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Evaluation of the Burden of Bone Fractures in People Living With Haemophilia: A Registry-Based Matched Cohort Study

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ABSTRACT

Background: Bone diseases, such as low bone mineral density and osteoporosis is an emerging concern in people with haemophilia (PWH). As a consequence, PWH might experience fractures more frequently than the general population. Our primary aim was to compare the incidence of bone fractures in PWH and controls without bleeding disorders. The secondary aim was to identify factors associated with fractures in PWH.

Methods: This was a retrospective, matched cohort, study based on data from the Canadian Bleeding Disorders Registry and data from the Institute for Clinical Evaluative Sciences (ICES). PWH were eligible if alive on 1 January 2017. They were followed up to 31 March 2018. Age- and sex-matched controls were randomly selected with a 20:1 ratio. We analysed the data using multivariate regression models, adjusting for age, severity, inhibitor status, and comorbidities (Charlson Comorbidity index).

Results: 1080 PWH and 21,597 controls were included. 8.7% of PWH and 5.7% of controls experienced a fracture during the follow-up period. The adjusted hazard ratio (aHR) for a fracture was 1.46 [95% confidence interval (CI) 1.19; 1.80] in PWH. Severe haemophilia [adjusted odds ratio (aOR) 1.72, 95% CI 1.02; 2.93] and the presence or history of an inhibitor (aOR 2.42, 95% CI 1.08; 5.42) were risk factors for a fracture, after adjusting for age and comorbidities.

Conclusions: PWH have a higher risk of bone fractures than the general population. Amongst PWH, the severity of haemophilia and the presence or history of an inhibitor are risk factors for a bone fracture.

1 | Introduction

Haemophilia is an inherited bleeding disorder characterised by a deficiency of coagulation factor FVIII (haemophilia A) or FIX (haemophilia B). Bleeding, spontaneous, post-surgical or following minor trauma, is a hallmark manifestation in people living with haemophilia (PWH). PWH experience short-term (pain, immobility) and long-term (chronic joint pain, disability) complications associated with recurrent bleeding [1]. Over the years, the availability of several treatment options and improved care coordination and delivery have resulted in increased longevity of PWH, from 40 years in 1960s to 63–70 in recent years.[2–5] As a result, there is an increasing number of PWH dealing with comorbidities like cardiovascular disease, diabetes or cancer.[6] Age-related bone diseases, such as low bone mineral density (BMD) and osteoporosis are emerging concerns in PWH. Gallacher et al. reported significantly lower BMD in 19 males with severe haemophilia compared to age- and sex-matched controls [7]. In another study conducted on 30 patients with moderate haemophilia Gerstner et al. found that 70% of them had decreased BMD. Risk factors of decreased BMD are lower serum 25-hydroxyvitamin D levels, lower body mass index,

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lower activity scores and decreased joint range of motion [8]. A study using high-resolution peripheral quantitative computed tomography demonstrated that low trabecular and cortical bone density contributed to low BMD and weaker bones (decreased bone strength) in PWH [9]. A meta-analysis of 13 studies found that PWH had a significant reduction in both lumbar spine and hip BMD as compared to control population [10]. More importantly, low BMD was also observed in both paediatric and adult patients [10]. Lower BMD is associated with the risk of fracture in the general population. A meta-analysis of 11 studies, involving 90,000 patient-year observation time, found that a reduction in the BMD of one standard deviation (SD) below the age-adjusted mean was associated with an increased risk of osteoporotic fracture, with a relative risk (RR) of 2.3 [95% confidence interval (CI) 1.9 to 2.8], measuring at the spine, and of 2.6 (95% CI 2.0 to 3.5), measuring at the hip.[11] Studies of fragility fractures due to low BMD in postmenopausal women and non-haemophilia men demonstrated increased morbidity, mortality and hospitalisation rates as well as a decrease in the quality of life.[12–14] A recent retrospective, single centre study in 316 PWH A and 66 PWH B reported an increased incidence of fractures in PWH (24.8 fractures per 1000 patient-year) as compared to a control population (9.6 fractures per 1000 patient-year) [15]. However, data on the incidence of bone fractures in PWH are limited in peer reviewed literature [16]. A better understanding of the burden of fractures in PWH would enable haemophilia specialists and other stakeholders to scope the problem and allocate adequate resources for prevention and treatment. In addition, this information would enable determination of the utility of BMD measurements in assisting with future screening and surveillance programs in haemophilia care. We obtained data from the Canadian Bleeding Disorder Registry (CBDR) and the Institute for Clinical Evaluative Sciences (ICES) to explore the burden of bone fractures in PWH in Ontario, Canada.

2 | Objectives

To assess the incidence of bone fractures in PWH, compared to Controls.

To identify the risk factors associated with bone fractures in PWH.

Our pre-specified hypotheses were the following:

1. That PWH had a higher incidence of bone fractures as compared to controls.
2. That PWH with a more complicated disease, defined as worse severity of haemophilia, with present or historical inhibitor, and multiple comorbidities, were at increased risk of bone fractures.

3 | Methods

3.1 | Study Design and Reporting

This was a retrospective, matched cohort, registry-based study. The manuscript has been prepared following the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines [17]. The study was not registered, but the protocol was written and approved by a funding agency before accessing the data.

3.2 | Population and Setting

Eligible participants were PWH A or B of any severity from the CBDR with a primary HTC in Ontario, who were alive on 1 January 2017. Age- and sex-matched controls (i.e., people without haemophilia) were randomly selected from the ICES database, with a 1:20 cases: controls ratio [18]. More details on the creation of the study dataset is provided in the supplementary material. The end date for follow up was defined as the date of death, the end date for Ontario Health Insurance Plan (OHIP) eligibility, or 31 March 2018 $\pm$ random 14 days.

3.3 | Data Sources and Variables

CBDR is a national clinical database that collates demography, clinical information, patient outcomes and treatment product utilisation of people with bleeding disorders in Canada [5]. CBDR is used daily by haemophilia treatment centres (HTC) across the country, except for two centres in British Columbia whose data are aggregated with the rest to be reported collectively. Diagnoses are based on clinical history, laboratory, and genetic testing. Factor utilisation and a range of outcomes are directly reported by patients. For the purposes of this study, CBDR has been used to identify a reference cohort of persons living with Haemophilia in Ontario.

ICES is an independent, not-for-profit organisation that houses coded and linkable health data on over 13 million Ontarians with universal health coverage [19]. ICES has been specially designated to collect and use health information which can be used to monitor and evaluate the health care system in Ontario and for various research projects. For the purposes of this study, ICES data was used to identify a cohort of age and sex-matched controls for the haemophilia reference cohort which was obtained through CBDR. For both PWH and controls, we obtained data from ICES on the following characteristics: age, sex at birth, presence of congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), diabetes, and Charlson comorbidity index (CCI) [20]. Furthermore, for PWH, we extracted the following data from CBDR: haemophilia type (A versus B), severity (mild, moderate, or severe), inhibitor status (current inhibitor or history of inhibitor, versus no inhibitor), and HCV infection. Information about the data measurements and sources are provided in Table S1.

3.4 | Statistical Analysis

The characteristics of the two cohorts were reported using measures of central tendency and variability for continuous variables, counts (frequencies) for categorical variables. The prevalence of fractures amongst PWH and controls in Ontario during 1993–2016 was tabulated and compared using the McNemar test. The prevalence of fractures for different age groups (less than 16 years, 17–26, 27–36, 37–46, 47–56, 57–66, 67–76, and over 76

years) were compared using side-by-side bar diagrams between the two groups. Hazards of fracture between the haemophilia and control patients were compared using Cox regressions. To explore associations of disease severity (mild/moderate vs. severe haemophilia); inhibitor status (no inhibitor vs. current/history of inhibitor); and comorbidities (CCI) with fracture amongst the haemophilia patients, a multivariable Cox proportional hazard regression was performed. Missing/unknown inhibitor status, was imputed as absent current or historical inhibitor. The same analysis was repeated 1) without imputting missing/unknown inhibitor status (complete case analysis) and 2) removing the inhibitor status variable from the model. All the analyses were done with SAS, version 9.4. The graphs were prepared using STATA, version 15.1 and Microsoft Excel 2016.

3.5 | Sample Size Considerations

To maximize the power of our analysis, we aimed at including as many PWH as possible, i.e. all the PWH from CBDR that could be matched in the ICES database. Considering the wide data availability in the ICES database and the small effort required to increase the number of controls, the cases: control ratio was set to a higher than usual level of 1:20.

3.6 | Ethics

The project received approval from the Hamilton Integrated Research Ethics Board (HIREB), with project ID 4454. The HIREB granted a waiver for participants' informed consent, considering the retrospective nature of the study, the fact that collecting the consent would not have been feasible, and the very low risk for the participants privacy.

3.7 | Data Sharing Statement

Study data are available upon reasonable request directed to the corresponding author.

4 | Results

4.1 | Characteristics of the Population

1080 PWH and 21597 controls were included in the study. The participants selection flow is described in the supplementary material. The characteristics of the study population are reported in Table 1. Participants were more frequently males (97.7%) in the 17 to 56 years age range. The mean (SD) CCI was 0.4 (1.2) in PWH and 0.2 ± 0.8 in controls, the median CCI was 0 in both groups (see Figure S1 for the distribution of the CCI in the two populations). In particular, the frequencies of congestive heart failure, chronic obstructive pulmonary disease, and diabetes were similar at around 2%, 5% and 8%, respectively, in PWH and controls. Ninety-four (8.7%) PWH and 1230 (5.7%) controls experienced a fracture during the study period, respectively ($p < 0.0001$). The distribution of fractures by age groups in PWH and controls is reported in Figure 1. The characteristics of PWH and controls with and without a fracture are reported in Table S2, S3. 75.8% of PWH had haemophilia A. 48.3% had mild, 19.6% moderate, and 32.1% severe haemophilia. The percentage of missing data in PWH and controls is reported in Table S4.

TABLE 1 | Demographic characteristics, prevalence of fracture, comorbidities, and mortality amongst people living with haemophilia and age-sex matched control patients in Ontario.

	PWH	Controls
N	1080	21597
Age (year)		
<7	51 (4.7)	1020 (4.7)
7–16	101 (9.4)	2020 (9.4)
17–26	202 (18.7)	4040 (18.7)
27–36	210 (19.4)	4200 (19.4)
37–46	161 (14.9)	3220 (14.9)
47–56	128 (11.9)	2560 (11.9)
57–66	106 (9.8)	2119 (9.8)
67–76	80 (7.4)	1598 (7.4)
76 +	41 (3.8)	820 (3.8)
Sex		
Female	25 (2.3)	497 (2.3)
Male	1055 (97.7)	21100 (97.7)
Fracture[a]	94 (8.7)	1230 (5.7)
Fracture by age categories		
<27 year	23 (6.5)	231 (3.3)
27–36	24 (11.4)	318 (7.6)
37–46	11 (6.8)	176 (5.5)
47–56	8 (6.3)	120 (4.7)
57–66	12 (11.3)	136 (6.4)
66 +	16 (13.2)	249 (10.3)
Comorbidities		
CCI, mean ± SD, *n*	0.4 ± 1.2, 936	0.2 ± 0.8, 12438
CHF	23 (2.1)	431 (2.0)
COPD	63 (5.8)	1102 (5.1)
Diabetes	93 (8.6)	1688 (7.8)
Death	40 (3.7)	1009 (4.7)

Abbreviations: CCI, Charlson comorbidity index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; PWH, people living with haemophilia.

[a] *p* value comparing PwH vs. control < 0.0001.

4.2 | Main Results

The adjusted hazard ratio (aHR) for a fracture was 1.46 (95% CI 1.19; 1.80) in PWH as compared to age-sex matched controls (Figure 1). Amongst PWH, after adjusting for age-sex (matching) and CCI, the aHR for fracture was 1.72 (95% CI 1.02; 2.93) in people with severe haemophilia, 2.42 (95% CI 1.08; 5.42) in PWH with a current or historical inhibitor (Table 2). The aHR for

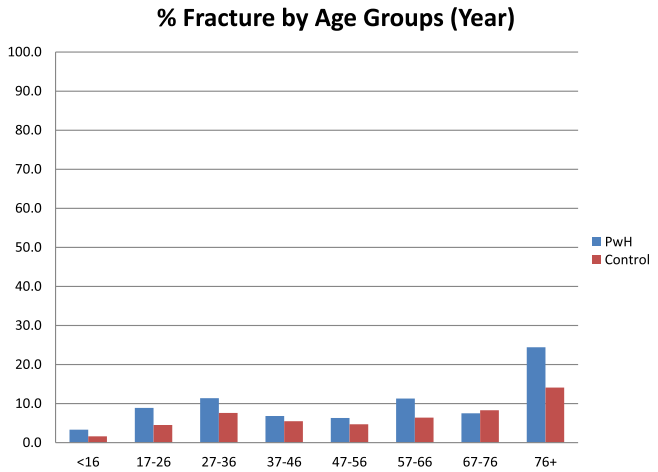


FIGURE 1 | Distribution of fractures by age groups amongst people with haemophilia (PWH) and age-sex controls.

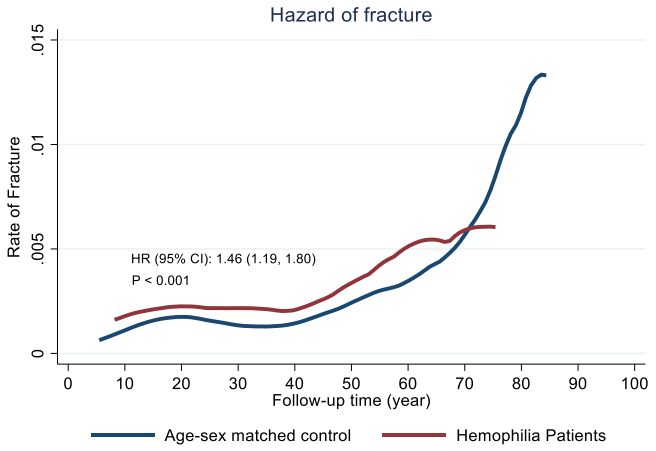


FIGURE 2 | Hazard of fracture amongst people living with haemophilia (PWH) and controls.

TABLE 2 | Factors associated with fracture amongst people leaving with haemophilia.

	Adjusted HR (95% CI)	*p* value
Severity		
Mild	1	
Moderate	1.44 (0.82, 2.53)	0.210
Severe	1.72 (1.02, 2.93)	0.044
Inhibitor status		
No inhibitor	1	
Current/ Hx of inhibitor	2.42 (1.08, 5.42)	0.032
Charlson Comorbidity Index	0.88 (0.72, 1.06)	0.181

Note: Unknown or missing inhibitor status was imputed as no inhibitor. 857 observations, 83 fractures.
Abbreviations: CI, confidence interval; HR, hazard ratio.

CCI was 0.88 (95% CI 0.72; 1.06). The results were similar when including only people with known inhibitor status (Table S5) and when removing the inhibitor status from the model (Table S6). The hazard of fracture in PWH is reported in Figure 2 for all patients, and in Figure 3 stratified by inhibitor status and severity of haemophilia.

5 | Discussion

In this study, we aimed to investigate the incidence of bone fractures in PWH and compared it with sex and age-matched controls without a bleeding disorder. Also, we assessed the importance of specific risk factors associated with bone fractures in PWH. In particular, in our multivariate regression models we included age, severity, and inhibitor status, and comorbidities using the CCI.

PWH experienced a fracture more frequently than the general population (8.7% versus 5.7%), with an aHR for fracture of 1.46 (95% CI 1.19; 1.80). Amongst PWH, the risk for fracture was higher in people with severe disease [aHR 1.72 (95% CI 1.02; 2.93)] and current or historical inhibitor [aHR 2.42 (95% CI 1.08; 5.42)]

Low bone mineral density increases the risk of fractures. Previous studies have reported an association between low bone mineral density and PWH [21]. It has been proposed that this phenomenon could be due to a variety of mechanisms, [22, 23] and it appears plausible that a combination of the recurrent bleeding episodes, development of arthropathy and pain can lead to impaired mobility and movement restriction that can alter the normal structural development and capacity to reach a normal peak bone mass. Although the relationship between low bone mineral density and PWH has been established, data on the relevance of fractures in PWH are still lacking.

Interestingly, a comparative study including patients with haemophilia A and B totaling 2053 patient years of observation showed a significantly higher incidence of fractures in PWH compared with the general population (24.8 cases per 1000 patient-years vs. 9.6 fractures per 1000 patient-years) with a relative risk of 10.7 [95% CI: 8.2–10.4] [15]. However, this was a study comparing data on PWH from a single centre retrospective data analysis with data from a previously published prospective cohort study in the United States, that measured fracture rates in the general population. The authors also found a trend towards higher fracture incidence PWH with an inhibitor compared to those without an inhibitor, but no statistically significant difference in fracture risk was found (relative risk 1.84, 95%CI 0.86; 3.97).

In a recent retrospective study, with a similar design to ours, the investigators did not find a difference in overall fractures, but they did find a higher occurrence of osteoporotic fractures in PWH (14 events, 10.7%) than in controls matched for age, gender, and CCI (76 events, 5.8%) [24]. This difference was not confirmed in the multivariate analysis adjusting for osteoporosis, supporting the role of low bone mineral density as a mediator in this setting. Unfortunately, in our study, we did not have information about the type of fracture (osteoporotic or not).

The possible mechanisms of bone remodelling and bone loss in PWH may be multifactorial and whether there is a functional role

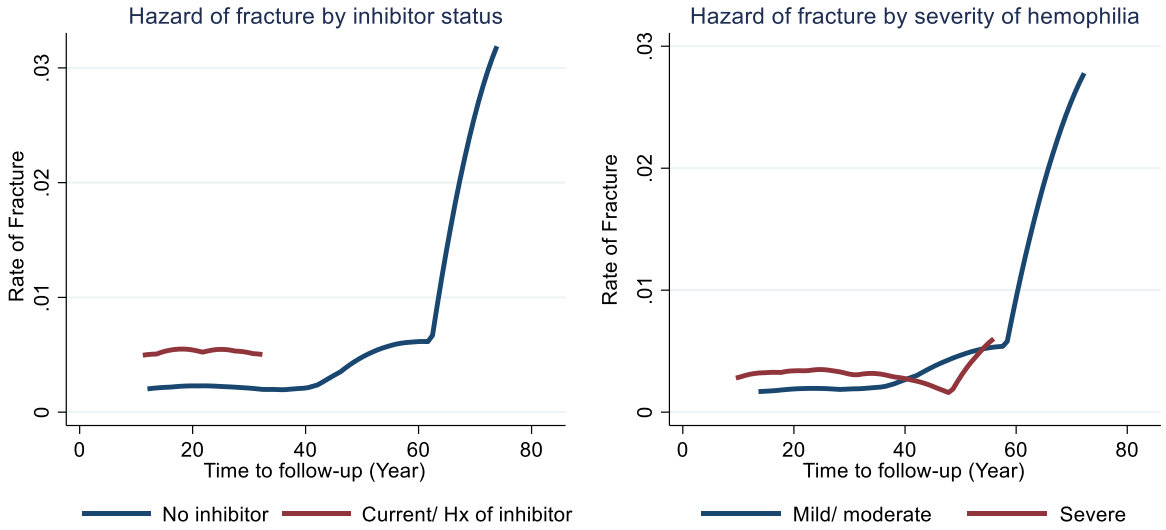


FIGURE 3 | Hazard of fracture amongst people living with haemophilia, stratified by inhibitor status and severity of haemophilia.

for FVIII in bone metabolism or not has been the subject of debate [25–27] Several research groups have hypothesised that FVIII plays a role outside the coagulation system and reported possible effects via the RANK/RANKL/OPG pathway and/or modulating cytokines and other factors.[28–30]

5.1 | Strengths and Limitations

Strengths of our data were the multicentre nature of the study, the possibility to use curated data from the CBDR, and the robust statistical analysis. However, our study had some limitations. The databases, especially ICES, were not created to answer the specific research question. This limited our capacity to adjust for potential confounders, increased the chances of misclassification bias, and translated in a high proportion of missing data for inhibitor status in PWH, and CCI in the control population. We partially addressed this limitation performing sensitivity analyses, that confirmed the results of the main analysis. Moreover, considering that our data was collected in Ontario, Canada, the external validity of the results should be carefully interpreted. Finally, this study used data from a period when emicizumab was not available. Whether the use of emicizumab for prophylaxis in patients with inhibitors changes the risk of fractures remains to be explored in future studies. It has been speculated that there is an effect of FVIII on bone health beyond its haemostatic function, but the evidence for this possible protective effect in PWH is lacking. (Figure 3)

6 | Conclusions

PWH have a higher risk for fractures than the general population. Amongst PWH, severe disease and presence or history of inhibitor are associated with an increased risk for fracture.

Author Contributions

C. C. A. and A. I. conceived the present study. M. R., E. I., A. K., and Q. I. worked on matching the databases. Q. I. conducted the statistical analysis. F. G., D. M., A. K., and Q. I. interpreted the results. All the authors had access to the primary study data. F. G., C. C. A., D. M., Q. I., and A. K. drafted the manuscript. All authors read, provided feedback, and approved the final manuscript.

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Conflicts of Interest

The authors' institution received research funding from NovoNordisk, Roche, Takeda, Bayer, Pfizer, BioMarin, CSL, Freeline, Grifols, Octapharma, Sanofi, Spark, and Uniqure. Davide Matino: Grant/Research support from: Novo Nordisk, Bayer, Pfizer, Octapharma, Sanofi, Spark, Consultant for: Octapharma, Pfizer, Sobi, Sanofi, Bayer, Novo Nordisk, UBI, Speaker Bureau of: Pfizer, Novo Nordisk, Octapharma, Sanofi, Sobi.

Data Availability Statement

Data from the Canadian Bleeding Disorders Registry (CBDR) available upon reasonable request, subject to restrictions from the Association of Hemophilia Clinic Directors of Canada (AHCDC). Data from the Institute for Clinical Evaluative Sciences not available due to privacy restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting Table 1: variables classification, measurement, and sources.

Supporting Table 2: Comparison of demographic characteristics, disease severity and type, inhibitor status, and comorbidities between patients with and without fractures in the haemophilia population.

Supporting Table 3: Comparison of demographic characteristics and comorbidities between patients with and without fractures in the control population. **Supporting Table 4**: Missing data in PWH and controls **Supporting Table 5**: Factors associated with fracture amongst patients with haemophilia in Ontario, 1993–2016 **Supporting Table 6**: Factors associated with fracture amongst patients with haemophilia in Ontario, 1993–2016 **Supporting Figure 1**: Distribution of the Charlson comorbidity index (CCI) amongst people living with haemophilia and people with no bleeding disorder.