



Universiteit
Leiden

The Netherlands

Developments in modern hemophilia care

Hassan, S.

Citation

Hassan, S. (2023, January 24). *Developments in modern hemophilia care*. Retrieved from <https://hdl.handle.net/1887/3513307>

Version: Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/3513307>

Note: To cite this publication please use the final published version (if applicable).

Chapter 3

Mortality, life expectancy and causes of death of persons with hemophilia in the Netherlands 2001-2018

Shermarke Hassan, Rory C. Monahan, Evelien P. Mauser-Bunschoten, Lize F.D. van Vulpen, Jeroen Eikenboom, Erik A.M. Beckers, Louise Hooimeijer, Paula F. Ypma, Laurens Nieuwenhuizen, Michiel Coppens, Saskia E.M. Schols, Frank W.G. Leebeek, Cees Smit, Mariëtte H. Driessens, Saskia le Cessie, Erna C. van Balen, Frits R. Rosendaal, Johanna G. van der Bom, Samantha C. Gouw

Journal of Thrombosis and Haemostasis. 2021;19(3):645-653

Summary

Background

Treatment of patients with hemophilia has advanced over the past decades, but it is unknown whether this has resulted in a normal life expectancy in the Netherlands.

Objective

This observational cohort study aimed to assess all-cause and cause-specific mortality in patients with hemophilia in the Netherlands between 2001-2018 and to compare mortality and life-expectancy with previous survival assessments from 1973 onwards.

Methods

All 1066 patients with hemophilia who participated in a nationwide survey in 2001 were followed until July 2018.

Results

Information on 1031 individuals (97%) was available, of whom 142 (14%) deceased during follow-up. Compared with the general Dutch male population, mortality of patients with hemophilia was still increased (standardized mortality ratio: 1.4, 95% confidence interval: 1.2-1.7). Intracranial bleeding and malignancies were the most common causes of death. Estimated median life expectancy of patients with hemophilia was 77 years, six years lower than the median life expectancy of the general Dutch male population (83 years). Over the past 45 years, death rates of patients with hemophilia have consistently decreased, approaching the survival experience of the general population. Over the past decades, mortality due to human immunodeficiency virus and hepatitis C virus infections has decreased, death due to intracranial hemorrhages has increased and death due to ischemic heart disease has remained consistently low over time.

Conclusions

Survival in patients with hemophilia in the Netherlands has improved over time but is still lower than that of the general population.

Introduction

Hemophilia is a hereditary disease caused by a deficiency of clotting factor VIII or IX. The introduction of clotting factor concentrates in the 1970s¹⁻³ and other improvements such as prophylactic treatment, home treatment and low dose immune tolerance drastically improved life expectancy of patients.²

Unfortunately, exposure to human immunodeficiency virus (HIV) and hepatitis C virus (HCV) through contaminated blood products in the 1980s led to a sharp increase in mortality.⁴⁻¹⁰ Through the use of viral inactivation techniques, the transmission of both HIV and HCV has been halted since 1992.² From 1999 onwards, hemophilia treatment in the Netherlands was gradually centralized and quality criteria were introduced for the comprehensive hemophilia treatment centers.¹¹ In addition, dosages for prophylactic treatment have steadily increased since the 1970s.¹² It is still insufficiently known whether these treatment advances have resulted in a completely normalized life expectancy in the Netherlands.

This observational cohort study aimed to evaluate all-cause and cause-specific mortality in patients with hemophilia in the Netherlands from 2001 to 2018 and to compare mortality and life-expectancy over the past 45 years. In addition, we investigated potential determinants of mortality of patients with hemophilia during this period.

Methods

Study design

This was an observational cohort study following patients from 1973-2018. From 1973-2001, three cohort studies evaluated mortality of patients with hemophilia in the Netherlands.^{9, 10, 13} The studies were performed from Jan 1st 1973 to Jan 1st 1986 (the 1973-1986 cohort); Jan 2nd 1986 to May 31st 1992 (the 1986-1992 cohort); and June 1st 1992 to June 30th 2001 (the 1992-2001 cohort). The current study followed patients who participated in a nationwide survey from July 1st 2001 to July 1st 2018. An invitation to participate in the survey was sent to all 1567 known patients with hemophilia via their hemophilia physician or the Netherlands Hemophilia Patient Society. In total, 1066 patients (68%) completed the survey.⁹ The present study was approved in 2018 by the Committee of Medical Ethics of the Leiden University Medical Center.

Patient characteristics at inclusion

All male patients with mild, moderately severe and severe hemophilia A and B who participated in the 2001 survey were included. The following self-reported information, obtained from the 2001 patient survey, was collected at baseline; date of birth, hemophilia severity, HIV status and HCV status. If the self-reported data on HIV or HCV was missing, it was obtained from the medical files.

Hemophilia severity was categorized as severe (< 0.01 IU/mL), moderate ($0.01 - 0.05$ IU/mL) or mild ($> 0.05 - 0.40$ IU/mL). Information on hemophilia severity and type were verified from the medical files. Patients born after 1985 or who reported no treatment with clotting factor between 1979-1985 were considered to be HIV-negative. Patients born after 1992 or who reported no treatment with clotting factor before 1992 were considered to be HCV-negative. If HIV/HCV status was missing, the information was obtained from the medical files. HCV status was categorized as “never infected with HCV”, “HCV infection cleared” and “chronic hepatitis C”. As a double-check, HCV status as reported by the patients was compared with HCV status from the medical files for a random sample of patients ($N = 92$).

Follow-up and outcomes

Patients were followed from July 1st 2001 until July 1st 2018 or until their last known hospital visit. Date of death and cause of death were obtained from the medical files. The primary cause of death, as written on the death certificate was not directly available, but the same information was also reported in the patients’ medical file at the time of death. Causes of death were then manually classified according to the 10th revision of the International Classification of Injuries, Diseases and causes of Death-10 (ICD-10).¹⁴ All-cause mortality, cause-specific mortality and life expectancy of the general male population of the Netherlands for the years 1973-2017 retrieved from the Dutch Central Bureau of Statistics (CBS).¹⁵

All-cause mortality, cause-specific mortality and life expectancy

The standardized mortality ratio (SMR) is a measure of the change in mortality in a given population, with respect to a reference population. SMRs were calculated for the years 2001-2018 to estimate the risk of all-cause and cause-specific death among patients compared to the general male population, while adjusting for the age distributions of the two populations. The SMR is calculated by dividing the observed number of deaths in a study population, by the expected number of deaths in the study population (which is based on the age distribution of the study population and the age-specific death rates of the general male population). When calculating

cause-specific SMRs, other causes of death were censored. To assess all-cause and cause-specific death rates over time, we calculated crude death rates for the current and previous cohort studies, stratified by 15-year age categories.

The median life expectancy at birth for the 2001-2018 cohort was calculated from a life-time survival curve using age as the time scale. To calculate median life expectancy, patients had to survive until the start of the study observation period (2001). A standard analysis of the data would have induced a type of bias, which is sometimes called length bias.¹⁶ To correct for this problem, we adjusted for left truncation, i.e. patients were included in the analysis from the start of the study observation period instead of their date of birth. Median life expectancy was defined as the age at which cumulative survival was 50%. To assess changes in median life expectancy over time, information on median life expectancy for the previous cohort studies was obtained from previously published data.^{9, 10, 13}

Potential determinants of mortality

Crude and adjusted associations between hemophilia severity/HIV status/HCV status and mortality were assessed with the Cox proportional hazards model, in the standard way, using time on study as the time-scale and with patients being included in the risk-set of the model from the time of study entry (2001). Participants with missing values were excluded from the analysis.

Sensitivity analysis

Severely ill patients may not have participated in the 2001 survey, which could have led to an underestimation of death rates during follow-up. We examined a possible 'healthy cohort effect' by performing a sensitivity analysis where we excluded the first three years of follow-up.

Data sharing statement

For original data, please contact S.C.Gouw@lumc.nl.

Results

Patient characteristics

In the current cohort study we included 1031 out of 1066 (97%) patients with available data. Thirty-five patients with missing follow up data were excluded. Eighty-seven percent of patients had hemophilia A and 13% had hemophilia B (*Table 1*). In total, 412 patients (40%) suffered from severe hemophilia, 175 (17%) from moderate

Table 1. Patient characteristics at baseline (2001)

Baseline variable	N = 1031
Age in years	
Mean (SD, min-max)	33.9 (20.5, 0.1-89.3)
Severity of disease (n, %)	
Severe	412 (40)
Moderate	175 (17)
Mild	444 (43)
Type of hemophilia (n, %)	
Hemophilia A	893 (87)
Hemophilia B	138 (13)
Severity of disease, hemophilia A (n, %)	
Severe	351 (39)
Moderate	154 (17)
Mild	388 (43)
Severity of disease, hemophilia B (n, %)	
Severe	61 (44)
Moderate	21 (15)
Mild	56 (41)
HIV infection (n, %)	
No (in 2001)	984 (95)
Yes (in 2001)	29 (3)
Unknown	18 (2)
HCV infection (n, %)	
Never infected with HCV (in 2001)	581 (56)
HCV infection cleared (in 2001)	96 (9)
Chronic hepatitis C (in 2001)	336 (33)
Unknown	18 (2)

hemophilia and 444 (43%) from mild hemophilia. In 2001, 29 patients were known to be infected with HIV (3%) and 336 patients had chronic hepatitis C (33%).

In the random sample of 92 patients of whom HCV status was verified from medical records, 92% (85/92) accurately reported their hepatitis C status. Stratified by HCV status, 93%, 75% and 100% correctly reported their HCV status in patients with chronic HCV, patients who previously cleared the virus, and patients who were never infected, respectively. Median follow-up time was 17.0 years (min-max: 0.3-17.4) and

the mean age at baseline was 33.9 years (SD: 20.5, min-max: 0.1-89.3) in 2001. For comparison, the mean age of the Dutch male population in 2001 was 37.1 years. The age distribution of the study population and the general male population in the Netherlands in 2001 is presented in *Supplemental Figure 1*. The total number of deaths per age group in the study population is presented in *Supplemental Figure 2*.

All-cause mortality

In total, 142 patients died during follow-up (14%) at a median age of 69.8 years (min-max: 16.4-98.0). A life-time survival curve for the study cohort is presented in

Figure 1. Life-time survival curve for 2001-2018 cohort.

Legend: The figure shows the survival curve for patients with mild, moderate and severe hemophilia, using age as the timescale. The cumulative probability of survival is shown on the Y-axis, the age in years is shown on the X-axis.

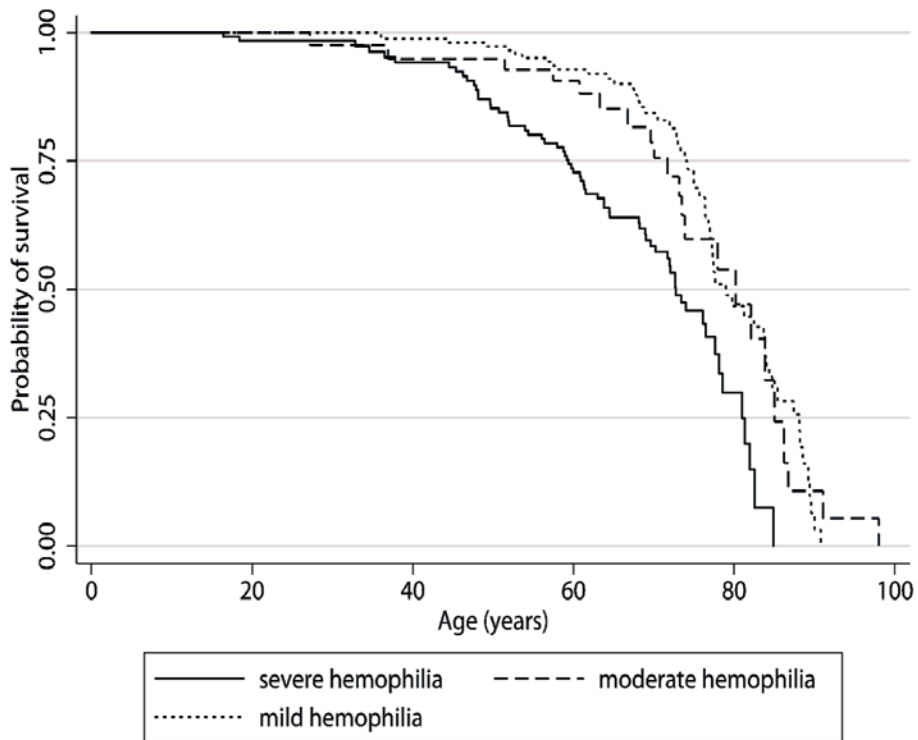


Figure 1. The overall crude death rate was 8.9 deaths per 1000 person-years. The crude death rate in the general male population was 8.2 per 1000 person-years in the period 2001-2017. Overall, age-standardized mortality in patients with hemophilia was 40% higher compared with the general male population (SMR 1.4, 95% CI 1.2-1.7) (*Table 2*). Crude death rates for the period 1973-2018, stratified by age are presented as a graph (*Figure 2*) and as a table (*Table 3*). Overall, crude death rates followed a decreasing trend for all age-categories. For the period 1973-2018, crude death rates changed from 0.7 to 0 deaths per 1000 person years for persons aged 0-14 years, 2.4 to 0.8 deaths per 1000 person years for persons aged 15-29 years, 4.7 to 2.3 deaths per 1000 person years for persons aged 30-44 years, 13.8 to 19.4 and then to 8.1 deaths per 1000 person years for persons aged 45-59 years and 57.9 to 33.7 deaths per 1000 person years for persons aged 60 years and older.

Cause-specific mortality

From 2001-2018, frequent causes of death were non-hepatic malignancies (26%) and intracranial bleeding (14%). AIDS (2%), chronic liver disease (7%), and hepatocellular carcinoma (7%) were less frequent causes of death. (*Table 2*)

Table 2. All-cause and cause-specific Standardized Mortality Ratios (SMR) in patients with hemophilia from the Netherlands between 2001-2018.

Cause of death	N*(%)	SMR (95% CI) [†]
All-cause mortality	142 (100)	1.4 (1.2 - 1.7)
AIDS	3 (2)	27.9 (5.8 - 81.6)
Hepatocellular carcinoma	10 (7)	13.2 (6.3 - 24.2)
Chronic liver disease	10 (7)	9.1 (4.3 - 16.6)
Ischemic heart disease	3 (2)	0.3 (0.1 - 0.9)
Ischemic stroke	1 (1)	1.1 (0.03 - 6.0)
Intracranial bleeding	20 (14)	12.8 (7.8 - 19.8)
Malignancies (non-hepatic)	37 (26)	1.0 (0.7 - 1.4)
All other causes [‡]	33 (23)	not applicable
Unknown	25 (18)	not applicable

* Number of deaths.

[†] Standardized mortality ratio, ratio of the observed and expected number of deaths and 95% confidence intervals.

[‡] bacterial infections (11), gastrointestinal bleeding, intra-abdominal bleeding or pericardial bleeding (6), sudden cardiac death (5), trauma (3), chronic heart failure (2), suicide/substance abuse (3) or other causes (3).

In comparison with the general male population, mortality due to AIDS (SMR 27.9, 95% CI 5.8-81.6) and due to HCV infection (SMR 13.2, 95% CI 6.3-24.2 for hepatocellular carcinoma, SMR 9.1, 95% CI 4.3-16.6 for chronic liver disease) were increased (*Table 2*). In addition, mortality due to intracranial bleeding was increased (SMR 12.8, 95% CI 7.8-19.8). Mortality due to ischemic heart disease was decreased (SMR 0.3, 95% CI 0.1-0.9) while mortality due to ischemic stroke was similar (SMR 1.1, 95%CI 0.03-6.0) compared with the general male population. Lastly, mortality due to non-hepatic malignancies was also similar to that of the general male population (SMR 1.0, 95%CI 0.7-1.4).

Cause-specific crude death rates over the past 45 years are presented in *Table 4*. Mortality due to AIDS was first reported in the period 1986-1992, reaching its peak in the period 1992-2001, and decreased thereafter. A similar pattern is seen for chronic liver disease, although the decrease in mortality after 2001 is less pronounced. Mortality due to ischemic heart disease was low in all cohorts between 1973-2018.

Table 3. Deaths, person-time and death rates for different age categories, stratified by study cohort.

Age category	1973-1986			1986-1992			1992-2001			2001-2018		
	n*	PY [†]	death rate [‡]	n*	PY [†]	death rate [‡]	n*	PY [†]	death rate [‡]	n*	PY [†]	death rate [‡]
0-14	1	1530	0.7	0	873	0	0	452	0	0	1920	0
15-29	7	2978	2.4	6	1887	3.2	1	995	1.0	3	3630	0.8
30-44	9	1906	4.7	10	1797	5.6	8	1246	6.4	8	3424	2.3
45-59	11	799	13.8	8	839	9.5	18	929	19.4	33	4075	8.1
60+	15	259	57.9	21	372	56.5	16	466	34.3	98	2906	33.7

* N: deaths; [†]PY: person-years; [‡]crude death rate per 1000 person-years

Table 4. Cause-specific crude death rates (per 1000 person-years) over time.

Cause of death	1973-1986 (N = 717) (PY* = 7788)		1986-1992 (N = 919) (PY* = 5753)		1992-2001 (N = 967) (PY* = 8868)		2001-2018 (N = 1066) (PY* = 15909)	
	n [†]	death rate [‡]	n [†]	death rate [‡]	n [†]	death rate [‡]	n [†]	death rate [‡]
AIDS	0	0	12	2.09	24	2.71	3	0.19
Hepatocellular carcinoma	NR	NR	NR	NR	5	0.56	10	0.63
Chronic liver disease	0	0	5	0.87	10	1.13	10	0.63
Ischemic heart disease	1	0.13	0	0	6	0.68	3	0.19
Ischemic stroke	3	0.39	0	0	0	0	1	0.06
Intracranial bleed	3	0.39	9	1.56	4	0.45	20	1.26
Non-hepatic malignancies	13	1.67	7	1.22	12	1.35	37	2.33

* PY: person-years, [†]n: number of deaths, [‡]death rate per 1000 person-years, NR: not reported in original publication

Median life-expectancy

Median life-expectancy from 1973-2018 is presented in *Figure 3* and additional information on the number of deaths/total person-time is presented in *Table 5*. Median life expectancy of the cohort increased from 66 years in 1973-1986 to 77 years in 2001-2018, a gain of 11 years. In comparison, median life expectancy of the general male population increased from 79 years to 83 years during the same timeframe. (a gain of 4 years) For the 2001-2018 cohort, median life expectancy of patients with severe hemophilia was 73 years (SMR 2.4, 95% CI 1.8-3.0), whereas median life expectancy was 80 years for patients with moderate hemophilia (SMR 1.1, 95%CI 0.7-1.7) and 79 years for patients with mild hemophilia (SMR 1.0, 95%CI 0.8-1.4). Although patients with severe hemophilia had the lowest median life expectancy they also showed the biggest gains after 2001 (59 years in the 1992-2001 cohort vs 73 years in the 2001-2018 cohort).

Potential determinants of mortality

Compared with patients with mild hemophilia, mortality in patients with severe hemophilia was 80% higher (adjusted HR 1.78, 95%CI: 1.08-2.94) (*table 6*). Twenty-nine patients were HIV positive in 2001, 8 patients died during follow-up. Three patients died due to AIDS-related complications, 2 patients died due to HCV-related complications and 3 patients died due to other causes. Compared with HIV-negative patients, mortality among HIV-positive patients was increased (adjusted HR 2.65, 95%CI:

1.26-5.58). (Table 6) In total, 336 patients were HCV positive in 2001. Compared with HCV-negative patients, mortality among HCV-positive patients was slightly increased (adjusted HR 1.25, 95%CI: 0.85-1.83). (Table 6)

Sensitivity analysis

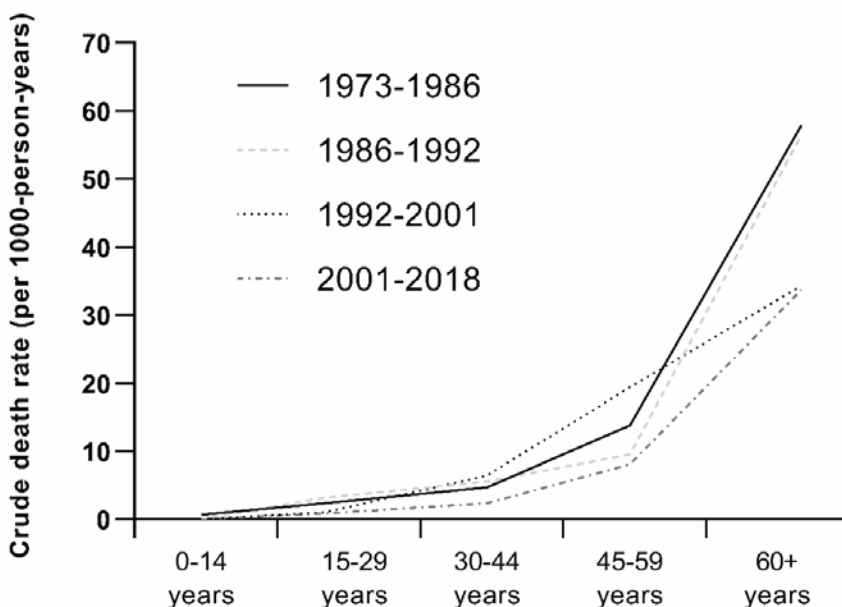
The sensitivity analysis excluding the first three years of follow-up yielded similar results as the overall analysis (Supplementary table 1).

Discussion

From 1973-2019, life expectancy slowly increased, except for the period 1986-2001 (which coincides with the HIV/HCV epidemic). This temporary dip in life expectancy

Figure 2. Crude death rates over time.

Legend: The line-chart shows the crude death rates (per 1000 person-years) for different age categories, stratified by study cohort. The accompanying table (Table 3) shows the total number of deaths, total person-time, and resulting death rate for different age categories, stratified by study cohort.



was, as expected, strongest in patients with severe hemophilia (who were most exposed to clotting factor products). Overall, the life expectancy of patients with hemophilia increased by 11 years vs. 4 years for the general male population. The differences in mortality rates between time-periods were most pronounced in the older age groups. (*Figure 2*) This was most likely simply due to the high baseline risk of dying in older patients. However, mortality is still increased when compared with the general male population.

The cause of the decrease in mortality is most likely a combination of two main factors; namely the increased prophylactic dosages and the decrease in HCV- and HIV-related deaths over time. Evidence from the literature shows that integrated care most likely also decreases mortality.¹⁷ We hypothesized that this would also be the case in our study, however, it was impossible to estimate the effect of integrated care on mortality directly as there were no patients that were treated outside of this care model in our study. (i.e. there was no control group to compare against our care model)

Our findings are in line with a study among Italian patients with hemophilia, which showed a similar decrease over time (SMR 2.0 95%CI 1.5-2.5 from 1990-1999, SMR 1.1 95%CI 0.8-1.4 from 2000-2007).¹⁸ A study among Brazilian patients of the period 2000-2014 reported a SMR of 1.13 (95% CI: 1.01-1.16), the same outcome as that of the 2000-2007 Italian cohort.¹⁹ However, it should be noted, that SMRs from different populations cannot be compared directly when the reference populations are not the same.²⁰ Compared to the Italian cohort, a similar HCV-related death rate (1.12 deaths per 1000 person-years) and a higher HIV-related death rate (0.84 deaths per 1000 person-years) than in our study was reported.¹⁸

In our study, 20 out of 142 patients died due to intracranial bleeding (14% of total deaths), a thirteen-fold increase compared to the general male population. The proportion of patients that died due to intracranial bleeding was similar for patients with severe hemophilia (2.4%, 95%CI 1.2-4.5) and mild hemophilia (2.0%, 95%CI 1.0-3.9). A European/Australian cohort study that followed 2709 non-severe hemophilia A patients who were treated with factor VIII from 1996-2010 reported a 3.5 fold increased risk (95%CI 2.0-5.8), compared with the general population.²¹ As only patients with non-severe hemophilia were included, the lower mortality risk seems plausible. A recent retrospective study from Brazil based on mortality data from the entire male population for the period 2001-2014 found more similar results, as 137 out of 784 deaths in this cohort (17.5%, 95%CI 14.9-20.3) were due to intracranial bleeding.¹⁹ Intracranial hemorrhages in neonates are a known complication of

hemophilia²²⁻²⁴, but these patients were not included in our study. In our population, median age at death from intracranial bleed was similar to other causes (67 vs. 68 years). Further studies are needed to mitigate the risk for intracranial bleeding.

Hemophilia potentially complicates treatment of age-related conditions such as malignancies and ischemic heart disease, which are becoming more common as the population ages.²⁵⁻²⁹ For example, patients with a malignancy may need additional hemostatic replacement during surgical interventions or after chemotherapy-induced thrombocytopenia. Bleeding symptoms will also develop at an earlier stage in patients with gastro-intestinal malignancies.³⁰ In our cohort, the incidence of deaths due to non-hepatic malignancies is now similar to that of the Dutch male population. This is most likely due to the fact that patients are living longer, and due to less hemophilia-related deaths like bleeding-related complications or HCV/HCV.

Based on the literature, it seems that patients with hemophilia have an unfavorable cardiovascular risk profile, compared to the general population.^{31, 32} In our cohort, the mortality due to ischemic heart disease was lower than in the general population, which is also in line with literature.³⁰ The low clotting factor levels may hinder

Figure 3. Median life expectancy in patients with hemophilia in the Netherlands between 1973-2018.

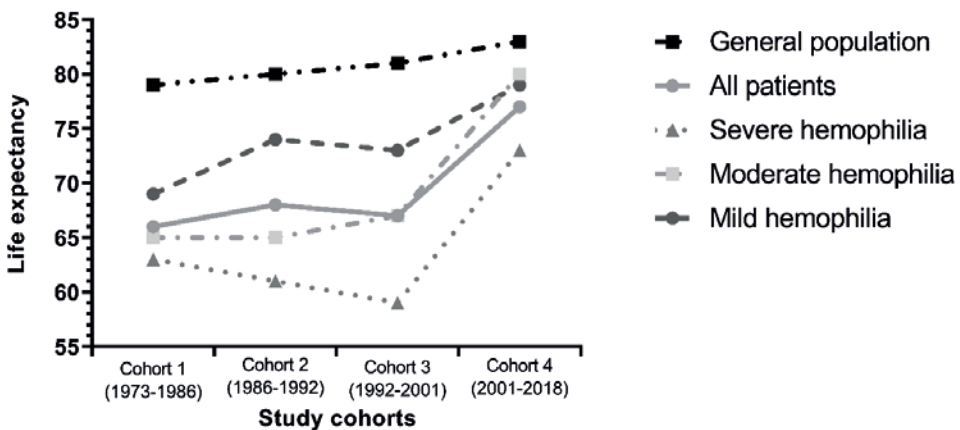


Table 5. The number of deaths and total person-time for each study cohort, stratified by severity.

	1973-1986		1986-1992		1992-2001		2001-2018	
	deaths	PY*	deaths	PY*	deaths	PY*	deaths	PY*
All patients	43	7776	45	5753	94	8314	142	15909
Severe hemophilia	20	3649	19	2396	47	3259	65	6406
Moderate hemophilia	10	1861	11	1070	15	1454	22	2683
Mild hemophilia	13	2266	15	2287	32	3600	55	6819

* PY: person-years

thrombus formation at the site of plaque rupture.³³ The optimal evidence-based anti-platelet/anti-coagulant therapy to reduce thrombotic risk as well as bleeding risk has not yet been identified.³⁰

Hemophilia severity, HIV status and HCV status were independently associated with mortality. Compared to HCV-negative patients, the increased risk of mortality for HCV-positive patients was relatively minor. This is probably because the vast majority of patients were successfully treated with either (peg)interferon-based treatment and/or the newer direct acting antivirals. Pre-treatment severity of fibrosis is strongly associated with mortality after successful treatment.³⁴ As information on the extent of liver damage was not available, we were not able to assess this in our dataset.

Our study has several strengths. Firstly, due to the availability of data from 1972 onwards we could study trends in mortality during the last 45 years. Secondly, this study included the majority of patients with hemophilia in the Netherlands, with little loss-to-follow-up (3%) during the period 2001-2018. Our study also has limitations. Other important determinants of mortality such as inhibitor status, immune tolerance induction, bleeding phenotype, joint status and prophylaxis were not assessed. Lastly, as we were not able to collect information on all possible confounding factors (such as bleeding phenotype, treatment adherence, the level of cirrhosis, inhibitor status, prophylaxis etc.) some residual confounding may still exist. In our cohort, we only reported the combined results for hemophilia A and B. However, some retrospective studies have reported that patients with hemophilia B have a milder phenotype, but this has not been confirmed in subsequent studies.³⁵

Table 6. Mortality rates and hazard ratios, according to HIV status and HCV status in 2001-2018.

Group	N	Deaths (%)	PY*	Crude rate (per 1000 PY*)	Crude hazard ratios (95%CI)	Adjusted hazard ratios (95%CI)
Overall	1031	142 (13.8)	15909	8.9	-	-
Mild	444	55 (12.4)	6819	8.1	ref	ref
Moderate	175	22 (12.6)	2683	8.2	1.00 (0.61-1.64)	1.24 (0.63-2.44) [†]
Severe	412	65 (15.8)	6406	10.2	1.28 (0.89-1.83)	1.78 (1.08-2.94) [†]
¶ HIV -	984	127 (12.9)	15260	8.3	ref	ref
¶ HIV +	29	8 (27.6)	415	19.3	2.33 (1.14-4.76)	2.65 (1.26-5.58) [‡]
# HCV -	677	61 (9.0)	10652	5.7	ref	ref
# HCV +	336	74 (22.0)	4997	14.8	2.58 (1.84-3.62)	1.25 (0.85-1.83) [§]

* Person years.

† Adjusted for age.

‡ Adjusted for age, HCV status and hemophilia severity.

§ Adjusted for age, HIV status and hemophilia severity.

¶ HIV status was unknown in 18 patients.

HCV status was unknown in 18 patients.

Also, there were only 29 patients with HIV, with only 3 deaths due to AIDS. However, the incidence of AIDS in the general population was far lower, resulting in a very high SMR of 27.9 (95CI: 5.8-81.6). Due to the small sample size, the estimate of the SMR is not very precise (hence the wide confidence intervals around the estimate). Furthermore, as some information was self-reported, there was a risk of misclassification bias. To reduce this bias, hemophilia type, severity and HCV status were checked from the medical files. In the case of HCV status, this was done for a random sample of patients (N = 92). Results showed that the self-reported HCV status was correct in most cases (92%). Furthermore, life expectancy estimates should be interpreted with caution as these are always future projections based on current trends. It is expected that age-specific mortality rates will further decrease over time (despite the current transient effect of the COVID-19 epidemic on mortality) due to improvements in health care and novel treatment options. For example, direct-acting antivirals that are used to treat HCV have an almost 100% success rate.³⁶ Furthermore, compared

to treatment with clotting factor products, novel non-gene therapy options such as emicizumab offer better bleeding management (especially for patients with an inhibitor) and possibly a better safety profile as well.³⁷

Conclusion

A decrease in mortality and an increase in life expectancy in patients with hemophilia in the Netherlands over the period 1973-2018 was seen. However, survival is still lower than that of the general population and warrants further improvements in hemophilia care.

Acknowledgements

We thank all participants and Dutch hemophilia treatment centers for their participation.

References

1. Larsson SA. Life expectancy of Swedish haemophiliacs, 1831-1980. *Br J Haematol*. Apr 1985;59(4):593-602.
2. Franchini M, Mannucci PM. The history of hemophilia. *Semin Thromb Hemost*. Jul 2014;40(5):571-6. doi:10.1055/s-0034-1381232
3. Mannucci PM. Hemophilia: treatment options in the twenty-first century. *J Thromb Haemost*. Jul 2003;1(7):1349-55.
4. Centres for Disease Control and Prevention (CDC). pneumocystis carinii pneumonia among persons with hemophilia A. *MMWR Morb Mortal Wkly Rep*. Jul 16 1982;31(27):365-7.
5. Centres for Disease Control and Prevention (CDC). Update on acquired immune deficiency syndrome (AIDS) among patients with hemophilia A. *MMWR Morb Mortal Wkly Rep*. Dec 10 1982;31(48):644-6, 652.
6. Biggs R. Jaundice and antibodies directed against factors 8 and 9 in patients treated for haemophilia or Christmas disease in the United Kingdom. *Br J Haematol*. Mar 1974;26(3):313-29.
7. Darby SC, Ewart DW, Giangrande PL, et al. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. UK Haemophilia Centre Directors' Organisation. *Lancet*. Nov 15 1997;350(9089):1425-31.
8. Eyster ME, Schaefer JH, Ragni MV, et al. Changing causes of death in Pennsylvania's hemophiliacs 1976 to 1991: impact of liver disease and acquired immunodeficiency syndrome. *Blood*. May 1 1992;79(9):2494-5.
9. Plug I, Van Der Bom JG, Peters M, et al. Mortality and causes of death in patients with hemophilia, 1992-2001: a prospective cohort study. *J Thromb Haemost*. Mar 2006;4(3):510-6. doi:10.1111/j.1538-7836.2006.01808.x
10. Triemstra M, Rosendaal FR, Smit C, Van der Ploeg HM, Briet E. Mortality in patients with hemophilia. Changes in a Dutch population from 1986 to 1992 and 1973 to 1986. *Ann Intern Med*. Dec 1 1995;123(11):823-7.
11. Leebeek FW, Fischer K. Quality of haemophilia care in The Netherlands: new standards for optimal care. *Blood transfusion = Trasfusione del sangue*. Apr 2014;12 Suppl 3:s501-4. doi:10.2450/2014.0041-14s
12. Fischer K, van der Bom JG, Mauser-Bunschoten EP, et al. Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia : the official journal of the World Federation of Hemophilia*. Sep 2001;7(5):446-52. doi:10.1046/j.1365-2516.2001.00545.x

13. Rosendaal FR, Varekamp I, Smit C, et al. Mortality and causes of death in Dutch haemophiliacs, 1973-86. *Br J Haematol*. Jan 1989;71(1):71-6.
14. World Health Organization (WHO). International Statistical Classification of Diseases and Related Health Problems, 10th revision. 1994, update 2016.;
15. STATLINE. Central Bureau of Statistics (CBS) Website. <http://www.cbs.nl/nl/statline>. Accessed May 23, 2018.
16. Wolkewitz M, Allignol A, Harbarth S, de Angelis G, Schumacher M, Beyersmann J. Time-dependent study entries and exposures in cohort studies can easily be sources of different and avoidable types of bias. *Journal of clinical epidemiology*. Nov 2012;65(11):1171-80. doi:10.1016/j.jclinepi.2012.04.008
17. Yeung CH, Santesso N, Pai M, et al. Care models in the management of haemophilia: a systematic review. *Haemophilia : the official journal of the World Federation of Hemophilia*. Jul 2016;22 Suppl 3(Suppl 3):31-40. doi:10.1111/hae.13000
18. Tagliaferri A, Rivolta GF, Iorio A, et al. Mortality and causes of death in Italian persons with haemophilia, 1990-2007. *Haemophilia : the official journal of the World Federation of Hemophilia*. May 2010;16(3):437-46. doi:10.1111/j.1365-2516.2009.02188.x
19. Jardim LL, van der Bom JG, Caram-Deelder C, Gouw SC, Leal Cherchiglia M, Meireles Rezende S. Mortality of patients with haemophilia in Brazil: First report. *Haemophilia*. Mar 15 2019;doi:10.1111/hae.13730
20. Julious SA, Nicholl J, George S. Why do we continue to use standardized mortality ratios for small area comparisons? *J Public Health Med*. Mar 2001;23(1):40-6.
21. Loomans JI, Eckhardt CL, Reitter-Pfoertner SE, et al. Mortality caused by intracranial bleeding in non-severe hemophilia A patients. *J Thromb Haemost*. Jun 2017;15(6):1115-1122. doi:10.1111/jth.13693
22. Nelson MD, Jr., Maeder MA, Usner D, et al. Prevalence and incidence of intracranial haemorrhage in a population of children with haemophilia. The Hemophilia Growth and Development Study. *Haemophilia : the official journal of the World Federation of Hemophilia*. Sep 1999;5(5):306-12.
23. Ljung RC. Intracranial haemorrhage in haemophilia A and B. *Br J Haematol*. Feb 2008;140(4):378-84. doi:10.1111/j.1365-2141.2007.06949.x
24. Witmer CM. Low mortality from intracranial haemorrhage in paediatric patients with haemophilia. *Haemophilia : the official journal of the World Federation of Hemophilia*. Sep 2015;21(5):e359-63. doi:10.1111/hae.12716
25. Dunn AL, Austin H, Soucie JM. Prevalence of malignancies among U.S. male patients with haemophilia: a review of the Haemophilia Surveillance System. *Haemophilia : the official journal of the World Federation of Hemophilia*. Jul 2012;18(4):532-9. doi:10.1111/j.1365-2516.2011.02731.x

26. Fransen van de Putte DE, Fischer K, Makris M, et al. History of non-fatal cardiovascular disease in a cohort of Dutch and British patients with haemophilia. *Eur J Haematol*. Oct 2012;89(4):336-9. doi:10.1111/j.1600-0609.2012.01835.x
27. Huang YC, Tsan YT, Chan WC, et al. Incidence and survival of cancers among 1,054 hemophilia patients: A nationwide and 14-year cohort study. *Am J Hematol*. Apr 2015;90(4):E55-9. doi:10.1002/ajh.23947
28. Minuk L, Jackson S, Iorio A, et al. Cardiovascular disease (CVD) in Canadians with haemophilia: Age-Related CVD in Haemophilia Epidemiological Research (ARCHER study). *Haemophilia : the official journal of the World Federation of Hemophilia*. Nov 2015;21(6):736-41. doi:10.1111/hae.12768
29. Tagliaferri A, Di Perna C, Santoro C, et al. Cancers in patients with hemophilia: a retrospective study from the Italian Association of Hemophilia Centers. *J Thromb Haemost*. Jan 2012;10(1):90-5. doi:10.1111/j.1538-7836.2011.04566.x
30. Shapiro S, Makris M. Haemophilia and ageing. *Br J Haematol*. Mar 2019;184(5):712-720. doi:10.1111/bjh.15745
31. Fransen van de Putte DE, Fischer K, Makris M, et al. Unfavourable cardiovascular disease risk profiles in a cohort of Dutch and British haemophilia patients. *Thromb Haemost*. Jan 2013;109(1):16-23. doi:10.1160/th12-05-0332
32. Humphries TJ, Ma A, Kessler CM, Kamalakar R, Pocoski J. A second retrospective database analysis confirms prior findings of apparent increased cardiovascular comorbidities in hemophilia A in the United States. *American journal of hematology*. May 2016;91(5):E298-9. doi:10.1002/ajh.24336
33. Biere-Rafi S, Zwiers M, Peters M, et al. The effect of haemophilia and von Willebrand disease on arterial thrombosis: a systematic review. *Neth J Med*. May 2010;68(5):207-14.
34. Ioannou GN, Beste LA, Green PK, et al. Increased Risk for Hepatocellular Carcinoma Persists Up to 10 Years After HCV Eradication in Patients With Baseline Cirrhosis or High FIB-4 Scores. *Gastroenterology*. Nov 2019;157(5):1264-1278.e4. doi:10.1053/j.gastro.2019.07.033
35. Castaman G, Matino D. Hemophilia A and B: molecular and clinical similarities and differences. *Haematologica*. Sep 2019;104(9):1702-1709. doi:10.3324/haematol.2019.221093
36. Rumi MG, Di Marco V, Colombo M. Management of HCV-Related Liver Disease in Hemophilia and Thalassemia. *Semin Liver Dis*. May 2018;38(2):112-120. doi:10.1055/s-0038-1655774
37. Shima M. Bispecific Antibodies and Advances in Non-Gene Therapy Options in Hemophilia. *Res Pract Thromb Haemost*. May 2020;4(4):446-454. doi:10.1002/rth2.12337

Supplemental Table 1. Sensitivity analysis for healthy cohort effect, excluding the first three years of follow-up (i.e. follow-up starts from 2004 instead of 2001).

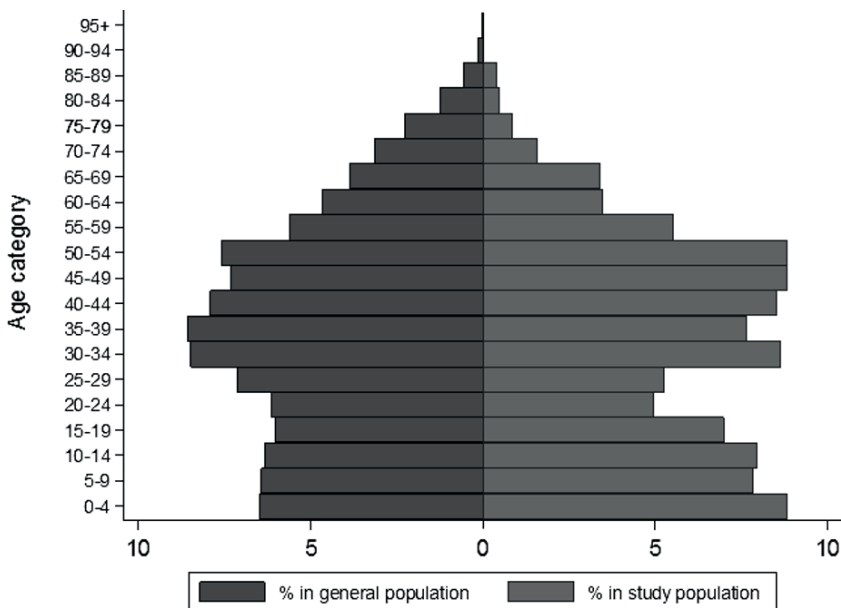
N	PY*	Deaths	SMR [‡]	Life expectancy
First three years of follow-up included				
1031	15910	142	1.4 (1.2-1.7)	77
First three years of follow-up excluded				
999	12861	116	1.3 (1.1- 1.6)	78

* Person-years.

[‡] Standardized mortality ratio.

Supplemental Figure 1. Population pyramid of study population and general male population.

Legend: The graph shows the population age structure of the study population (on the right side) and the Dutch general male population (on the left side) in 2001. On the Y-axis, the age categories are shown. For each age category, the number of people as a percentage of the total population is shown.



Supplemental figure 2. Total number of deaths per age group.

Legend: This bar chart shows the number of deaths per age group in the 2001-2018 study cohort.

