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ORIGINAL ARTICLE

Clinical haemophilia

Associated comorbidities, healthcare utilization & mortality in hospitalized patients with haemophilia in the United States: Contemporary nationally representative estimates

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Abstract

Introduction: Current in-hospital burden and healthcare utilization patterns for persons with haemophilia (PWH) A and B, including both children (ages < 18 years) and adults (ages ≥ 18 years), in the United States (US) are lacking.

Aim: To evaluate healthcare utilization, the prevalence of comorbidities, and mortality in hospitalized paediatric and adult PWH using a contemporary nationally representative cohort.

Methods: Hospitalizations of PWH either as the primary reason for admission (principal diagnosis) or one of all listed diagnoses were identified using ICD-10 codes from the 2017 Nationwide Inpatient Sample (NIS), the largest publicly available all-payer inpatient discharge database in the US. Sampling weights were applied to generate nationally representative estimates.

Results: The contemporary cohort included 10,555 hospitalizations (paediatrics, 18.3%; adults, 81.7%) among PWH as one-of-all listed diagnoses (n = 1465 as principal diagnosis). Median age (interquartile range) was 46 (24–66) years overall; adults, 54 (35–70) years and paediatric, 4 (1–11). The most common comorbidities in adults were hypertension (33.4%), hyperlipidaemia (23.6%), and diabetes (21.1%).

In children, hemarthrosis (11.4%), contusions (9.6%), and central line infections (9.3%) were the most common. The overall mortality rate was 2.3%. Median hospital charges per haemophilia admission were $52,616 ($24,303–$135,814) compared to $26,841 ($12,969–$54,568) for all-cause admissions in NIS.

Conclusion: Bleeding and catheter-related infections are the significant reasons for paediatric haemophilia admissions. Adult haemophilia admissions tend to be associated with age-related comorbidities. Costs for haemophilia-related hospitalizations are higher than the national average for all-cause hospitalizations.

KEYWORDS

epidemiology, haemophilia, hospitalization, mortality, NIS, United States

1 | INTRODUCTION

Haemophilia A and B, X-linked recessive disorders caused by genetic variants that result in deficiencies/dysfunction of Factor VIII and Factor IX, respectively, are among the most commonly inherited bleeding disorders.[1] Haemophilia A is estimated to affect one in 5000 males, and Haemophilia B is estimated to affect one in 30,000 males in the United States (US).[2] According to the US Centers for Disease Control (CDC), approximately 33,000 patients with Haemophilia A and B are currently living in the United States.[3]

The clinical severity of the disease varies based on the percentage of coagulation factor activity with severe disease in patients who have < 1% factor activity, moderate disease with 1–5%, and mild disease with factor levels > 5–40% of normal activity.[4,5] Haemophilia, once considered a fatal disease, but now with access to haemophilia therapeutics and establishment of comprehensive haemophilia care, the life expectancy in various studies is gradually increasing from 60 years to closer to 70 years.[6–16] As the aging population with haemophilia increases, these individuals are likely to suffer from more chronic diseases and comorbidities associated with aging, increasing the burden on the health care system.[17] Therefore, it is essential to understand the prevalence of related comorbidities and mortality in PWH to develop targeted preventative strategies.

We have previously reported the prevalence of age-related comorbidity and mortality among hospitalized PWH and their health care expenditure.[9] This report aims to examine contemporary patterns in healthcare utilization, associated comorbidities, and mortality for hospitalized paediatric and adult patients with Haemophilia A and B.

2 | MATERIALS AND METHODS

This data-driven study utilized the National Inpatient Sample (NIS), the largest publicly available inpatient health care database in the United States, for 2017. The NIS developed as a federal-state-industry partnership by the Agency for Healthcare Research and Quality (AHRQ) for the Healthcare Cost and Utilization Project (HCUP). Before 2012, NIS used a 20% stratified probability sample of hospitals instead of discharges.[18] Following a redesign in 2012, the NIS adopted a sampling design that uses a stratified probability sample of 20% of all HCUP discharges from participating hospitals for each calendar year. This sampling scheme is estimated to cover 90–97% of the United States population across different years.[19] The unit of analysis is a single hospitalization and not a specific patient; therefore, a single patient may be represented in multiple observations. Observations are self-weighted and calculated by strata; defined by census division (census region before 2012), bed size, location, teaching status, and hospital ownership.[20]

Information in NIS is in a discharge abstract format, without individual patient or hospital-level identifiers. These data includes one primary or principal diagnosis and up to 39 secondary diagnosis codes, one primary and up to 24 secondary procedure codes, including major operating room procedures during hospitalization. The primary reason for admission is called the 'principal diagnosis' and is coded in the first diagnosis field. The principal diagnosis plus additional conditions that either coexist at the time of admission or that develop during the hospitalization and impact the treatment or the length of stay in the hospital are coded as all-listed diagnoses (Dx1 to Dx40). *International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM)* diagnosis, and procedure codes were used. Haemophilia cases were identified by ICD-10 codes D66 Hereditary Factor VIII deficiency (Haemophilia A) and D67 Hereditary Factor IX deficiency (Haemophilia B) as both primary and as one of all diagnoses.

The data collection included demographics such as age, gender, and race. Hospital-level characteristics were identified from the database. These include hospital location (urban vs. rural), teaching versus non-teaching, bed size (small, medium, and large according to the criteria defined by HCUP for the region of the US and the teaching status).[18] Admission and discharge status, total charges, expected payment source, and the length of hospital stay were also identified. All Patients Refined Diagnostic Related Groups (APRDRG) severity index is a clinical severity index defined by HCUP-NIS available for all patients. APRDRGs are a validated inpatient classification system widely used in the United States as a case-mix measure and account

for the severity of illness, the risk of mortality, prognosis, treatment difficulty, need for intervention, and resource intensity. Data on laboratory values and pharmacological therapies administered during an inpatient stay are not included in the HCUP dataset. Hospital size classifications varied based on the number of beds, teaching status, and geographic region.

The NIS is a de-identified, publicly available data set. Therefore, the study was deemed exempt from review by the Johns Hopkins Institutional Review Board. This analysis was conducted following the HCUP data use agreement guidelines, including suppression of values of tabulated data values between 10 and 1 due to the risks of disclosure.

Demographic and clinical characteristics were described as counts, percentages, mean (standard deviations), and median (interquartile range) as appropriate. The Wilcoxon–Rank Sum testing analysed nonparametric statistics. All p-values were two-tailed and statistical significance was set at $p < .05$. Cost analyses were collected from HCUP online or NIS data which were reported as hospital charges, not including professional fees or non-covered charges. Data were analysed using STATA, version 15 (Statacorp, College Station, TX, USA), using survey analysis commands applying the sampling weights as determined by HCUP.

3 | RESULTS

In 10,555 hospitalizations, Haemophilia A ($n = 8690$) or B ($n = 1975$) was one of all listed diagnoses (110 patients were coded as both Haemophilia A and B). There were 1465 hospitalizations in which either Haemophilia A or B was listed as the principal diagnosis or the coded primary reason for admission. Among total Haemophilia A & B admissions, 18.3% were paediatric admissions. The median age at admission (interquartile range) was 46 (24-66) years, 54 (35-70) years for adults and 4 (1–11) years for paediatrics. The majority of admissions were in Caucasians (64.4%) and males (72.7%) (Table 1).

3.1 | Hospitalization characteristics

Admissions to the hospital were more often for non-elective (urgent/emergent) care (82.1%). Patients with haemophilia were more likely to be treated at large hospitals (62.5%), with care primarily being at urban teaching hospitals (82.9%) (Table 1). Most admissions had higher severity of illness with major or extreme loss of function per the APRDRG scoring systems for severity of illness (major loss of function in 73.2% and extreme loss of function for 22% for all patients). The highest mortality risk (APRDRG extreme risk of mortality stratification) was reported in 7.1% of admissions (Table 1).

3.2 | Associated diagnoses

The most common comorbid diagnoses reported in adult hospitalizations with haemophilia were hypertension (33.4 ± 1.2%), hyperlipidaemia (23.6 ± 1.1%), and type 2 diabetes (21.1 ± 1.0%) (Figure 1A). Other notable diagnoses in adult admissions include post haemorrhagic anaemia (14.4 ± .8%), coronary artery disease (14.3 ± .9%), congestive heart failure (12.4 ± .9%), sepsis (10.6 ± .7%), and central line infection (2.1 ± .4%) (Figure 1A). Concomitant diagnoses of blood-borne or potential transfusion-associated infections included HIV/AIDS in 6.2 ± .6%, and hepatitis C in 14.6 ± 1.0% of admissions, with the youngest age with the diagnosis being 27 and 22 years, respectively. Interestingly, neither intracranial haemorrhage nor hemarthrosis was reported in adults top 10 most common diagnoses (Figure 1A).

The most common comorbidities in paediatric haemophilia admissions were hemarthrosis (11.4 ± 1.6%), contusions (9.6 ± 1.6%), and central line infection (9.3 ± 1.4%). Infusion catheter-related complications (non-infectious) were noted in 3.9 ± .9% of admissions. No paediatric admissions reported an associated diagnosis of HIV/AIDS or hepatitis C (Figure 1B).

3.3 | Mortality

The all-cause in-hospital mortality was 2.3% (95% Confidence Interval (CI) 1.7%-3.1%) ($n = 245$) for all Haemophilia A/B-related admissions (Table 2). The median (interquartile range = IQR) age at death for PWH was 68 (61–77) years that was less than the age for inpatient mortality in all hospitalizations of 73 (61–83) years ($p < .05$). The number of paediatric hospitalizations with inpatient mortality was below the HCUP reportable limit. The most common diagnoses associated with in-hospital mortality included respiratory failure (67.3 ± 5.2%), acute renal failure (65.3 ± 4.9%), and sepsis (49.0 ± 5.1%) (Figure 2). The youngest age for in-hospital death among adults was 26 years.

3.4 | Health care utilization

Of all haemophilia admissions, 93.5% had insurance coverage with the distribution as follows: Medicare: 37.5%, Medicaid: 27.9%, private insurance: 28.1%. The median hospital stay length per haemophilia admission was 3 days (2–6) which was similar to all hospital stays at 3 days (2–5) (Table 2). 84.9% of admissions had a length of stay greater than or equal to 2 days. The median hospital charge per haemophilia admission was $52,616 compared to $26,841 for all NIS hospital admissions (Table 2). The mean hospital charges for a haemophilia admission were $181,414 (SD = $530,121) and ranged from the lowest reported charge of $857 and the highest charge being maxed at $9,999,999 as the highest reportable limit in HCUP (Figure 3).

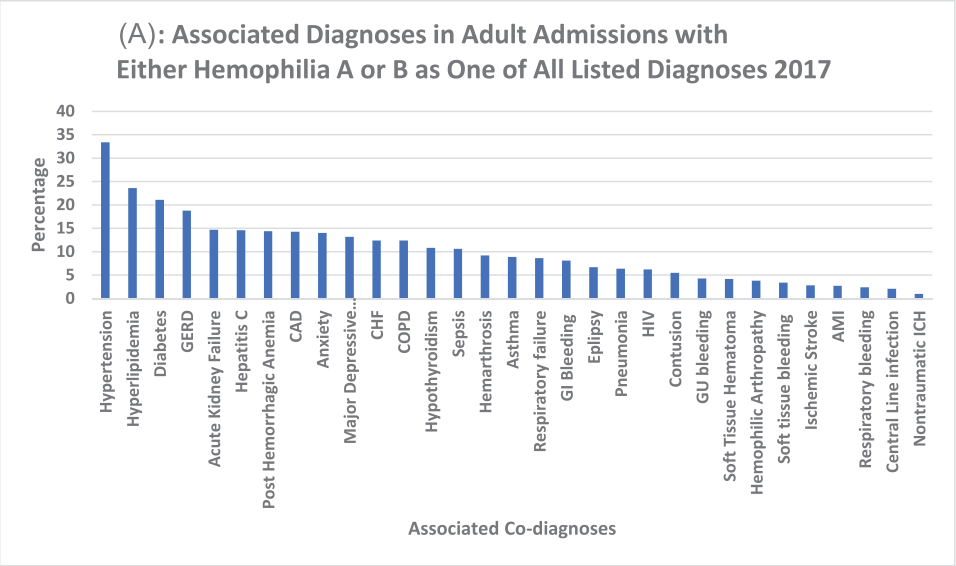
4 | DISCUSSION

This nationally representative study from contemporary data reveals adult haemophilia hospitalizations are related to non-bleeding complications and parallel the comorbidities of the general aging population. In contrast, paediatric admissions are more closely associated

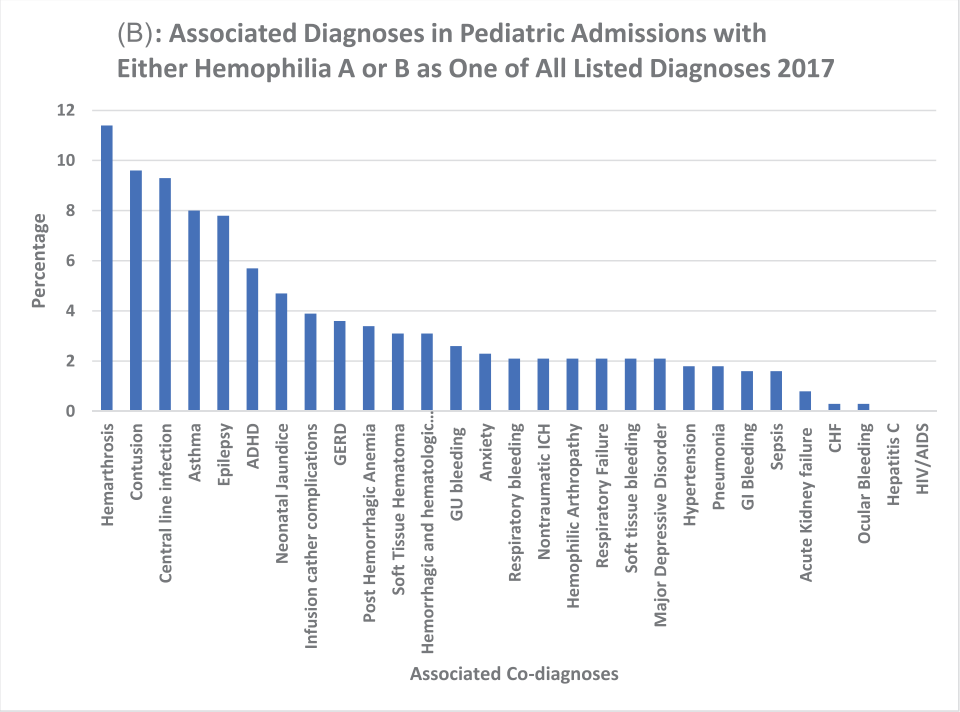
TABLE 1 Characteristics of patients admitted with haemophilia as one of all diagnoses from national inpatient sample, 2017

	Hemophilia A and B N (%)	Hemophilia A N (%)	Hemophilia B N (%)
One in all diagnoses of Hemophilia	10555 (100)	8690 (82.3)†	1975 (18.7)†
Primary diagnosis Hemophilia	1465 (13.9)	1185 (80.9)	280 (19.1)
Demographics			
Age Categories			
Age 0-17	1930 (18.3)	1575 (18.1)	365 (18.5)
Age 18-44	3205 (30.4)	2580 (29.7)	655 (33.2)
Age 45-64	2590 (24.5)	2120 (24.4)	515 (26.1)
Age 65+	2830 (26.8)	2415 (27.8)	440 (22.3)
Mean age (SD)	44.3 (25.8)	44.8 (25.8)	42.5 (25.5)
Median age (IQR)	46 (24-66)	46 (24-67)	42 (24-62)
Adult Admissions	54 (35-70)	54 (35-70)	52 (32-67)
Pediatric Admissions	4 (1-11)	5 (1-12)	2 (0-9)
Gender			
Males	7675 (72.7)	6180 (71.2)	1590 (80.5)
Female	2875 (27.3)	2505 (28.8)	385 (19.5)
Race			
White	6605 (64.6)	5385 (63.9)	1300 (68.1)
African American	1740 (17.0)	1450 (17.2)	310 (16.2)
Hispanic	1285 (12.6)	1075 (12.8)	215 (11.3)
Asian/Pac Island	220 (2.2)	190 (2.3)	30 (1.6)
Other	375 (3.6)	325 (3.8)	55 (2.9)
Hospital and Temporal Characteristics			
Elective vs non-elective admissions			
non-Elective	8650 (82.1)	7145 (82.3)	1600 (81.4)
Elective	1890 (17.9)	1540 (17.7)	365 (19.3)
Hospital Bed Size			
Small	1515 (14.4)	1275 (14.7)	260 (13.2)
Medium	2480 (23.5)	2045 (23.5)	460 (23.3)
Large	6560 (62.2)	5370 (61.8)	1255 (63.5)
Hospital Teaching Status			
Rural	460 (4.4)	370 (4.3)	95 (4.8)
Urban Non-Teaching	1350 (12.8)	1165 (13.4)	205 (10.4)
Urban Teaching	8745 (82.9)	7155 (82.3)	1675 (84.8)
APDRG Severity of Illness			
Minor loss of function	140 (1.3)	110 (1.3)	30 (1.5)
Moderate Loss of function	360 (3.4)	320 (3.7)	40 (2.0)
Major Loss of function	7730 (73.2)	6290 (72.4)	1510 (76.5)
Extreme Loss of function	2325 (22.0)	1970 (22.7)	395 (20.0)
APDRG Risk of Mortality			
Minor	5770 (54.7)	4660 (53.6)	1160 (58.7)
Moderate	2215 (21.0)	1810 (20.8)	435 (22.0)
Major	1825 (17.3)	1565 (18.0)	285 (14.4)
Extreme	745 (7.1)	655 (7.5)	95 (4.8)

†110 patients noted as being coded with both Hemophilia A & B



GERD – Gastroesophageal Reflux Disease; CAD – Coronary Artery Disease; HIV – Human Immunodeficiency Virus; GU – Genitourinary; AMI – Acute Myocardial Infarction; ICH – Intracranial Hemorrhage



ADHD - Attention Deficit Hyperactivity Disorder; GERD – Gastroesophageal Reflux Disease; GU – Genitourinary; ICH – Intracranial Hemorrhage; GI – Gastrointestinal; CHF - Congestive Heart Failure; HIV – Human Immunodeficiency Virus

FIGURE 1 (A) Associated diagnoses in adult admissions with either haemophilia A or B as one of all listed diagnoses 2017. (B) Associated diagnoses in paediatric admissions with either haemophilia A or B as One of All Listed Diagnoses 2017

TABLE 2 Outcomes and hospital charges for patients with haemophilia

	Haemophilia A & B	Haemophilia A	Haemophilia B
Adult outcomes			
Mortality (*n*(%))	240 (2.8)	220 (3.1)	20 (1.2)
LOS (days)			
Mean (sd)	5.9 (7.4)	5.9 (7.4)	5.7 (7.6)
Median (IQR)	4 (2–7)	4 (2–7)	4 (2–6)
Paediatric outcomes			
Mortality	†	†	0
LOS (days)			
Mean (sd)	5.9 (13.1)	5.4 (9.5)	8 (22.8)
Median (IQR)	3 (1–5)	3 (2–5)	3 (1–5)
Health care utilization			
Medicare	3950 (37.5)	3325 (38.4)	670 (33.9)
Medicaid	2935 (27.9)	2430 (28.0)	535 (27.1)
Private insurance	2960 (28.1)	2365 (27.3)	630 (31.9)
Self pay	365 (3.5)	305 (3.5)	60 (3.0)
No charge	25 (.2)	20 (.2)	†
Other	295 (2.8)	220 (2.5)	75 (3.8)
Cost			
Mean (SD)	$181,414 (530,121)	$174,891 (529,658)	$209,660 (529,885)
Median (IQR)	$52,616 (24,303 –135,814)	$51,433 (24,116 –126,251)	$58,019 (24,871–160,738)
Min & Max cost	$857–9,999,999	$1590–9,999,999	$857–5,475,850

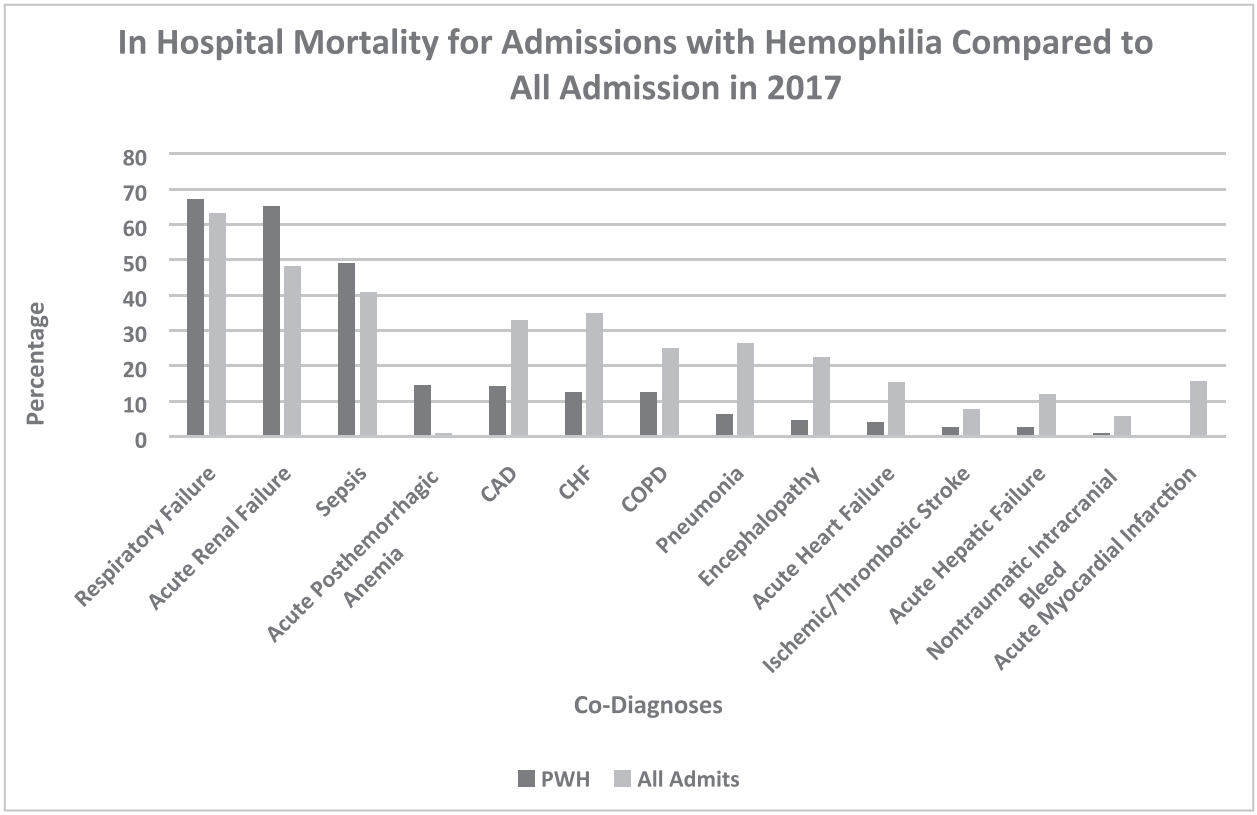
† Values are suppressed as being below the reportable limits for NIS.
Beginning with the 2012 data, the National Inpatient Sample (NIS) was redesigned to optimize national estimates. The nationwide statistics in HCUPnet for years prior to 2012 were regenerated using new trend weights in order to permit longitudinal analysis. The regenerated data were posted to HCUPnet on 7/2/2014. The statistics for years prior to 2012 currently on HCUPnet will differ slightly from statistics obtained prior to 7/2/2014. For more information about the NIS redesign and trend weights, please view the Overview of the NIS.
Citation: HCUPnet, Healthcare Cost and Utilization Project. Agency for Healthcare Research and Quality, Rockville, MD. https://hcupnet.ahrq.gov/. For more information about HCUP data see http://www.hcup-us.ahrq.gov/.

with complications from haemophilia or its treatment with the top reasons for admissions being hemarthrosis and central line infections.

Management of haemophilia has been one of the great successes of modern medicine. The overall life expectancy for PWH in the 1920s being barely 12 years is now beginning to approach that of individuals without haemophilia.[12–15,21,22] Our study showed that the median age at death for hospitalized PWH for this US in-hospital study is 68 years, compared with 73 years of age for all hospitalizations, unchanged from 2007.[9]

The in-hospital median age at death for PWH is also less than the overall life expectancy for the United States in 2017 of 78.6 years.[23] This difference is likely accounted for by the differences in populations with patients expected to be more ill in the inpatient setting. It may also be influenced by additional unique factors. Variability can be seen in the overall life expectancy between patients in the United States (~79 years) or other high-income countries like the Netherlands (~83 years).[9,15,23,24] While 15 paediatric in-hospital deaths (7% mortality rate) were captured in NIS in 2007, the child mortality numbers in this study with 2017 data, decreased to below the reportable limits of 10 by HCUP guidelines, which could be due to variability in the data given the rarity of events.[9] Overall improvements in lifespan could be attributable to the improvements in comprehensive care at federally funded haemophilia treatment centres (HTCs), improved safety of blood products and derivatives including the factor concentrates, access to prophylaxis regimens, improvements in haemophilia therapeutics; specifically access to extended half-life factor concentrates and consequently increased adherence to prophylaxis regimens and decrease in bleeding.[7,8,25]

Historically, mortality in PWH was greatly impacted by HIV in the 1980s and complications of hepatitis C in the 1990s.[7,26–28] Interestingly, this study showed that the reported prevalence of blood-borne/transfusion-associated infections, that is, HIV and Hepatitis C as reported codiagnosis during hospitalization, was lower than other age-related comorbid conditions. This is not surprising as improvements in HIV treatment with improved antiretroviral therapy and the introduction of new hepatitis C antiviral therapies likely



CAD – Coronary Artery Disease; CHF – Congestive Heart Failure

FIGURE 2 In-hospital mortality for admissions with haemophilia compared to all admissions in 2017

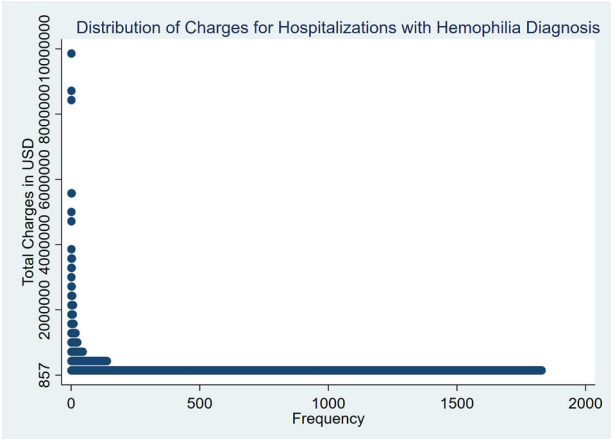


FIGURE 3 Distribution of charges for hospitalizations with haemophilia diagnosis

contributing to these changes. Additionally, improved safety of plasma-derived factors, as well as access to recombinant factor concentrates, further reduced these risks.[7,11,25] Hepatitis C rates are substantially lower than 2007 (21.8% in 2007 to 14.6% in 2017).[9] HIV/AIDS rates were relatively stable between 2007 and 2017 at 5.6% and 6.2%, likely reflecting improved survival and cumulative prevalance.[9] The analyses in both 2007 and 2017, found no reported HIV or hepatitis C cases among children with haemophilia, again reflecting the safety of factor concentrates.[9]

The morbidity and mortality from haemophilia has also been affected by care outside the hospital including novel therapies, prophylactic therapy, or on-demand treatment.[29–32] Safety and quality of care have significantly improved with HTCs as reflected by a 40% reduction in mortality and hospitalizations for haemophilia related events.[8,33] Such improvement in outpatient treatment may reduce complications and admissions for haemophilia related complications.

It is noteworthy that for adult hospital admissions, in the 10 most frequent diagnoses associated with mortality, the only diagnosis related to a bleeding event or its consequence was posthemorrhagic anaemia. Further reductions were observed in mortality due to intracranial haemorrhage 1.0% versus 2.3% compared to prior analyses.[9] This is likely related to increased utilization of prophylaxis regimens among the adult population. Nevertheless, the rate of arthropathy has modest changes from 2.7% in 2007 to 3.8% in 2017[9] (Figure S1).

Comorbidities associated with admissions for PWH continue to reflect overall improvements in clinical care and many of the leading diagnoses now are common chronic age-related conditions as seen among the non-haemophilia population as well, including but not restricted to hypertension, type 2 diabetes, hyperlipidaemia, and coronary artery disease, and these rates have increased from previously reported studies.[9] Besides the above listed comorbidities, many of the acute conditions or medical complications of adult PWH admitted to the hospital are among the most common inpatient diagnoses in the US, such as heart failure, acute renal dysfunction, acute infections, or diabetes related complications.[34]

For paediatric patients, more haemophilia associated bleeding events and catheter related complications remain in the top 10 associated diagnoses. For admissions both for 2007 and 2017, prevalence of bleeding complications across the decade appears to have increased.[9] Although no direct statistical comparison was performed, we observed that hemarthrosis prevalence rates increased from 4.5% to 11.4%. We also observed modest increases in haemophilic arthropathy from 0.9% to 2.1% between 2007 and 2017.[9] The hemarthrosis and haemophilic arthropathy prevalence for inpatients need to be explored further, but could be related to more diligent coding, early awareness/diagnosis, or driven by behavioural changes with improved treatments allowing haemophilia patients much more flexibility and range of motion and an active lifestyle.[9,35] Rates of genitourinary bleeding, have decreased from 3.4% to 2.6%.[9] Importantly, both infectious and non-infectious central line related complications were common; however, trates appear to have decreased some from 15.2% in 2007 to 9.3% in 2017.[9] Reductions in infectious and central catheter complications have similarly been reported in a CDC study of complications in babies with haemophilia (1998–2011).[36] The most common sites of bleeding in children were soft tissue, oral/nasal, head injury, joint bleeding, and intramuscular hematoma, respectively.[36] Importantly, the prevalence of intracranial haemorrhage is no longer in the top 10 list of most common diagnoses for paediatric cases for 2017 admissions (Figure S2). This may corroborate the trends reported by the CDC that incidence of ICH which accounted for 11 out of 203 visits in 2007 and continued to decrease until 2011, when 0 cases were reported.[36]

Cost remains a challenge associated with haemophilia therapy given requirements for long term factor replacement.[37] Fortunately, the vast majority of hospitalized PWH had some form of insurance coverage. Previous studies have shown that even young adults with haemophilia have higher rates of being insured (90.1%) than the United States population in general (81.6%).[38] However, in contrast to other nationally representative data, this study revealed that the majority of patients either had Medicaid or Medicare, leaving private insurance a minority. According to the CDC, the percentage of private insurance payers comprised 53%, compared to this study's 28%.[39] This result in payer differences could result from the lack of outpatient data. In addition, as NIS is not designed to capture readmissions, some of the same patients could be captured multiple times thus the payers could be over/underrepresented. The cost of care for patients with haemophilia remains high: in an analysis of private insurance data from 2008, the annual health care expenditures for both inpatient and outpatient were on average $155,136 [median $73,548] and the costs for patients who develop inhibitors were approximately five fold higher.[40] For individuals with Medicaid the annual costs were $142,987 [median, $46,737], and for those with an inhibitor were 3.6 times higher.[41] The Haemophilia Utilization Group Studies Part Vb (HUGS Vb) showed that annual costs associated with Haemophilia B, in data from 2009 to 2014, to be $140,240 (median $63,617) for those without inhibitors and having any level of disease severity.[42]

This study reveals a continued high overall median cost for haemophilia inpatient care, $52,616 as compared to all NIS hospitalizations; however, the overall median cost for inpatient haemophilia care is down from $76,823 as reported in NIS in 2007.[9] Decreases in costs may be due to reduction in frequency of hospitalization due to bleeding diathesis, the success with increased adherence to outpatient prophylaxis regimens and advances in multidisciplinary outpatient services such as physical therapy at the HTC's, and shorter hospital stays. Generally, only a fraction of the total hospital charges is paid, so the true 'cost' is likely much less than the estimated national bill of $442,188,499 for 2016.[34] The high cost of care as revealed in this study underscores the continued need for efforts to reduce the health care expenses specifically the cost of haemophilia therapeutics for patients and the health care system.

Strengths of this study include the use of the NIS which is the largest all-payer inpatient care database in the US. However, this study has several important limitations. The NIS data are limited to hospitalizations alone. The study does not capture morbidity, cost, or mortality outside of the inpatient setting which is a significant component of the care for PWH. This also introduces a selection bias for patients who are more ill and require hospitalization. Further, although the sampling approach has been validated against other inpatient databases, it does not capture all hospitalized patients or all hospitals and assumes that a representative sample of all hospitalizations would be representative of PWH. However, use of the NIS does constitute a validated and methodologically sound sampling approach that correlates well with national surveys.[43] Further it becomes difficult to classify severity of disease as laboratory data were not available, ICD-10-CM does not subclassify haemophilia severity as mild, moderate or severe. The lack of laboratory data and limitations of ICD-10-CM do not allow for identification of patients who have developed or have a factor inhibitor. ICD-10-CM and differences between ICD-9-CM classifications makes comparisons before and after 2015 difficult. It is possible that the estimates may be driven by a handful of patients with multiple hospitalizations. The accuracy of all results is limited by the billing/coding for patients at discharge. For example, ~1.0% of cases were coded as both Haemophilia A and Haemophilia B. This likely reflects some coding errors or uncertain diagnoses. Also, some frequent diagnoses and comorbidities as identified may not be haemophilia related at all but may represent background prevalence of some diagnoses like type-2 diabetes. Given the limitations, some estimates may not be directly applicable to the overall haemophilia care.

5 | CONCLUSION

In summary, this analysis from NIS 2017 shows bleeding diatheses and catheter-related infections remain the major reasons for paediatric haemophilia admissions. In contrast, adult haemophilia admissions are most frequently associated with comorbidities related to aging.

Future efforts in paediatric PWH should focus on early recognition of bleeding events and complications. Future efforts for improving outcomes in adult PWH should focus on evaluation and prevention of age-related comorbidities such as cardiovascular disease, to reduce the healthcare burden.

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CONFLICT OF INTERESTS

CT serves on the Genentech Advisory board for Haemophilia and Novartis DSMB Aplastic Anaemia Trial.

AUTHOR CONTRIBUTION

Research performed by Jonathan R. Day, Anjali Sharathkumar, Sarah Makhani, Ruchika Goel. Study was designed by Jonathan R. Day, Clifford Takemoto, Ruchika Goel. Data was analysed by Jonathan R. Day, Anjali Sharathkumar, Sarah Makhani. Paper was written by Jonathan R. Day, Clifford Takemoto, Anjali Sharathkumar, Sarah Makhani, Ashwin Gupta, Stephanie Bitner, Cassandra D. Josephson, Evan M. Bloch, Aaron A. R. Tobian, Lakshmanan Krishnamurti, Ruchika Goel.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in HCUP National Inpatient Sample and can be found at https://www.distributor.hcup-us.ahrq.gov/Databases.aspx, HCUP Central Distributor Ordering Website. December 2021. Agency for Healthcare Research and Quality, Rockville, MD. https://distributor.hcup-us.ahrq.gov/Databases.aspx.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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