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IN FOCUS

Mortality and causes of death in patients with hemophilia, 1992–2001: a prospective cohort study[1]

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Summary. *Background:* Clotting factor products have been safe for HIV since 1985, and for hepatitis C since 1992. Few studies have reported on mortality in the total population of hemophilia patients after the period of risk of viral infection transmission. *Objectives:* We studied the mortality, causes of death, and life expectancy of hemophilia patients between 1992 and 2001. We compared these findings with those of previous cohorts, together spanning the periods before, during, and after the use of potentially contaminated clotting products. *Patients and methods:* We performed a prospective cohort study among 967 patients with hemophilia A and B. Death rates, overall and cause-specific, were compared with national mortality figures for males adjusted for age and calendar period as standardized mortality ratio (SMRs). *Results:* Between 1992 and 2001, 94 (9.7%) patients had died and two patients were lost to follow-up (0.2%). Mortality was 2.3-times higher in hemophilia patients than in the general male population (SMR 2.3 95% confidence interval 1.9–2.8). In patients with severe hemophilia, life expectancy decreased from 63 (1972–1985) to 59 years (1992–2001). Exclusion of virus-related deaths resulted in a life expectancy at birth of 72 years. *Conclusions:* AIDS was the main cause of death (26%) and 22% of deaths were because of hepatitis C. In patients not affected by viral infections, there still appeared to be a trend toward a moderately increased mortality compared with the Dutch male population. Thus, mortality of patients with hemophilia is still increased; this is largely because of the consequences of viral infections.

Keywords: hemophilia, life expectancy, mortality, viral infections.

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Introduction

Hemophilia is an X-linked genetic bleeding disorder caused by deficiency of coagulation factor VIII (FVIII) (hemophilia A) or factor IX (FIX) (hemophilia B). Because of the hereditary pattern of hemophilia, patients are almost invariably male, while women can be carriers of the disease. Severe forms are characterized by major bleeding occurring spontaneously or after minor trauma. These hemorrhages often occur into joints eventually causing the disabling arthropathy [1].

Before the introduction of clotting factor preparations, the mean life expectancy of patients with hemophilia was < 30 years [2], and patients mostly died of intracranial or other hemorrhages [3–5]. Since the 1960s, FVIII and FIX preparations have been available for the treatment of hemophilia. This rapidly led to medical and social improvements, with a decrease in the frequency of hemorrhages and considerably improved life expectancy of patients with hemophilia.

Despite these positive developments, mortality of patients with hemophilia again increased during the 1980s. In 1982, the first case of acquired immunodeficiency syndrome (AIDS) in a patient with hemophilia was reported [6,7]. Since then, many more cases have been reported worldwide, of whom many have died. In addition, about 80% of the patients treated with clotting factor products before 1992 became infected with hepatitis C [8,9]. The full consequences of hepatitis C infections are only recently being recognized [10].

Since 1985, virally safe [human immunodeficiency virus (HIV)] products have been available and since 1992 virally safe products for hepatitis C (HCV). Today, the most important complication of clotting factor treatment is the development of neutralizing antibodies (inhibitors) against FVIII or IX [11].

Few studies have reported on mortality in the total population of hemophilia patients after the period of the risk of viral infection transmission. Several studies have aimed at describing mortality within a specific subpopulation, such as hemophilia patients infected with HIV [12–14]. This study completes the inventory of mortality in patients with hemophilia over the last 30 years in the Netherlands, and describes the period after the use of potentially contaminated clotting products [15,16].

Objectives

We studied mortality, causes of death, and life expectancy of hemophilia patients between 1992 and 2001. We compared these findings with those of previous cohorts from our national surveys on hemophilia, starting in 1972.

Material and methods

Study design

A prospective cohort study was performed as part of a survey among all known patients with hemophilia in the Netherlands. In June 1992, we sent questionnaires to all patients who were listed with the Netherlands Hemophilia Society, with the hemophilia treatment centers, or on the updated mailing lists from previous surveys in 1972, 1978, and 1985 [17]. For this national study, 1292 patients (93% of the total Dutch hemophilia population, $n = 1389$) were sent a questionnaire of whom 967 (75%) responded. In total, 70% of all Dutch hemophilia patients participated. Vital status at the end of study date was determined by the response to the survey of 2001, from the attending physician or from municipal population registries. Of patients who had died during the follow-up, dates of death were obtained from municipal registries and physicians. This study is part of the Hemophilia in the Netherlands (HIN-S study), which has been approved by the Committee of Medical Ethics of the Leiden University Medical Center.

Cause of death

The causes of death were obtained from the treating physicians or general practitioners and were categorized according to the 10th revision of the International Classification of Diseases, Injuries, and Causes of Death-10 (ICD-10) [18]. Overall and cause-specific mortality of the general Dutch male population was retrieved from the Central Bureau of Statistics (CBS) [19]. Date of birth, severity of hemophilia, HIV status, and information on inhibitory antibodies were derived from the self-reported answers to the questionnaire. Severity of disease and type of hemophilia were verified with the patients' physicians. Severity of hemophilia, depending on the residual clotting factor activity was categorized as severe (< 0.01 IU mL^{-1} FVIII or FIX), moderate (0.01–0.05 IU mL^{-1}), or mild (> 0.05–0.40 IU mL^{-1} FVIII or FIX). The HIV status was based on the self-reported answers of the patients. If patients were born after 1985 or if they reported no treatment with the clotting factor between 1979 and 1985, HIV status was considered to be negative.

Statistical analysis

Indirect standardization Standardized mortality ratios (SMRs) were calculated to estimate the rate of overall and cause-specific death of patients with hemophilia relative to that of the general male population adjusted for age and calendar period. An SMR is the number of observed deaths divided by the number that was expected if the mortality rate in the cohort, with its specific age-distribution, was the same as that in the general population. Patients were followed from 1 June 1992 to 1 July 2001. We used mortality rates from the Dutch general male population between 1992 and 2001. Ninety-five percent confidence intervals (95% CI) were based on a Poisson's distribution for the observed number of deaths.

Cause-specific SMRs were calculated by studying the specific cause of death as endpoint and censoring patients with other endpoints.

Direct standardization In direct standardization, mortality ratios are calculated by using an external standard as weight factor. In our study, we used the WHO standardization weight factors (http://www3.who.int/whosis/discussion_papers/pdf/paper31.pdf). To put our findings into perspective mortality, figures were compared with those of the previous cohort studies between 1972–1985 ($n = 717$) [15] and 1985–1992 ($n = 919$) [16].

Life expectancy Median life expectancy was calculated with left truncated survival analysis and was expressed as the median age at which cumulative survival was 50%. In a left truncated survival analysis, patients are included in the analysis from the start of the follow-up instead of data of birth.

Exclusion of viral infections Two methods were used to exclude the effect of viral infections on mortality: (i) exclusion of patients who reported to be HIV positive in 1992; and (ii) censoring patients whose death was a result of HIV (AIDS) or HCV (liver cirrhoses, hepatocellular carcinoma) at the date of death.

Results

Table 1 shows the general characteristics of the patients with hemophilia in 1992. Between 1992 and 2001, the total number of patient-years of follow-up was 8868 [mean 8.6 (range 0–9) years], 94 patients died and two patients were lost to follow-up. Of all 967 patients in the cohort, 796 (87%) patients had hemophilia A and 125 (13%) patients had hemophilia B; 386

Table 1 General characteristics of participants at entry (1992)

	$n = 967$
Age (years)	32 (0–82)
Severity of disease	
Severe (< 0.01 IU mL^{-1})	386 (40)
Moderate (0.01–0.05 IU mL^{-1})	167 (17)
Mild (> 0.05–0.40 IU mL^{-1})	414 (43)
Type of hemophilia	
Hemophilia A	796 (87)
Hemophilia B	171 (13)
HIV infection	53 (6)
Inhibitor present*	50 (5)

Data presented are means (range) or numbers (percentages).
*Inhibitory antibodies against the deficient clotting factor.

Table 2 Standardized mortality ratios (SMR) for severity and type of hemophilia taking into account the HIV status

		SMR (95% CI)†	
	Observed deaths*	All patients	HIV-negative patients‡
All	94	2.3 (1.9–2.8)	1.7 (1.3–2.1)
Severity			
Severe	47	5.1 (3.8–6.8)	2.8 (1.9–4.2)
Moderate	15	2.6 (1.5–4.3)	2.3 (1.3–3.9)
Mild	32	1.3 (0.9–1.9)	1.2 (0.8–1.6)
Type of hemophilia			
Hemophilia A	81	2.3 (1.9–2.9)	1.7 (1.4–2.2)
Hemophilia B	13	2.3 (1.3–4.0)	1.3 (0.6–2.7)

*Data presented are absolute numbers of observed deaths.
†95% confidence interval.
‡Only including patients who reported to be HIV-negative or patients who were born after 1985.

(39%) patients had severe hemophilia, 167 (17%) patients had moderate hemophilia and 414 (43%) had mild hemophilia; the mean age was 32 (range 0–82) years; 50 (5%) patients reported having inhibitory antibodies against the deficient clotting factor; and 53 patients (6%) were HIV-positive. The mean age at death was 52 years, with a range from 14 to 83 years.

The expected number of deaths during this same calendar period was 39. The SMR was 2.3 (CI 1.9–2.8), indicating that the overall mortality rate of patients with hemophilia was two times higher than in the general male population. In patients with severe hemophilia, mortality was five times higher than the expected, SMR 5.1 (CI 3.8–6.8). Standardized mortality ratios, taking into account HIV infection and severity of disease, are shown in Table 2. Restriction of the analysis to HIV-negative patients revealed that mortality in patients with hemophilia was 70% higher than that in the general population (SMR 1.7, CI 1.3–2.7). After exclusion of deaths related to either HIV or HCV, mortality rate among patients with hemophilia was 20% higher than among the general population (SMR 1.2, CI 0.9–1.6), in patients with severe hemophilia this was 40% (SMR 1.4, CI 0.8–2.4).

Direct standardization of mortality rates made comparisons between time periods possible. We found that mortality of the whole cohort of patients with hemophilia did not change over three time periods. Relative rate, compared with subjects without hemophilia, i.e. the general population, was 1.6 between 1972 and 1985, 2.1 between 1985 and 1992 and 2.0 between 1992 and 2001. However, stratification for severity of hemophilia revealed that the rate of death of patients with severe hemophilia might have increased over the last 3 decades. It was 3-fold greater during the period between 1985 and 1992, and it was 4.5-fold greater during the last period of follow-up.

Table 3 Primary causes of death according to the ICD-10 classification

Cause of death (ICD-10* Code)	1973–1986 $n = 43$ (%)	1986–1992 $n = 45$ (%)	1992–2001 $n = 94$ (%)
AIDS† (B20–34)	0 (0)	12 (27)	24 (26)
Hepatitis C			21 (22)‡
Hepatocellular carcinoma (C22)			5 (5)
Chronic liver disease (K70, K72.9, K73–K74, and C78.7)	0 (0)	5 (11)	10 (11)§
Diseases of the circulatory system (I00–I99)	4 (9)	10 (24)	16 (17)
Ischemic heart disease (I200–I25)	1 (2)	0 (0)	6 (6)
Cerebrovascular disease (I60–I69)	3 (7)	9 (20)	4 (5)#
Malignancies (C00–D48)	13 (30)	7 (15)	12 (15)
Hemorrhages	20 (47)	1 (2)	9 (10)
Caused by trauma (T14.9)			4 (4)
Other (A40.3, A41.9, J18, R06.8, and R54) or not natural cause of death (V01–Y98)	3 (5)	6 (9)	9 (10)¶
Sudden death, cause unknown (R96, R99)**	3 (7)	4 (9)	3 (3)

*ICD-10, international classification of diseases, 10th revision.
†AIDS, acquired immunodeficiency syndrome.
‡Two patients died because of complications of liver transplantation, five of hepatocellular carcinoma, 10 of chronic liver disease, in four patients only hepatitis C mentioned as cause of death.
§In four patients, a hemorrhagic shock was reported.
#All deaths because of hemorrhagic stroke.
¶Trauma, pneumonia or septic shock, murder, suicide, and old age.
**One patient died from 'natural causes'.

Cause-specific mortality

Table 3 shows the primary causes of death between 1992 and 2001. Between 1992 and 2001, 24 (26%) patients died of AIDS of whom 22 (87.5%) had severe hemophilia. In 21 patients (22%), death was because of a HCV infection; in two of these patients, complications of a liver transplantation were the cause of death, while in five patients a hepatocellular carcinoma or metastasis of a liver carcinoma was reported. Death because of chronic liver disease was reported in 10 patients of whom five died of a hemorrhagic shock. In four patients, only hepatitis C was mentioned as cause of death. A co-infection with HIV and HCV was observed in five of the deaths resulting from hepatitis C. Mortality of AIDS and chronic liver disease was highest in patients with severe hemophilia although these causes of deaths were also observed in four patients (27%) with moderate hemophilia. Among patients in which death was not related to HCV or HIV ($n = 49$), the main cause of death was hemorrhage (13/49, 27%), which also includes intracranial hemorrhages ($n = 4$) and hemorrhages resulting from trauma ($n = 4$). Compared with the Dutch male population, the incidence of death from intracranial hemorrhages is higher in patients with hemophilia, 0.1 per 1000 person-years and 0.5 per 1000 person-years (5/8868 person-years), respectively. Death from malignant neoplasm (including hepatocellular carcinoma) was reported in 22% of patients. Although the percentage of patients with mild hemophilia that died as a result of malignancies was increased compared with the Dutch male population, at 41% vs. 31%, overall mortality of malignancies was decreased, at 19% vs. 31%. Death because of disease of the circulatory system, including ischemic heart disease and cerebrovascular disease, was lower in patients with hemophilia than in the Dutch male population 17% and 28%, respectively. Myocardial infarction ($n = 4$) and cardiac arrest ($n = 3$) were the most prevalent ischemic heart disease. The cause of death remained unknown in two patients.

In 20% ($n = 20$) of deceased patients, the presence of an inhibitor was reported at the time of death. In these patients, either AIDS ($n = 11$) or carcinoma ($n = 4$) was the main cause of death. Hemorrhage or hemorrhage-related deaths were reported in three patients (including one intracranial death).

The proportion of patients that died of AIDS stayed constant during the last two periods of follow-up. Death because of hepatitis C increased compared with the period between 1985 and 1992, 11% vs. 22%. No deaths of AIDS or hepatitis C were reported in the first period of follow-up (1972–1985). The occurrence of cerebral vascular disease was lower than in 1986–1992, when it accounted for 20% of all deaths compared with 4% in the current period of follow-up.

In Table 4, cause-specific SMRs are shown. Mortality because of AIDS infections was 117 times higher than in the general population, and mortality because of HCV was 16 times (SMR 16.2, CI 7.7–33.8) higher in patients with hemophilia than in the general population.

Table 4 Primary cause of death-specific SMRs

Cause of death (ICD-10 Code)	Observed*	SMR (95 CI)†
AIDS (B20–B24)	24	117.2 (77–178)
Hepatitis C		
Hepatocellular carcinoma (C22)	5	17.2 (5.2–35.9)
Chronic liver disease (K70, K72.9, and K73–K74)	10	16.1 (7.7–33.8)
Ischemic heart disease (I20–125)	6	0.5 (0.2–1.1)
Cerebrovascular disease (I60–I69)	4	1.0 (0.2–2.2)
Malignancies	18	1.5 (1.0–2.5)
Malignancies (no liver)	12	1.1 (0.6–1.9)

*Absolute numbers of death observed.
†95% confidence interval.

Life expectancy

Life expectancy was calculated and stratified for severity of hemophilia and based on the extrapolation from the observed death rates (Table 5). In patients with severe hemophilia, a life expectancy of 59 years at birth was observed, and censoring of

Table 5 Life expectancy (years) according to severity in 30 years of follow-up

			1992–2001		
	1972–1985	1985–1992	All patients ($n = 967$)	HIV negative* ($n = 511$)	HIV and HCV† negative ($n = 967$)
All patients (years)	66	68	67	70	74
Dutch males	71	74	76	76	76
Severity of hemophilia (IU mL^{-1})					
Severe (< 0.01)	63	61	59	70	71
Moderate (0.01–0.05)	65	65	67	71	75
Mild (> 0.05–0.40)	–	74	73	73	75
Type					
Hemophilia A	–	69	68	70	73
Hemophilia B	–	64	60	73	

*Patients of whom HIV status was negative or who were born after 1985.
†HIV- and HCV-related deaths were censored; in this analysis, patients were not considered to be dead but lost to follow-up. Therefore, no patients were excluded.

patients who died because of virus infections resulted in a life expectancy of 71 years in patients with severe and moderate hemophilia. Life expectancy at birth of patients with mild hemophilia was lower than that of the male population, at 73 years compared with 76 years. After censoring deaths because of viral infections, the life expectancy of mild hemophilia patients was 75 years.

The overall life expectancy of the patients with hemophilia did not notably change between 1972 and 2001. The life expectancy of patients with severe hemophilia, however, decreased from 63 in the period between 1972 and 1985 to 59 years during the follow-up between 1992 and 2001. For patients with moderate hemophilia, life expectancy increased from 65 to 67 years.

Discussion

During the last decade, hemophilia was characterized by an excess mortality when compared with the general population. HIV infection was responsible for the largest number of deaths ($n = 24$, 26% of deaths) and 16% of deaths were because of hepatocellular carcinoma or chronic liver disease ($n = 15$) resulting from a HCV infection. Overall, patients with severe hemophilia had a 5-fold higher risk of death than men in the general population. Without the effects of HIV and HCV, the rate of death among patients with severe hemophilia was 1.4-fold higher than expected. The remaining excess risk in all likelihood results from hemorrhages. Life expectancy of patients with severe hemophilia decreased compared with the earlier studies, mostly influenced by HIV. Patients with severe hemophilia not affected by hepatitis C or HIV had a life expectancy of 71 years, which can be compared with a life expectancy of the Dutch male population of 76 years.

In the survey of 1992, 93% of all Dutch hemophilia patients were sent a questionnaire, of whom 75% participated in the survey, and were subsequently followed for this study on mortality. Only two patients were lost to follow-up and we were able to retrieve 96% of all causes of death. This resulted in a complete cohort comprising a large population of hemophilia patients. There was no difference in severity of hemophilia or mean age between the responding and non-responding population to the questionnaire of 1992 and therefore we consider our data to be generalizable to the Dutch hemophilia population. Differences may exist between the responding and the non-responding population in the rates of HIV or hepatitis C. We cannot predict in which direction this might have influenced our results: either patients with HIV or hepatitis C are too ill to participate, which might lead to an underestimation of mortality, or are more willing to participate because of their disease. Theoretically, because the causes of death were reported by the treating hematologist or the general practitioner, there may have been discrepancies with the general population data gathered through the CBS. In some cases, the treating hematologists and general practitioners were present at time of death and informed the CBS on the cause of death, in other patients the physician present at the time of death informed both the treating hematologist and the CBS. Therefore, we do not expect this to be of large influence. As always in research on life expectancy, the findings may not hold for the present patients with hemophilia. Exclusion of effects of viral infections results in a reflection of the current situation for patients who have not been exposed to virally non-safe clotting products. In our cohort, no deaths were reported in the youngest age-category between 0 and 10 years. The youngest participant to this study was 4 months old, and therefore our study did not cover perinatal mortality. Because of the limited information on the presence of inhibitory antibodies, we have not been able to study the impact on mortality.

Our study shows a 2-fold increased mortality for patients with hemophilia; in patients with severe hemophilia, this was even a 5-fold increase. We estimated the future mortality patterns in patients with hemophilia by excluding the death because of HIV or hepatitis C as these infections will not likely impact on the future mortality of patients with hemophilia. Although not statistically significant, there still appeared to be a trend toward a moderately but enduring increased mortality for patients with hemophilia, especially in severe hemophilia. As nowadays products are safe from transmission of HIV and hepatitis C, preventive efforts should focus on factors causing this remaining excess mortality. The most important factor is an increased risk of death of hemorrhages, either intracranial or resulting from trauma. Although mortality of HCV and HIV is extensive and the numbers for comparison with the general population are limited, there seems to be a higher incidence of death from intracranial hemorrhages in patients with severe, moderate, and mild hemophilia. This indicates the importance of adequate and specialized care for hemophilia patients. Although we also observed a high number of other hemorrhages, for example resulting from trauma, we were not able to make a comparison with the general population. A second factor of impact could be deaths from hepatitis C that had not been reported as such. However, as the hepatitis C status is well known and a good registration is used by treating physicians, this is probably of limited influence.

Over the last 3 decades, causes of death of patients with hemophilia have changed; during the 1970s and early 1980s patients with hemophilia died mostly of intracranial hemorrhages, while during the late 1980s AIDS became the main cause of death. Although in the Netherlands the impact of HIV was relatively low through the predominant use of products from local voluntary unpaid donors, AIDS was responsible for a quarter of all deaths during the 1990s. In the present follow-up period, about 80% of deaths from AIDS occurred before 1995, indicating that the impact of AIDS on mortality of patients with hemophilia is declining. This decreased influence is explained by a reduced number of survivors of HIV infection, and by improved survival of patients contaminated with HIV through highly active antiretroviral therapy (HAART) therapy [20]. The effects of hepatitis C infections on mortality have increased considerably during the last 10 years, and about 20% of deaths were because of the effects of hepatitis C, of which liver cirrhosis or

liver failure were the most prevalent. Our study shows a highly increased risk of death of hepatocellular carcinoma, which is similar to a study by Darby *et al*. [21] in which a 20-fold increased risk was reported in non-HIV infected patients with severe hemophilia. Although the introduction of new treatment methods combining PEG-interferon with ribavirin will positively influence the mortality of HCV-infected patients, the effects of HCV will remain in those patients in whom this therapy failed. For patients not affected by viral infections, hemorrhage was still a relatively frequent cause of death. As this is similar to the period before the impact of viruses transmitted by clotting products, we might conclude that the increased availability of clotting factor has not reduced the number of deaths because of hemorrhages. The number of deaths from malignant neoplasm was not higher than the expected in this population. In concordance with earlier studies and findings by Rosendaal *et al*. [22], we observed a reduced rate of mortality of ischemic heart disease in patients with hemophilia.

Life expectancy of patients with severe hemophilia was lower during the last decade when compared with earlier observations. An important part of this decline is explained by death because of viral infections. When AIDS and hepatitis C deaths were excluded, life expectancy improved but although the general life expectancy in European countries is approached, it remains to be lower especially in patients with severe hemophilia [23]. Walker *et al*. [24] published the same observations in a Canadian population. After exclusion of viral infections patients with mild and moderate hemophilia have a life expectancy that is about equal to the average Dutch male population.

Our data show that HIV and hepatitis C still largely influence mortality of hemophilia patients. The effects of hepatitis C will be present for many years to come. In patients with severe hemophilia not infected with viruses, mortality is still 40% higher when compared with the general population. Although this suggests that the current patient with hemophilia benefits from safe clotting products, life expectancy is still negatively influenced by this bleeding tendency.

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Addendum

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