or psychiatric comorbidities might be at higher risk of becoming LTFU, however, these data could not be collected in the CELINE project owing to the lack of information that could be obtained from medical records. To this end, we linked available data from Statistics Netherlands to constitute a comparison group of individuals with HCV who were treated with DAA and supplemented these data with demographic, healthcare, socio-economic and mortality data. From this database, we aimed to determine factors contributing to LTFU and whether LTFU is associated with mortality.

Key points

Loss to follow-up (LTFU) prevents people living with hepatitis C infection from being cured. This study shows that being incarcerated or institutionalized, having a low household income, or being diagnosed with psychiatric comorbidities are risk factors for LTFU. Furthermore, LTFU was associated with higher mortality, compared to people who have been treated for their infection. Care for these at risk individuals with hepatitis C should be improved to prevent LTFU.

2 | METHODS

2.1 | Study design and data sources

We conducted a secondary analysis leveraging individual data from the CELINE project and non-public microdata from Statistics Netherlands.

The methods of the CELINE project are described in detail elsewhere.[4] Briefly, CELINE was a nationwide retrieval project in the Netherlands targeting LTFU individuals with HCV. These individuals were identified using laboratory and patient records in 45 healthcare centres. Participating centres were asked to identify individuals with HCV (i.e., those with a positive HCV RNA or, if unavailable, anti-HCV antibody test at their last clinical visit) who were not scheduled for an HCV-related outpatient visit. These individuals were defined as being LTFU. Individuals <18 years old at time of assessment were excluded. Using the Municipal Personal Records database, we verified whether individuals LTFU were still alive and had a known address in the Netherlands (i.e., eligible for retrieval). These individuals were then invited for re-evaluation between 2018 and 2021. Individuals who visited the outpatient clinic were considered as 'retrieved', whereas all others were considered 'non-retrieved'.

Statistics Netherlands is an independent organization that collects, processes and publishes reliable statistical data on Dutch residents. The Statistics Netherlands Act constitutes the legal basis for Statistics Netherlands, and Statistics Netherlands is adherent to the EU General Data Protection Regulation.

2.2 | Ethical clearance

The list of participating centres can be found in Table S1. Centralized approval of the CELINE project was waived by -the Ethical Review Board in Arnhem-Nijmegen. The Institutional Review Boards of all

participating centres reviewed and approved the CELINE study as well as the use of data from the CELINE project to be linked to data from Statistics Netherlands. Informed consent from participants was not required for this type of study.

2.3 | Study population

We first constructed a group of individuals LTFU from the CELINE project. For this study, we selected only data from participating centres with >25 individuals LTFU who were eligible for retrieval. LTFU individuals who died after becoming LTFU were still included. Excluded were individuals invited for retrieval who were cured or linked to care at another hepatitis treatment centre, according to self-report, those who were LTFU before 2012 or after 2019, and those with HIV/HCV co-infection, based on diagnosis treatment combination (DTC) code data extracted from Statistics Netherlands. The lattermost group was excluded because retention in HCV-related care is largely correlated with HIV-related care[5–9] and others have already investigated the care cascade for this key population in the Netherlands.[10,11]

We then constructed a comparison group of individuals treated with DAAs using data from Statistics Netherlands. For this study, individuals using medications registered under the Anatomical Therapeutic Chemical (ATC) code J05AP, which represents use of DAA and/or ribavirin, between 2012 and 2019 were selected. This ATC code does not allow us to distinguish individuals receiving DAA treatment for HCV from ribavirin monotherapy for chronic hepatitis E virus (HEV) infection. For this reason, individuals with a medical co-morbidity associated with being at risk of developing chronic HEV without an ATC code indicating hepatitis B virus (HBV) or HCV were excluded. These medical co-morbidities included solid organ transplant (excluding liver transplants), primary immune deficiency disorders and haematological malignancies. Additionally, individuals with HIV/HCV co-infection and persons younger than 18 years were excluded.

Individuals who were identified as belonging to both the LTFU and DAA-treated group were excluded. However, if an individual was known to have received DAA treatment in the calendar year during or after LTFU assessment of the CELINE project, this individual was considered as belonging to the LTFU group.

2.4 | Data linkage and study variables

For individuals in the LTFU group, data from the CELINE project were linked with data from Statistics Netherlands using the social security numbers of participants. The dataset was subsequently pseudonymized by Statistics Netherlands. Variables from the CELINE data included year of LTFU (i.e., the calendar year following that of the last positive HCV test), year of retrieval invitation and retrieval outcome. Due to strict privacy regulations from Statistics Netherlands, no other clinical variables could be included in this study.

For individuals in the LTFU and DAA-treated groups, variables obtained from Statistics Netherlands included demographic characteristics (i.e., year of birth, sex at birth, migration background, household composition), socio-economic characteristics (i.e., education level, household income, main source of household income), medical diagnoses based on DTC codes, medication use based on ATC codes, utilized healthcare facilities based on declaration data (i.e., general practitioner (GP), psychiatric care, including psychiatric inpatient stay) and mortality data (i.e., primary cause of death, year of death). Causes of death were categorized based on the 10th Edition of the International Classification of Diseases and Related Health Problems (ICD-10) codes (Table S2). The databases from Statistics Netherlands do not contain any detailed clinical data. DTC codes and declaration data were provided in part by Vektis C.V., a national database containing data on insurance expense reports, and were linked through Statistics Netherlands.

An overview of available variables and definitions can be found in Tables S2 and S3. In the overall database, data on LTFU individuals who were retrieved pertains to the calendar years 2018–2020, data on LTFU individuals who were non-retrieved pertains to the calendar year of their last clinical visit or most recent HCV test result, and data on DAA-treated individuals pertains to the year in which DAAs were given.

2.5 | Statistical analysis

Descriptive data were reported as number (percentage) and median (interquartile range [IQR]). Due to the privacy regulations stipulated by Statistics Netherlands, categories representing <10 individuals cannot be reported. Any category with <10 individuals was then regrouped with the most relevant category(ies).

We first compared characteristics for the LTFU and DAA-treated groups. For individuals in the DAA-treated group who had multiple prescriptions in different years, we only included data from the earliest year. Missing data were imputed as follows: any available observation was used for migrant status, observations from any preceding year were used for the highest level of completed education, and observations 2 years before or after were used for household composition and income. After imputation, individuals with any missing data were excluded from analysis.

We then modelled the probability of being LTFU compared to DAA-treated using logistic regression. We included the following covariates a priori to construct a multivariable model: age, sex at birth, migration status, receiving benefits, income relative to the social minimum, institutionalized status, psychiatric comorbidity, psychiatric inpatient stay and utilization of GP care. Odds ratios (OR) and 95% confidence intervals (CI) were estimated for each covariate using maximum likelihood methods. Multicollinearity between covariates was assessed. Additionally, we tested whether the ORs were different between calendar periods (i.e., 2012–2014, 2015–2017 and 2018–2019) by including and testing an interaction term between each individual covariate and period in separate models.

Within the group of LTFU individuals, we also compared characteristics for those who were unable to be retrieved into care (i.e., non-retrieval) and for those who were able to be retrieved. The same imputation methods as above were used in this analysis. The determinants of non-retrieval compared to retrieval were assessed using univariable models with the same covariates as the model described above. Multivariable analysis was precluded by the few numbers of individuals retrieved.

Finally, we compared the rates of all-cause mortality between the LTFU and DAA-treated groups. For this analysis, we reconstructed follow-up for each individual beginning on 1 January 2012 (assuming that all individuals LTFU or DAA-treated were alive and had HCV infection on this date) and ending at the date of death or on 31 December 2019, whichever occurred first. We modelled the probability of all-cause death using a piecewise parametric exponential survival model. We included the following covariates: time-period, in which time was divided into three calendar year segments (i.e., 2012–2014, 2015–2017 and 2018–2020); LTFU or DAA-treated group, and the interaction between the two. We included the calendar year 2020 in this analysis to allow inclusion of deaths that could have occurred 1 year after the last possible year of LTFU (i.e., 2019). We calculated the mortality rates per 100 person-years (PY) and their 95% CI for each time period and group from this model using the 'contrast' post-estimation command in STATA. We performed a joint test to determine differences in mortality rates between groups across periods. Median age at death was compared between groups and periods using the Kruskal–Wallis test.

Statistical significance was defined as a p-value <.05. Data were analysed using SPSS (Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) or STATA (2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

3 | RESULTS

3.1 | Description of the study population

Flowcharts depicting the selection of the LTFU and DAA-treated groups are displayed in Figure S1. A total of 966 LTFU individuals from 13 participating centres (including four university medical centres) were linked to data from Statistics Netherlands, of whom 479 were excluded because they were LTFU prior to 2012 or after 2019. After excluding those not fulfilling eligibility criteria, 254 individuals were analysed (127 from 2012–2014, 84 from 2015–2017 and 43 from 2018–2019). A total of 7537 individuals who received DAA between 2012 and 2019 were identified using prescription data. After excluding those not fulfilling eligibility criteria, 5547 individuals were analysed (1242 from 2012–2014, 3298 from 2015–2017 and 1007 from 2018–2019).

3.2 | Determinants of becoming lost to follow-up

Characteristics of the LTFU and DAA-treated groups are presented in Table 1. A little under half of migrants were from non-Western countries (n = 52/199, 44% and n = 1378/3045, 45% in the LTFU and DAA-treated groups, respectively).

The determinants of being LTFU versus DAA-treated, as determined from the multivariable logistic regression model, are summarized in Figure 1. In multivariable analysis, receiving benefits (vs. not, p = .004), household income below the social minimum (vs. income higher than the social minimum, p = .003), institutionalization (vs. not p < .001) and psychiatric comorbidity (vs. not, p = .014) were significantly associated with becoming LTFU. Being in a multi-person household (vs. single-person household or institutionalized, p = .025) and utilization of GP care (vs. not, p < .001) were inversely associated with becoming LTFU.

Increased age was more strongly associated with LTFU in 2012–2014 (per year, OR = 1.03, 95% CI = 1.00–1.05) compared to 2015–2017 (per year, OR = 1.00, 95% CI = .98–1.02) and 2018–2019 (per year, OR = .98, 95% CI = .95–1.01) (p for interaction = .038). Psychiatric comorbidities were more strongly associated with LTFU in 2018–2019 (OR = 3.94, 95% CI = 1.60–9.70) compared to 2015–2017 (OR = 1.24, 95% CI = .76–2.02) and 2012–2014 (OR = 1.14, 95% CI = .73–1.77) (p for interaction = .039). There were no significant differences in OR across periods for all other covariates.

3.3 | Determinants of non-retrieval

In the group of 175 LTFU individuals included in analysis for retrieval, 54 (31%) were able to be retrieved and 121 (69%) were unable to be retrieved. The flowchart depicting the selection of individuals included in this analysis is displayed in Figure S2. Characteristics between retrieved and non-retrieved groups are presented in Table S4. Between groups, there were similar proportions of non-Western migrants (n = 12/26, 46% and n = 32/56, 57% in the retrieval and non-retrieval groups, respectively). The determinants of retrieval, as determined from univariable logistic regression models, are summarized in Figure S3. Having an income below or at the social minimum (vs. income higher than the social minimum, p = .005, respectively) and having a psychiatric comorbidity (vs. not, p = .014) were associated with a lower odds of retrieval.

3.4 | Association between lost to follow-up and all-cause mortality

In the analysis on mortality rates, an additional 134 individuals were excluded because they died prior to 2012. Of the remaining 5667, there were 603 deaths during the study period: 60 in individuals LTFU and 543 in those treated with DAAs, Mortality rates were significantly higher in individuals LTFU compared to those DAA-treated (2.99 vs. 1.15/100PY, p < .0001). As shown in Figure 2, mortality rates were higher in the LTFU versus DAA-treated group at each calendar period (overall p < .0001). For those LTFU, the period mortality rate slowly increased during the study period, from 1.38/100PY in 2012–2014 to 4.99/100PY in 2018–2020 (Figure 2). For DAA-treated individuals, the period mortality rates also increased from .22/100PY in 2012–2014 to 2.25/100PY in 2018-2020. The median

TABLE 1 Characteristics of LTFU and DAA-treated individuals with HCV.

	LTFU[a] (*n* = 254)	DAA[b] (*n* = 5547)
Age in years (median, IQR)	52 (46–58)	55 (47–61)
Male sex at birth	188 (74%)	3703 (67%)
Migrant background		
Dutch origin	135 (53%)	2502 (45%)
First generation migrant	97 (38%)	2693 (49%)
Second generation migrant	22 (9%)	352 (6%)
Education level[d]		
Low	92 (36%)	1849 (33%)
Middle	45 (18%)	1064 (19%)
High	11 (4%)	570 (10%)
Missing	106 (42%)	2064 (37%)
Household composition		
Single	122 (48%)	2190 (39%)
Multi-person	69 (27%)	3136 (57%)
Institutional	63 (25%)	221 (4%)
Household income[e]		
Institutional	72 (28%)	227 (4%)
Below social minimum	33 (13%)	428 (8%)
Within social minimum	59 (23%)	1222 (22%)
Above social minimum	90 (35%)	3670 (66%)
Main source of income		
Wages, business or retirement	64 (25%)	3134 (56%)
Benefits[f]	190 (75%)	2413 (44%)
Medical comorbidities[c]		
No medical comorbidity	65 (26%)	994 (18%)
Cirrhosis(−related complications) or other liver-related conditions	18 (7%)	812 (15%)
Other	187 (74%)	4464 (80%)
Psychiatric comorbidities[c]		
No psychiatric comorbidity	76 (30%)	3215 (58%)
Addiction disorder	140 (55%)	1384 (25%)
Schizophrenia	31 (12%)	207 (4%)
Mood or anxiety disorder	21 (8%)	605 (11%)
Other	39 (15%)	477 (9%)
Utilized healthcare facilities[c]		
General practitioner	195 (77%)	4917 (89%)
Psychiatric inpatient stay >24 h	29 (11%)	189 (3%)
Methadone use	28 (11%)	300 (5%)

Note: All statistics are *n* (%) unless noted otherwise.

Abbreviations: DAA, direct-acting antivirals; HCV, hepatitis C virus; LTFU, lost to follow-up.

[a]Characteristics reported at the moment of becoming lost to follow-up, defined as 1 year after the last known HCV antibody, RNA or genotype test.

[b]Characteristics reported at the year of DAA prescription. For individuals with multiple DAA prescriptions over several calendar years, the year of first DAA prescription was chosen.

[c]Individuals can belong to two or more categories.

[d]Classified according to the International Standard Classification of Education (ISCED).[12] Low: ISED level 0 = 2; middle: ISCED level 3 = 4; high: ISCED level 5–8.

[e]The social minimum is the minimal amount of financial resources with which people can achieve a 'minimally acceptable lifestyle'. It is determined and annually adjusted by the Ministry of Social Affairs and Employment.

[f]Includes disability, unemployment and social welfare benefits.

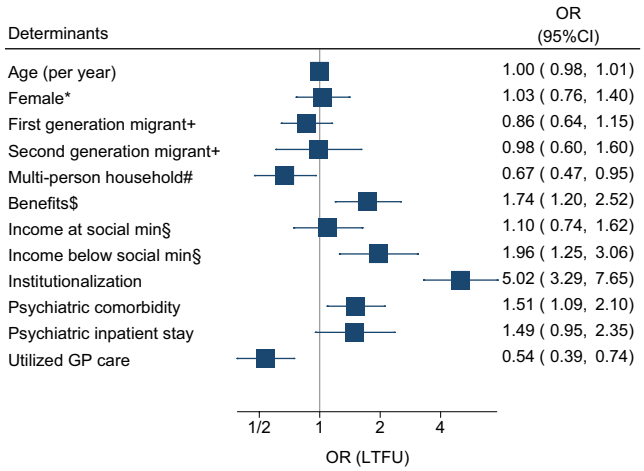

FIGURE 1 Determinants associated with becoming lost to follow-up from hepatitis C care. Results were obtained using multivariable logistic regression. Reference groups were as follows: *Male; +Dutch origin; #Single-person household or institutionalized individuals; $Wages, business or retirement; §Income higher than the social minimum. CI, confidence interval; GP, general practitioner; OR, odds ratio; soc. min., social minimum.

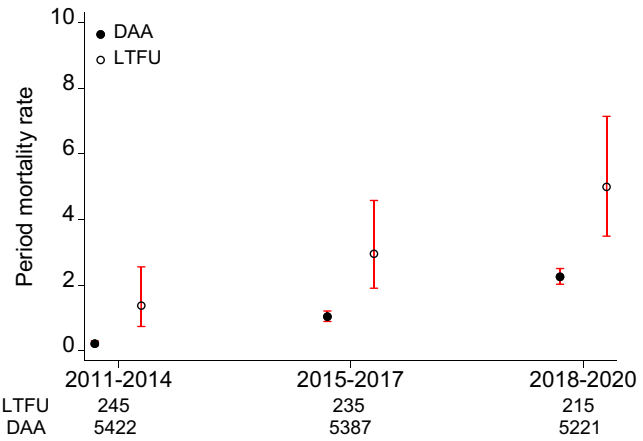

FIGURE 2 Period mortality rates in individuals lost to follow or treated with direct acting antivirals. Points represent the period mortality rate per 100 person-years and bands around the points represent 95% confidence intervals. The numbers below indicate the number of individuals remaining at risk of death. DAA, direct acting antivirals; LTFU, lost to follow-up.

age at death was stable in the LTFU group (59 years, IQR = 57–61 in 2012–2014 to 55 years, IQR = 49–61 in 2018–2020; $p = .16$), while increasing in the DAA-treated group (55 years, IQR = 50–59 in 2012–2014 to 59 years, IQR = 54–65 in 2018–2020; $p = .015$).

The distribution of primary causes of death for both groups is presented in Figure 3. There was no significant difference in liver-related mortality between groups ($n = 18/60$, 30% in LTFU vs. $n = 191/543$, 35% in DAA-treated groups, $p = .42$). Of the 209 liver-related causes, 13 (6%) were due to liver failure, 74 (35%) to hepatocellular carcinoma, 31 (15%) to unspecified liver malignancy, 41 (20%) to viral hepatitis, and 62 (30%) to other liver-related causes. LTFU Individuals compared to DAA-treated more often died from mental or substance abuse disorders ($n = 15/60$, 25% vs. $n = 16/543$, 3%, respectively, $p < .001$). There were no significant differences in the proportion of all other causes of death between groups.

The proportion of deaths due to liver-related diseases decreased substantially over time in individuals DAA-treated (vs. 2012–2014, OR in 2015–2017 = .51, 95% CI = .15–1.73 and OR in 2018–2020 = .41, 95% CI = .12–1.38) ($p = .22$), whereas this proportion did not decrease in those LTFU ($p = .82$). Meanwhile, the proportion of deaths due to non-HIV or non-liver related cancers increased over time in individuals treated with DAAs (vs. 2012–2014, OR in 2015–2017 = 2.18, 95% CI = .27–17.60 and OR in 2018–2020 = 3.52, 95% CI = .44–27.87) ($p = .060$, but not in those LTFU ($p = .36$). There were no noticeable changes in the other causes of death over calendar periods among individuals LTFU or DAA-treated.

4 | DISCUSSION

Losing patients from regular HCV care before they could have been cleared of their infection threatens HCV elimination efforts. By combining data from a nationwide retrieval project and Statistics Netherlands, we analysed predisposing determinants associated with LTFU and found that institutional settings (i.e., being incarcerated, in a mental institution or nursing home), low household income, receiving benefits and psychiatric comorbidities contributed to becoming LTFU. In those LTFU, the mortality rate was significantly higher compared to a population who has remained in care sufficiently long enough to have received DAA (i.e., those DAA-treated). DAA-treated individuals more often died due to non-liver-related malignancies, while LTFU individuals more often died due to mental or substance abuse disorders or external/unnatural causes.

Although many studies have quantified the number of individuals with HCV who are lost from each step in the cascade of HCV care, few have explored the reasons for which these individuals become LTFU. The most commonly observed risk factor across studies has been age, with some suggesting that younger individuals are more likely to become LTFU.[7,13–16] In contrast, we did not find a significant association between age and LTFU in our study. Second, our data showed that migrants were not at greater risk of LTFU and retrieval in this group was no different as compared to other populations. Nevertheless, only individuals with a social security number could be linked to data from Statistics Netherlands. Migrants who were denied asylum were unlikely to have received such a number and would therefore have not been included in this analysis. Any interpretation with respect to migrant status must be heeded with caution. Furthermore, ethnicity may be an important determinant for LTFU,[17] as people born in the Netherlands with an ethnic minority background might have disadvantaged access to healthcare. Interestingly, we did find a significant association between psychiatric comorbidity and becoming LTFU. This association has not been observed in several studies[7,17–21]; yet two more recent studies have linked the presence of psychiatric or dependency diagnoses with LTFU,[16,22] with the caveat that one of these studies did not account for confounding

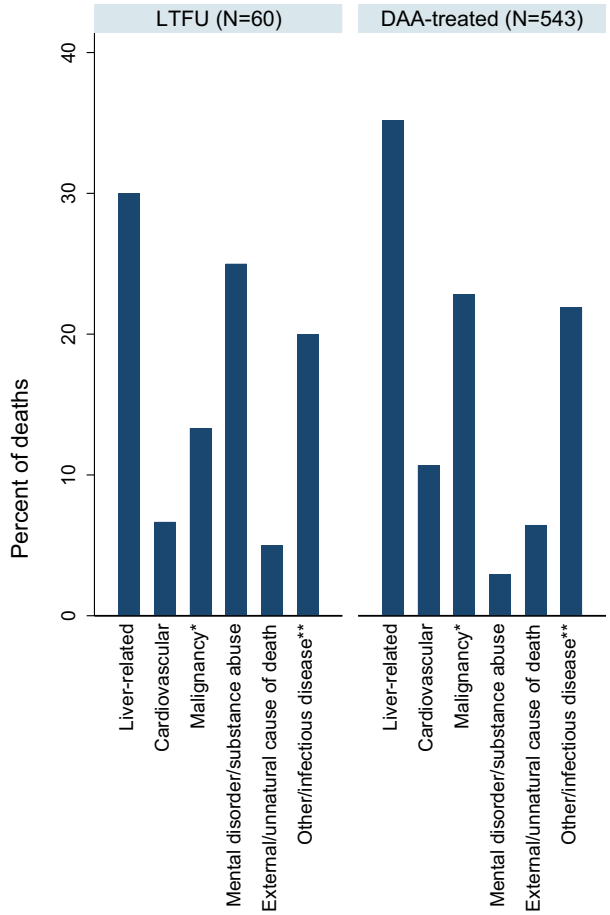

FIGURE 3 Distribution of causes of death for individuals lost to follow-up and treated with direct acting antivirals. The distribution of regrouped causes of death occurring during 2012–2020 are presented, while stratified on individuals LTFU or DAA-treated. *Non-HIV or liver-related malignancies. **Excluding viral hepatitis and HIV. Details on included ICD-10 codes can be found in Table S2. DAA, direct acting antivirals; HIV, human immunodeficiency virus; LTFU, lost to follow-up.

bias.[22] Possible solutions to prevent LTFU in this group include continuous patient education, patient-tailored approaches that provide support and involvement from other healthcare personnel and/or peers, and decentralization of HCV care.

An important gap in current literature is that the relevant socioeconomic factors have not been studied in relation to LTFU. We showed that several of these factors are related to becoming LTFU. Being in an institutionalized setting was a significant predictor for LTFU, suggesting that continuation of care when or after a person becomes institutionalized is insufficient in the Netherlands. Similar factors play a role in non-retrieval. Importantly, HCV treatment is not covered by insurance while incarcerated, but rather by the Ministry of Justice and Security. The expenses of treatment, combined with the fact that the average serving time for Dutch prisoners is a little under 3 months, may contribute to individuals not re-entering care while they remain incarcerated. A budget-appropriate plan for screening, treatment and transfer of care after release should be devised by stakeholders in healthcare, the justice system, and politics. Low household income was also significantly associated with becoming LTFU. The costs associated with the compulsory deductible for insured residents in the Netherlands ranges from €385–€885 per year. Although this deductible is financially compensated through the Dutch tax system, this reimbursement mechanism clearly does not prevent barriers to healthcare access, which could be exacerbated in individuals with low household incomes. Making infectious disease healthcare exempt from this compulsory deductible may prove beneficial for both patients and public health.

Preventing LTFU and strengthening the cascade of care for at risk patients should become a priority, as these individuals have a higher risk of mortality compared to patients who remain in care. The difference in mortality rates between groups became smaller over the years, mainly due to increased mortality in the DAA-treated group. This increase in mortality rate might be due to aging, as the age at death significantly increased over the years, particularly in the group treated with DAAs. This study did demonstrate a decrease in liver-related mortality after the introduction of interferon-free DAAs in 2015, in line with other studies,[23–28] yet this result was not significant. Part of this finding, however, might be a attributed to characteristics of the study population, which has a higher number of patients with more advanced liver disease who were treated in the first years after DAAs became available. Future research would need to consider the clinical characteristics of both the LTFU and DAA-treated groups, which were unfortunately not available in our study. One concerning finding was the higher risk of death from mental or substance abuse disorders in LTFU individuals compared to DAA-treated. This warrants a broader approach of care for these marginalized individuals.

Our study comes with strengths and limitations. We benefited from the presence of a robust, comprehensive, widely used, national database that was able to provide data on many relevant social, demographic and economic variables. For the LTFU group, data were presented at the year of becoming LTFU, which was based on an estimate (i.e., the calendar year following the last positive HCV test). This estimate may have been incorrect, as patients could have been in care for one or more years after their last test result. Furthermore, it would have been interesting to investigate clinical factors, such as current HCV viraemia and their influence on LTFU and mortality. However, due to strict privacy regulations, these data were not available or could not be obtained. Since 83% of retrieved LTFU patients in CELINE were HCV RNA-positive,[3] it is likely that a similar majority of non-retrieved LTFU patients in the current study were still viraemic at the time of analysis. In contrast, the vast majority of the DAA-treated group would not be viraemic considering the efficacy of DAAs. A third limitation was the large number of LTFU individuals who were excluded since they were not LTFU during 2012–2019—the period during which DAA treatment was given in the DAA-treated group. However, by aligning the same period for both groups, the risk of bias from temporal effects was reduced. The choice of comparison group may also be seen as a limitation. Ideally,

we would have compared individuals LTFU to patients remaining in care, independent of treatment status. However, this comparison was prevented by the lack of available data. Finally, certain detail for some of the variables used in this analysis was lacking. The highest completed level of education was missing in 30%–50% of cases, and was thus not included in the multivariable models. However, this covariate is likely highly correlated with income and main source of income, two variables that were included in the model. Other variables of interest, such as experiencing homelessness or previous injecting drug use were not available in the Statistics Netherlands database.

In conclusion, low socio-economic status, institutionalized setting and psychiatric comorbidity are associated with individuals with HCV becoming LTFU in the Netherlands. LTFU individuals have a higher risk of mortality. Success of HCV elimination will depend on improving the continuum of care for these risk groups.

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CONFLICT OF INTEREST STATEMENT

M.v.D. declares that the Radboudumc, on behalf of M.v.D., received honoraria due to participation in advisory boards of Abbvie and Gilead. C.J.I. has received research funding from Gilead, outside the submitted work. R.d.K. declares that the Erasmus University Medical Centre, on behalf of R.d.K., received honoraria for consulting/speaking from Gilead, Janssen, Bristol-Myers Squibb (BMS), Abbvie, Merck Sharp & Dohme (MSD) and Roche and received research grants from Abbvie, Gilead, GlaxoSmithKline and Janssen. J.P.H.D. declares that the Radboudumc, on behalf of J.P.H.D., received honoraria or research grants from Novartis, Ipsen, Otsuka, Abbvie, and Gilead. J.P.H.D. served as consultant for Gilead and Abbvie, and in the last 2 years has been member of advisory boards of Otsuka, Norgine Gilead, BMS, Janssen, and Abbvie. M.v.d.V. declares that Amsterdam UMC on behalf of M.v.d.V. received honoraria or research grants from Abbvie, Gilead, MSD, and ViiV Healthcare, all outside the submitted work. All other authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Statistics Netherlands. Restrictions apply to the availability of these data, which were used under licence for this study. Data are available from the author(s) with the permission of Statistics Netherlands.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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