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ORIGINAL ARTICLE

Hepatitis C virus in hemophilia: Health-related quality of life after successful treatment in the sixth Hemophilia in the Netherlands study

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Abstract

Introduction: Persons with hemophilia and hepatitis C virus (HCV) infection have a lower health-related quality of life (HRQoL) than those never HCV infected. However, it is unknown whether HRQoL after HCV eradication is comparable to individuals never HCV infected. We aimed to compare HRQoL between HCV-cured and never chronically HCV-infected persons with hemophilia.

Methods: All persons with hemophilia in the Netherlands were invited for a nation-wide study conducted in 2018–2019. For the current analysis, participants born before 1992 with data on HRQoL and HCV status were included. HCV status was collected from medical records. HRQoL was measured by RAND-36 questionnaire,

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with a minimally important difference set at 4.0 points. Multivariable linear regression was used to adjust for age, hemophilia severity, HIV status, and self-reported joint impairment.

Results: In total, 486 persons were eligible; 180 were HCV cured and 306 never chronically HCV infected. Compared with those never HCV infected, HCV-cured individuals were older (57 vs. 53 years), more often had severe hemophilia (67% vs. 21%), and reported more impaired joints (median 3 vs. 0). Compared with those never HCV infected, adjusted RAND-36 domain scores of HCV-cured individuals cured were lower on all RAND-36 domains except Pain, ranging from a difference of 4.5 (95% CI, −8.8 to −0.3) for Physical functioning to 11.3 (95% CI, −19.4 to −3.1) for Role limitations due to physical problems.

Conclusion: Despite effective HCV treatment, HRQoL of HCV-cured persons with hemophilia is still lower than HRQoL of those never chronically HCV-infected on all RAND-36 domains. This implies that careful psychosocial follow-up and support are indicated.

KEYWORDS
direct-acting antivirals, hepatitis C virus, hemophilia A, hemophilia B, patient reported outcome measures, RAND-36, viral hepatitis

Essentials

- Chronic hepatitis C virus (HCV) infection reduces quality of life (QoL) in hemophilia.
- We compared QoL between individuals with cured HCV or without previous chronic HCV infection.
- QoL of HCV-cured persons with hemophilia was lower than QoL of those never HCV-infected.
- We suggest screening for the need of psychosocial support for HCV-cured persons with hemophilia.

1 | INTRODUCTION

Hemophilia is an inherited X-linked bleeding disorder characterized by bleeding tendency because of clotting factor VIII or IX deficiency. Health-related quality of life (HRQoL) of Dutch persons with hemophilia is lower than in the general Dutch population, with the exception of mental health.[1] HRQoL of persons with hemophilia is mainly dependent on severity of hemophilia, age, orthopedic status, and comorbidities.[2,3] One of the main comorbidities in persons with hemophilia is hepatitis C virus (HCV) infection, which is widespread among persons with hemophilia as a result of receiving contaminated plasma-derived clotting factor concentrates before the 1990s.[4]

Hepatitis C virus infection affects HRQoL through fatigue, psychological effects (i.e., depression and cognitive impairment), and stigma.[5] In a cross-sectional study on HRQoL among persons with hemophilia in the Netherlands in 2001, chronic HCV infection was independently associated with a decreased score on the RAND-36 domains of General health and Energy/fatigue when compared with never HCV-infected persons with hemophilia.[2] Until 2014, HCV was treated with a combination of PEG-interferon and ribavirin, which was successful in fewer than 60% of cases and had many severe side effects, such as fatigue and depression.[4,6] In 2014, interferon-free direct-acting antiviral (DAA) therapy became available, with an effectivity >95% and minimal side effects.[7] This has made HCV elimination feasible.[8] Successful HCV treatment decreases long-term morbidity and all-cause mortality.[9,10] Additionally, studies in the general HCV monoinfected and HIV/HCV coinfected populations have shown that successful DAA treatment improves several domains of HRQoL.[11,12]

For persons with hemophilia, however, the effect of successful HCV treatment on HRQoL is insufficiently known. The only study on HRQoL of persons with hemophilia undergoing anti-HCV treatment reported decreasing RAND-36 domain scores during PEG-interferon treatment.[6] However, 4 weeks after cessation of treatment, RAND-36 domain scores approached pretreatment level, without any association between RAND-36 scores and virological response.[6] Persistent depression after cessation of therapy was also described.[6] It is unknown how HRQoL after HCV eradication compares with the HRQoL of those never chronically HCV-infected. Most HCV-cured persons with hemophilia had been infected for many decades, which might have left a physical, social, and psychological impact. Identifying whether HRQoL remains affected after HCV eradication could aid tailored psychosocial support for those

who need it. Therefore, we aimed to compare HRQoL between persons with hemophilia successfully treated for HCV and those never chronically infected.

2 | METHODS

2.1 | Design/Setting

The sixth Hemophilia in the Netherlands (HiN-6) study was the latest edition of a series of nationwide cross-sectional studies that assessed the medical, social, and psychological status of persons with hemophilia in the Netherlands. All persons with hemophilia known at one of the hemophilia treatment centers were invited for participation. The study was approved by the medical ethics committee of the Leiden University Medical Center, and all participants provided written informed consent for use of their data when required under Dutch law.

2.2 | Data collection

All participants completed a survey between June 2018 and July 2019 that included questions on sociodemographic characteristics (age, education, income), functional outcomes (including HRQoL), and clinical characteristics (severity of hemophilia, bleeding episodes, orthopedic status, comorbidities, use of clotting factor and other medication). Data on severity of hemophilia and comorbidities (HCV status, HIV status, liver fibrosis, liver-related complications) were taken from electronic patient records using a standardized electronic case report form after the participant provided written informed consent for extraction of these data.

2.3 | Selection criteria

All male adult and pediatric individuals with mild, moderate, or severe congenital hemophilia A or B receiving hemophilia care in the Netherlands were eligible for inclusion in the HiN-6 study. Inclusion criteria for the current analysis were available HRQoL data and HCV data from the survey and medical files, respectively. Exclusion criteria were current HCV infection (i.e., last known HCV RNA result was positive), ongoing antiviral therapy at the time of survey, and year of birth after 1991 because the risk of HCV infection through clotting factor replacement after 1991 was considered negligible.

2.4 | Outcomes and definitions

Study outcomes were differences in RAND-36 HRQoL domain scores between persons with hemophilia with cured HCV and those never chronically HCV-infected. HCV status was categorized as either HCV-cured (i.e., ever HCV RNA positive, with an undetectable HCV RNA at least 24 weeks after cessation of interferon-based treatment or at least 12 weeks after cessation of DAA treatment), spontaneous HCV clearance (i.e., a positive HCV antibody or RNA result followed by a negative HCV RNA result in absence of a history of antiviral treatment), or never HCV infected (i.e., negative HCV antibody status). Never chronically HCV infected was defined as either never HCV infected or spontaneous HCV clearance. We hypothesized that in persons with hemophilia and spontaneous HCV clearance, the physical and psychological impact of HCV infection on quality of life at present was very low because spontaneous clearance usually occurs within 12 months,[13] does not result in liver-related complications,[14] and these individuals were only informed about their HCV antibody and RNA status after testing became available in 1990s,[15] many years after HCV transmission for the vast majority of the cohort.

Health-related quality of life was assessed with the Dutch version of the RAND-36 questionnaire.[16,17] This questionnaire contains 36 items assessing the following eight domains: General health, Physical functioning, Energy/fatigue, Pain, Role limitations due to physical health problems, Role limitations due to emotional problems, Emotional well-being, and Social functioning. Domain scores (range, 0–100) were calculated when at least half of the items of a domain had been completed, in accordance with RAND-36 scoring instructions. Participants were included if a score on at least one domain was available. Participants with a missing score on a domain were not considered for that specific analysis. The minimally important difference (MID), the threshold at which a difference in a domain score between groups was considered relevant, was set at 4 points for all RAND-36 domains.[18,19]

Joint status was self-reported for the eight most commonly affected joints (i.e., left and right knees, elbows, ankles, and wrists), with scores reflecting functional limitation of 0 (no limitation), 1 (some limitation without daily problems), 2 (some limitation with daily problems), or 3 (severe limitation with complete loss of function). By summing up these joint scores, a total joint limitation score ranging from 0 to 24 was calculated. Presence of advanced liver fibrosis or cirrhosis was noted if the most recent Fibroscan result was ≥9.5 kPa or if there was a history of hepatocellular carcinoma, ascites, hepatic encephalopathy, bleeding esophageal varices, or liver transplantation. Within the HCV-cured group, a subgroup was defined as individuals with sequelae of the cured HCV infection, defined as either the presence of advanced liver fibrosis or cirrhosis, self-reported residual symptoms of the HCV infection, or self-reported ongoing side effects of previous antiviral therapy. HCV treatment was categorized as interferon-containing regimens (including regimens combining PEG-interferon and DAA) and interferon-free DAA regimens. Education status was reported as highest level of education according to the International Standard Classification of Education that was successfully completed.

2.5 | Statistical analysis

Descriptive data are presented as numbers (percentages), mean ± standard deviation (SD), or median (interquartile range [IQR]), depending on variable type and distribution. Multivariable

linear regression was performed to assess the association of a cured HCV status versus never chronically HCV infected on each of the eight RAND-36 domains and to adjust the RAND-36 domain score differences for potential confounding factors. Variables included as covariates were severity of hemophilia (categorized as mild [factor VIII/IX activity 0.05–0.4 IU/ml], moderate [factor VIII/IX activity 0.01–0.05 IU/ml], or severe [factor VIII/IX activity <0.01 IU/ml]), age, self-reported joint impairment score, and HIV status. In a sensitivity analysis, the use of prophylaxis was added as an additional covariate.

The main analysis included all participants either HCV cured or never chronically HCV infected. Furthermore, we conducted four subanalyses. First, to explore whether RAND-36 score differences were due to HCV infection sequelae, we compared RAND-36 domain scores between individuals never chronically HCV infected and cured persons with hemophilia excluding the subgroup of HCV-cured individuals with HCV infection sequelae. Second, for a more comparable control group regarding age and hemophilia severity, a subanalysis was conducted comparing HCV-cured persons with hemophilia and those with spontaneous HCV clearance. Third, we compared RAND-36 domain scores between HCV-cured participants and the never HCV-infected participants without those with spontaneous HCV clearance, thus only including successfully treated and HCV antibody-negative participants. Fourth, to assess the effect of prior interferon treatment on HRQoL, within the HCV-cured group, RAND-36 domain scores were compared between those who ever had interferon-containing treatment to those who only received interferon-free DAA regimens. This third subanalysis included a sensitivity analysis with the presence of advanced liver fibrosis or cirrhosis as an additional covariate. Additionally, effect of time since successful treatment on RAND-36 domain scores was analyzed as a continuous variable within the HCV-cured group using univariable linear regression. Data were analyzed using R (version 3.6.1).

3 | RESULTS

3.1 | Participant characteristics

Invitations for the HiN-6 study were sent to 1746 adult persons with hemophilia known at one of the eight Dutch hemophilia treatment centers (Figure 1). Fully or partially completed surveys were returned by 808 participants (response rate, 46%). After excluding individuals who were born ≥1992 (n = 122), who did not provide written informed consent for additional data collection from their medical records (n = 155), with ongoing HCV infection (n = 7), with an unclear HCV status (n = 2), with ongoing DAA therapy (n = 1), without scores on any of the RAND-36 domains (n = 31), or with successful treatment in between the date of returning the survey and the date of data collection from electronic patient record (n = 4), 180 HCV-cured persons and 306 never chronically HCV-infected persons were included in the current analysis. The group never chronically HCV-infected included 43 individuals who had spontaneously cleared HCV.

Compared with never chronically infected persons with hemophilia, cured participants more frequently had severe hemophilia (67% vs. 21%; Table 1), were older (median 57 vs. 53 years), reported more impaired joints (median number of three impaired joints, IQR 1–6, vs. 0, IQR 0–2; median joint impairment score 7, IQR 2–13, vs. 0, IQR 0–2), more often had an occupational disability (16% vs. 4%), and more often had HIV infection (8% vs. 1%). Of the 18 included

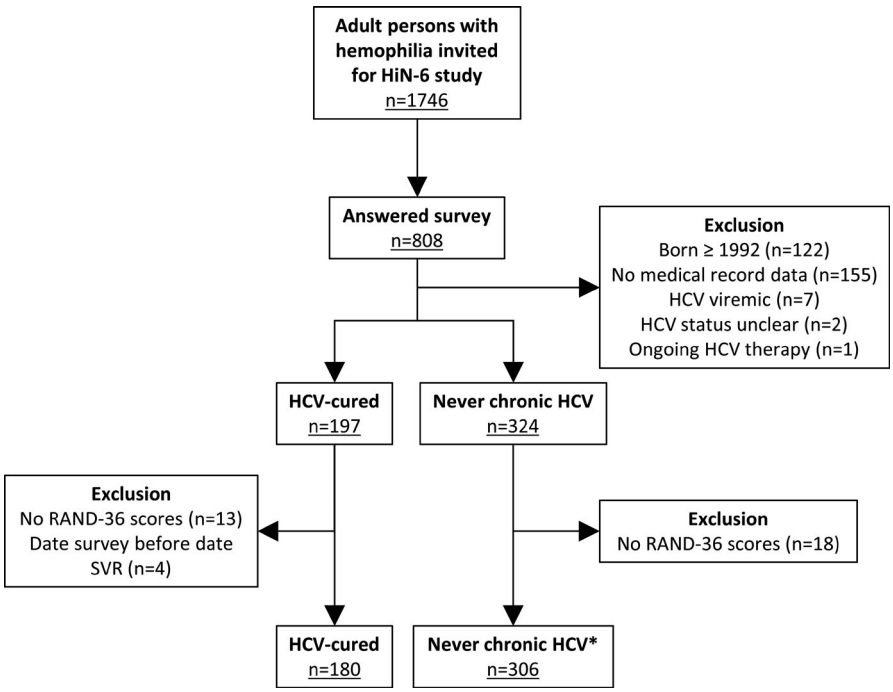

FIGURE 1 Flowchart of participant selection from the sixth Hemophilia in the Netherlands study (HiN-6). HCV, hepatitis C virus; HiN, Hemophilia in the Netherlands. *Including 43 participants with spontaneous clearance of HCV

TABLE 1 Characteristics of included persons with hemophilia

	Never chronic HCV ($n = 306$)	HCV-cured ($n = 180$)
Age (median, IQR)	53 (38–64)	57 (47–63)
Hemophilia A	282 (92%)	149 (83%)
Severity of hemophilia		
Mild	185 (60%)	35 (19%)
Moderate	57 (19%)	25 (14%)
Severe	64 (21%)	120 (67%)
Current use of prophylaxis	65 (21%)	107 (59%)
Joint bleeding in the past 12 months	59 (19%)	91 (51%)
Other bleeding in the past 12 months	94 (31%)	81 (45%)
Self-reported joint impairment score (median, IQR)	0 (0–2)	7 (1–13)
Alcohol use >20 units weekly (self-reported)	12 (4%)	6 (3%)
HIV infection	3 (1%)	15 (8%)
Advanced liver fibrosis or cirrhosis[a]	0	25 (14%)
HCV treatment history		
(PEG)-IFN ± ribavirin	n.a.	135 (75%)
PEG-IFN + DAA + ribavirin	n.a.	11 (6%)
DAA ± ribavirin	n.a.	70 (39%)
Years since SVR (median, IQR)	n.a.	9 (3–15)
SVR more than 5 years ago	n.a.	102 (57%)
Employment		
Currently employed/studying	210 (69%)	94 (52%)
Unemployed	5 (2%)	6 (3%)
Retired	57 (19%)	37 (21%)
Occupational disability	12 (4%)	28 (16%)
Missing/prefer not to say	22 (7%)	15 (8%)
Highest level of education completed		
Primary or lower secondary (ISCED 1/2)	79 (26%)	54 (30%)
Higher secondary (ISCED 3)	95 (31%)	56 (31%)
Bachelor/master or equivalent (ISCED 6/7)	118 (39%)	65 (36%)
Missing/prefer not to say	14 (5%)	5 (3%)

Abbreviations: DAA, direct-acting antivirals; HCV, hepatitis C virus; IQR, interquartile range; ISCED, International Standard Classification of Education; n.a., not applicable; (PEG)-IFN, pegylated-interferon; SVR, sustained virological response.

[a]Fibroscan value of ≥9.5 kPa or history of liver transplantation, hepatocellular carcinoma, or decompensated cirrhosis.

HIV-positive individuals, 17 had an undetectable HIV viral load, whereas one person was not receiving antiretroviral therapy and had a detectable HIV viral load. In the successfully HCV-treated group, 56% was cured with (PEG)-interferon with or without ribavirin between 1994 and 2013, 5% with an interferon-containing DAA regimen between 2012 and 2014, and 39% with interferon-free DAA between 2012 and 2018. Median number of years since successful HCV treatment was 15 (IQR 12–18), 5 (IQR 5–5), and 2 (IQR 2–3) for persons cured with (PEG)-interferon ± ribavirin, an interferon-containing DAA regimen or interferon-free DAA, respectively.

3.2 | Health-related quality of life

3.2.1 | HCV-cured and never chronically HCV-infected persons with hemophilia

HCV-cured persons with hemophilia had lower scores on all eight RAND-36 domains compared with those never chronically HCV-infected (Figure 2). After adjustment for age, severity of hemophilia, self-reported joint impairment score, and HIV status, a decrease in this difference was seen for all domains except emotional well-being and role limitations from emotional problems. Nonetheless, scores remained lower on all RAND-36 domains, with the difference exceeding the MID threshold of 4 points on all domains except for Pain. Largest differences were seen in the domains General health, Role limitations due to physical problems, and Role limitations due to emotional problems. The addition of prophylaxis as an additional confounder did not change the adjusted differences (data not shown).

3.2.2 | Individuals with and without HCV infection sequelae

In total, 41 cured individuals had sequelae of the previous HCV infection, such as advanced liver fibrosis or cirrhosis, self-reported residual symptoms or self-reported ongoing side effects of antiviral treatment. These 41 persons had lower scores on all eight RAND-36 domains than the other 139 HCV-cured individuals who did not have sequelae (Table 2). The 139 participants without HCV infection sequelae still had clinically relevant differences for the domains General health, Role limitations due to physical problems, and Role limitations due to emotional problems compared with never chronically infected individuals (Table 3).

3.2.3 | Persons with hemophilia either HCV-cured or with spontaneous HCV clearance

In the second subanalysis, RAND-36 domain scores were compared between the 43 persons with spontaneous HCV clearance and 180 HCV-cured individuals. Participants with spontaneous HCV clearance had a median age of 56 years (IQR 42–67; Table S1), 51% had severe hemophilia and median joint impairment score was 5 (IQR 0–10). Mean RAND-36 scores of individuals with spontaneous HCV clearance were higher than scores of successfully treated persons, with adjusted differences exceeding the MID threshold on all domains except Pain and Emotional well-being (Figure 3).

RAND-36 domain	Never chronic HCV (n=360) Mean ± SD	HCV-cured (n=180) Mean ± SD	Adjusted difference HCV-cured* Δ	95% CI
General health	67.2 ±20.7	54.1 ±21.8	-7.4	-12.2 – -2.6
Physical functioning	82.9 ±22.8	59.5 ±29.4	-4.4	-8.6 – -0.2
Role physical	81.4 ±33.7	59.1 ±43.1	-10.5	-18.5 – -2.4
Energy/fatigue	67.0 ±16.6	59.8 ±19.2	-4.5	-8.6 – -0.4
Pain	79.6 ±21.7	66.9 ±22.4	-2.7	-7.4 – 2.0
Emotional well-being	79.7 ±14.4	73.8 ±17.8	-5.3	-9.0 – -1.6
Role emotional	89.0 ±26.7	76.6 ±38.0	-9.2	-16.3 – -2.1
Social functioning	86.3 ±19.0	75.9 ±23.1	-5.4	-10.1 – -0.7

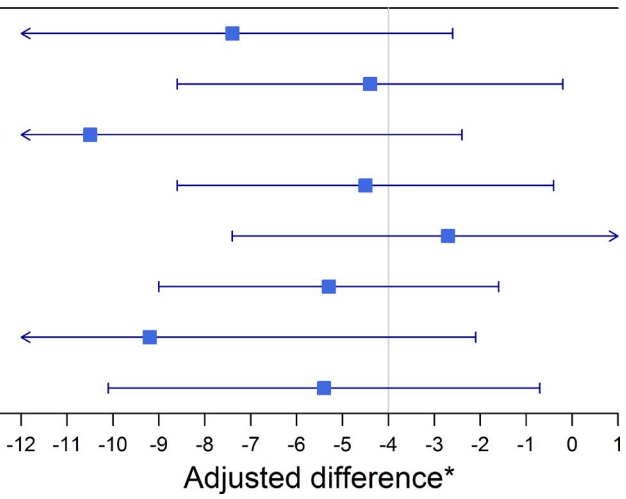

FIGURE 2 Differences in RAND-36 domain scores between HCV-cured persons with hemophilia and persons with hemophilia never chronically HCV infected. The minimally important difference was set at 4 points for all RAND-36 domains. *Adjusted for age, HIV, joint status, and hemophilia severity. CI, confidence interval; HCV, hepatitis C virus; SD, standard deviation

3.2.4 | Persons with hemophilia either HCV cured or never HCV infected

In the third subanalysis, participants with spontaneous HCV clearance were excluded from the never chronically HCV-infected group. The remaining group of HCV antibody-negative persons had mainly mild or moderate hemophilia (84%; Table S2), with a median self-reported joint impairment score of 0 (0–1). Adjusted RAND-36 domain scores were in favor of the HCV antibody-negative group on all eight domains (Table S3).

3.2.5 | Impact of interferon-containing treatment on HRQoL

In the fourth subanalysis, within the HCV-cured group, RAND-36 domain scores were compared between those who ever received (PEG)-interferon ($n = 135$) and those only treated with interferon-free DAA ($n = 44$), whereas one HCV-cured individual was excluded from this analysis as treatment type was unknown. After adjustment for age, HIV, and joint status and hemophilia severity, the only difference was found in the domain Energy/fatigue, with a difference of 4.7 points in favor of those ever treated with interferon (Table 4). Advanced liver fibrosis or cirrhosis was reported in 23% of the DAA group versus 11% of the interferon-experienced group. Additional adjustment for the presence of advanced liver fibrosis or cirrhosis in this subanalysis did not affect differences in domain scores between groups. The effect of time since successful treatment on RAND-36 domain scores was limited, with change in domain score per year since successful treatment ranging between −0.1 and 0.2 (data not shown).

4 | DISCUSSION

The vast majority of HCV-infected persons with hemophilia in the Netherlands has been successfully treated with anti-HCV therapy. Results from our nationwide study demonstrate that despite HCV eradication, previously HCV-infected persons report lower RAND-36 domain scores than individuals never chronically HCV-infected. Domain scores remain lower after adjustment for confounders for all domains except for Pain. Also, after excluding those with HCV-related sequelae, differences remained on the domains General health, Role limitations due to physical problems, and Role limitations due to emotional problems. These results imply that for some persons with hemophilia residual effects of the decades-long chronic HCV infection continue to affect multiple domains of their HRQoL.

There are several possible explanations for our findings. The subgroup of 41 participants with HCV infection sequelae had lower scores on all eight RAND-36 domains compared with the other 139 HCV-cured individuals. This indicates that in persons with hemophilia with advanced fibrosis and cirrhosis or with ongoing symptoms, the previous HCV infection has the largest residual impact on HRQoL. Nevertheless, also after exclusion of this group, differences still remained for the RAND-36 domains General health, Role limitations due to physical problems, and Role limitations due to emotional problems. Indeed, literature from the general population suggests that chronically HCV-infected individuals without advanced liver disease also have a reduced HRQoL.[5] Important factors reported to influence HRQoL of the general HCV population are stigma, fatigue, and psychological issues such as depression and cognitive impairment.[5] Especially because the majority of HCV-infected persons with hemophilia were

TABLE 2 Characteristics and mean RAND-36 domain scores of cured persons with hemophilia, stratified for presence of sequelae of the cured HCV infection[a]

Characteristics	Persons with hemophilia without sequelae ($n = 139$)	Persons with hemophilia with sequelae[a] ($n = 41$)
Age (median, IQR)	55 (46–63)	58 (52–65)
Severe hemophilia	95 (68%)	25 (61%)
Joint impairment score (median, IQR)	6 (2–13)	11 (0–13)
HIV infection	8 (6%)	7 (17%)
Advanced fibrosis or cirrhosis	0	25 (61%)
Employment		
Currently employed/studying	79 (57%)	15 (37%)
Unemployed	5 (4%)	1 (2%)
Retired	26 (19%)	11 (27%)
Occupational disability	17 (12%)	11 (27%)
Missing/prefer not to say	12 (9%)	3 (7%)
RAND-36 domain scores (mean + SD)		
General health	57 ± 21	45 ± 23
Physical functioning	62 ± 29	51 ± 30
Role physical	64 ± 42	43 ± 43
Energy/fatigue	62 ± 18	54 ± 21
Pain	69 ± 22	61 ± 24
Emotional well-being	75 ± 17	69 ± 20
Role emotional	78 ± 38	73 ± 38
Social functioning	79 ± 22	67 ± 25

Abbreviations: HCV, hepatitis C virus; IQR, interquartile range; SD, standard deviation.

[a]Sequelae of the cured HCV infection were defined as either the presence of advanced liver fibrosis or cirrhosis, self-reported residual symptoms of the HCV infection, or continuing self-reported ongoing side effects of previous antiviral therapy.

TABLE 3 Differences in RAND-36 domain scores between HCV-cured persons with hemophilia and persons with hemophilia never chronically HCV infected, stratified for presence or absence of sequelae of the cured HCV infection[a]

	Adjusted difference HCV-cured compared with never chronically infected participants[b] ($n = 180$ vs. $n = 306$)		Adjusted difference excluding participants with sequelae of the cured HCV infection[a,b] ($n = 139$ vs. $n = 306$)	
RAND-36 domain	Δ	95% CI	Δ	95% CI
General health	−7.6	−12.3 to −2.9	−4.5	−9.5 to 0.6
Physical functioning	−4.5	−8.8 to −0.3	−2.0	−6.3 to 2.5
Role physical	−11.3	−19.4 to −3.1	−5.9	−14.3 to 2.6
Energy/fatigue	−5.1	−9.2 to −1.0	−3.2	−7.5 to 1.2
Pain	−3.1	−7.8 to 1.5	−0.8	−5.7 to 4.1
Emotional well-being	−5.4	−9.0 to −1.7	−3.5	−7.4 to 0.3
Role emotional	−9.9	−17.1 to −2.7	−8.6	−16.2 to −0.9
Social functioning	−6.1	−10.8 to −1.4	−3.6	−8.5 to 1.3

Abbreviations: CI, confidence interval; HCV, hepatitis C virus; SD, standard deviation.

[a]Sequelae of the cured HCV infection were defined as either the presence of advanced liver fibrosis or cirrhosis, self-reported residual symptoms of the HCV infection, or continuing self-reported ongoing side effects of previous antiviral therapy.

[b]Adjusted for age, HIV status, joint score, and severity of hemophilia. Minimally important difference was established at a difference of 4 points.

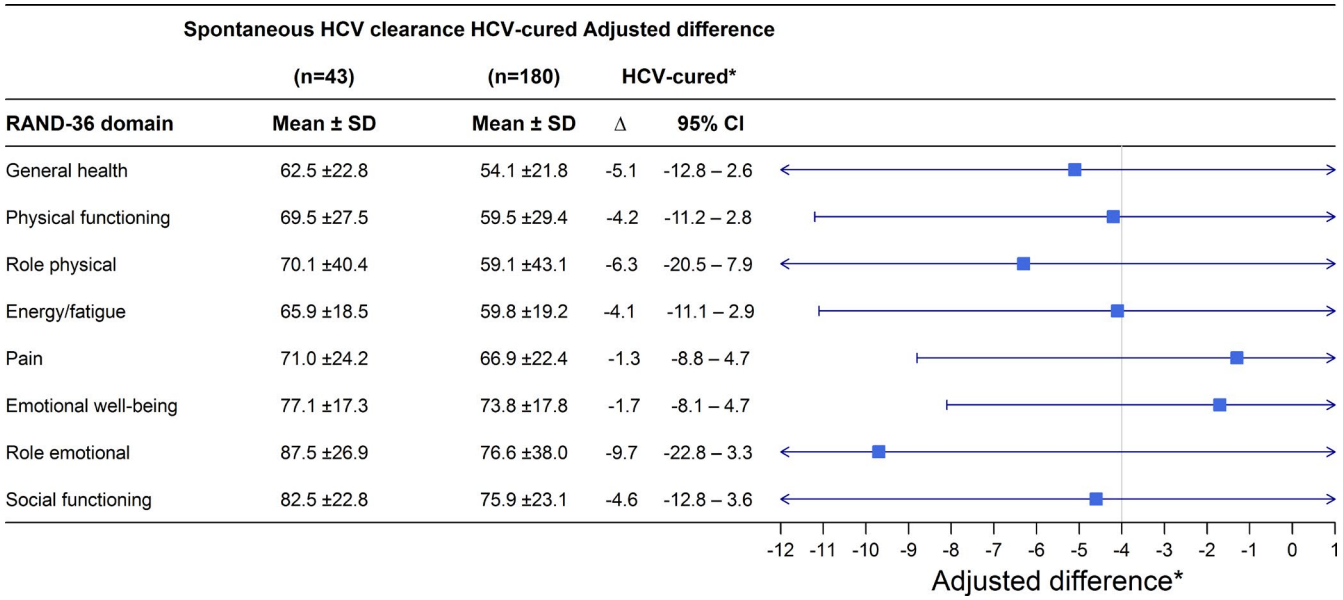

FIGURE 3 Differences in RAND-36 scores between HCV-cured persons with hemophilia and persons with hemophilia with spontaneous HCV clearance. The minimally important difference was set at 4 points for all RAND-36 domains. *Adjusted for age, HIV, joint status. and hemophilia severity. CI, confidence interval; HCV, hepatitis C virus; SD, standard deviation

TABLE 4 Differences in RAND-36 scores between HCV-cured persons with hemophilia with or without interferon treatment experience

	Only DAA treatment ($n = 44$)	(PEG)-Interferon experienced ($n = 135$)[a]	Difference (PEG)-Interferon experienced adjusted[b]		Sensitivity analysis, additional adjustment for presence of advanced fibrosis/cirrhosis	
RAND-36 domain	Mean ± SD	Mean ± SD	Δ	95% CI	Δ	95% CI
General health	52.2 ± 23.8	54.5 ± 21.2	1.0	−7.0 to 8.9	0.4	−7.6 to 8.4
Physical functioning	53.6 ± 29.8	61.5 ± 29.2	1.2	−6.6 to 9.1	0.1	−7.9 to 8.0
Role physical	55.5 ± 43.8	60.7 ± 42.7	−0.5	−15.8 to 14.9	−0.5	−16.1 to 15.0
Energy/fatigue	56.8 ± 20.5	60.9 ± 18.8	4.2	−3.1 to 11.5	4.1	−3.2 to 11.5
Pain	64.0 ± 24.0	68.0 ± 21.9	2.2	−5.5 to 9.9	2.5	−5.3 to 10.2
Emotional well-being	72.4 ± 19.9	74.2 ± 17.2	2.8	−3.8 to 9.4	2.8	−3.9 to 9.4
Role emotional	74.8 ± 40.0	77.2 ± 37.6	1.9	−12.5 to 16.4	1.8	−12.8 to 16.5
Social functioning	73.5 ± 27.6	76.9 ± 21.4	2.5	−6.1 to 11.0	2.2	−6.5 to 10.8

Note: Treatment type was unknown in one of the HCV-cured persons with hemophilia.

Abbreviations: CI, confidence interval; DAA, direct-acting antivirals; HCV, hepatitis C virus; SD, standard deviation.

[a]Including those treated with PEG-Interferon + Boceprevir/Telaprevir and those cured with interferon-free DAA after prior unsuccessful interferon-containing treatment.

[b]Adjusted for age, HIV status, joint score, and severity of hemophilia. Minimally important difference was established at a difference of 4 points.

infected for at least 30 years, some of these factors may continue to affect their HRQoL.

In line with higher frequency of clotting factor administration and inherent higher risk of HCV infection, severe hemophilia and self-reported joint impairment were more frequent in the HCV-cured group compared with the never chronically infected group. Both factors strongly affect HRQoL of persons with hemophilia.[2,3] Although multivariable analysis was used to adjust for the confounding effect of these variables, residual confounding cannot be excluded. Notably, in the subanalysis comparing the cured group with the more comparable group of individuals with spontaneous HCV clearance, differences were still seen for all RAND-36 domains except Pain and Emotional well-being. Therefore, we think that residual confounding alone is insufficient to explain our findings.

To our knowledge, this is the first study on differences in HRQoL between HCV-cured and never chronically HCV-infected persons with hemophilia. In an analysis from the previous HiN study in 2001, persons with hemophilia with ongoing HCV infection were compared with those never infected with HCV.[2] Statistically significant differences between groups in this HiN-5 study were only reported

for the domains General health and Energy/fatigue, whereas we found differences in seven domains. Several factors may explain this. First, as the previous study was conducted in 2001, infection duration was considerably shorter and advanced fibrosis or cirrhosis was less prevalent than in our study population. Second, unlike in the current analysis, the previous analysis also adjusted for employment status. For the current analysis, we regarded employment as an intermediate effect rather than a confounder and therefore chose not to include it in the multivariable analysis. If adjusted for, the only differences in our analysis would have been the domains General health and Role limitations due to emotional problems (data not shown). Finally, differences in domain scores were interpreted differently between both studies (i.e., based on MID in HiN-6 and based on statistical significance in HiN-5).

Whereas interferon-free DAA treatment in general is well-tolerated, interferon-based therapy was notorious for its severe side effects, such as fatigue, headache, hair loss, and depression.[6] Four weeks after cessation of interferon treatment, fatigue, concentration problems, and sleeping problems were still present in >30% of interferon-treated persons with hemophilia. Even suicidal thoughts were not uncommon (reported to be 4%–7% in the general HCV-infected population), although fortunately suicide attempts were rare (0.02%).[20] Nevertheless, although RAND-36 domain scores significantly decreased during interferon treatment in persons with hemophilia, it was reported that scores approached baseline level within 4 weeks after treatment cessation.[6] Furthermore, in a study of HCV patients without hemophilia, RAND-36 scores were similar between patients treated with DAA either with or without interferon at 24 weeks posttreatment.[21]

This is in line with the findings from our study, with similar RAND-36 domain scores for those ever receiving interferon and those only receiving DAA. In fact, the only difference was in favor of the interferon group, and was found on the Energy/fatigue domain. This difference could have been caused by the selection of patients for interferon therapy because mental and social stability were prerequisites for interferon therapy by random variation because of the relatively small numbers in this subanalysis, or because of a lower prevalence of liver fibrosis in the interferon group (although adjusting for this presence in a sensitivity analysis did not affect results). We did not find evidence for an effect of time since successful treatment on any of the RAND-36 domains within the HCV-cured group. Yet, as residual side effects of previous interferon treatment were reported in our study by 6% of HCV-cured individuals ever receiving interferon, the negative impact of previous interferon treatment on the individual level should not be disregarded. Therefore, negative side effects of interferon treatment on an individual patient level should be monitored by treating physicians.

4.1 | Strengths and limitations

To our knowledge, our study is the largest study reporting HRQoL of persons with hemophilia successfully treated for chronic HCV infection, with our sample representing a large portion of persons with hemophilia in the Netherlands. Data on severity of hemophilia and HCV status were extracted from medical records, reducing the risk of misclassification compared with self-reported data. Nevertheless, our study has several limitations. As previously discussed, patient characteristics such as hemophilia severity and joint impairment differed considerably between both groups, and despite multivariable analysis, residual confounding cannot be excluded. Furthermore, although all persons with hemophilia known in the Netherlands were invited for the study, only 653 (37%) adults completed the survey and approved data collection from medical records. In the 486 participants included in the current analysis, 99% was aged >26 years, compared with 67% in the general hemophilia population in the Netherlands.[22] Furthermore, the number of individuals with severe hemophilia in our analysis was slightly lower than in the general Dutch hemophilia population (38% and 54%).[22] Also, the number of participants with a history of (decompensated) cirrhosis or hepatocellular carcinoma was six (3%), which is smaller than expected based on natural history of HCV[14] and potentially indicates a selection of more healthy subjects in our sample. Furthermore, the interpretation of results depends on the used definition of the MID threshold. The threshold of 4 points was the average of the 3- to 5-point range that is often used for the MID,[18] and comparable to the MID of 4.2 that was set by an expert panel to estimate the MID of the RAND-36 domain Energy/fatigue in HCV.[5] In addition, we were not allowed to collect data on race or ethnicity, which would improve interpretation of our findings relative to other populations. Because we used the Dutch version of the SF-36 questionnaire, the response rate was likely lower among persons with hemophilia with poor Dutch language skills. We did report other social determinants of HRQoL (i.e., employment and educational status). Finally, the number of included participants with HIV/HCV coinfection or HIV monoinfection was small. Therefore, it is uncertain to what extent our results apply to HIV-infected individuals.

4.2 | Clinical implications and further research

Our study results emphasize that persons with hemophilia with a history of chronic HCV infection may have limitations on several domains of the RAND-36. We suggest that all HCV-cured persons with hemophilia are screened for the need of extra medical and psychosocial support, with special focus on individuals with HCV infection sequelae, such as advanced fibrosis or cirrhosis. Among patients with liver cirrhosis in the general population, poor social support is associated with decreased HRQoL.[23] To more specifically assess the needs of persons with hemophilia with an affected HRQoL following their cured HCV infection, future research that could be of value would be an in-depth qualitative analysis of HRQoL limitations in these persons.

5 | CONCLUSION

Complete HCV elimination among persons with hemophilia in the Netherlands is within reach. However, even after successful HCV

treatment, the RAND-36 domain scores of HCV cured persons with hemophilia remain lower than scores of those never chronically HCV infected. Compared with never HCV-infected individuals, the largest differences in domain scores were seen in HCV-cured individuals with cirrhosis or self-reported residual symptoms and on the domains General health, Role limitations due to physical, and Role limitations due to emotional problems. Although the differences in characteristics between HCV-cured and never chronically HCV-infected participants preclude any definitive conclusions, our results could imply that residual effects of a cured HCV infection still impact physical, mental, or social quality of life domains in some persons with hemophilia and careful medical and psychosocial follow-up and support for these individuals is indicated.

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SUPPORTING INFORMATION

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