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ORIGINAL ARTICLE

Inhibitors in hemophilia: association with surgery plans and outcomes in a retrospective cohort study

Omotola O. Olasupo[1] | **Charles Nakar**[2] | **Craig Haddix**[2] | **Thushara Matthew**[1] | **Davide Matino**[3] | **Lynn Malec**[4] | **Lawrence Mbuagbaw**[1] | **Jean-Eric Tarride**[1] | **Alfonso Iorio**[1,3] | **Amy D. Shapiro**[2]

[1]Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, Ontario, Canada

[2]The Indiana Hemophilia & Thrombosis Center, Indianapolis, Indiana, USA

[3]Department of Medicine, McMaster University, Hamilton, Ontario, Canada

[4]Blood Research Institute, Comprehensive Center for Bleeding Disorders, Versiti, Wisconsin, USA

Correspondence
Omotola O. Olasupo, Department of Health Research Methods, Evidence, and Impact, McMaster University, 1280 Main Street West, CRL-140, Hamilton, Ontario, Canada.
Email: olasupo@mcmaster.ca

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Abstract

Background: The development of antibodies (inhibitors) to clotting factors compromises the management of hemophilia A and B, resulting in resistance to clotting factor replacement and, in many cases, the need for bypassing agents to achieve hemostasis.

Objectives: To evaluate the association between the presence of inhibitors and achievement of perioperative hemostasis, development of complications, and presurgical plan deviations.

Methods: We conducted a retrospective study using data from the Indiana Hemophilia and Thrombosis Center surgical database (1998-2019). Associations between perioperative outcomes and inhibitor status were assessed while controlling for patient and procedural characteristics.

Results: A total of 1492 surgeries were performed in 539 persons with hemophilia, with 72 procedures performed in 20 patients with inhibitors (15 with hemophilia A; 5 with hemophilia B). High-responding inhibitors (>5 BU/mL) were present in 27 procedures, low-responding inhibitors (≤5 BU/mL) were present in in 13 procedures, and 32 procedures were performed in patients with historically persistent inhibitors. Adjusting for age, diagnosis, surgery setting, hemostatic agent, data collection period, and surgery type (major/minor), inhibitors were associated with a higher risk of inadequate perioperative hemostasis (33.4% vs 8.6%; adjusted relative risk [adjRR], 3.78; 95% CI, 1.89-7.56; *P* < .001). Reported complications include hemorrhage, fever, pain, thrombosis, and infections. Complications were not statistically different based on inhibitor status (31.7% vs 14.6%; adjRR, 1.25; 95% CI, 0.63-2.49; *P* = .526). Presurgical plan deviations (eg, hemostatic medication dose adjustments, procedure rescheduling, and changes in the length of postoperative hospitalization) occurred more frequently in surgeries involving inhibitors (70.8 vs 39.5%; adjRR, 1.47; 95% CI, 1.12-1.93; *P* = .005).

Conclusion: Inhibitors are associated with higher risks of adverse perioperative outcomes. Strategies to address inhibitor development should be prioritized to avoid undesirable perioperative outcomes.

KEYWORDS
complications, hemophilia, hemostasis, inhibitors, surgery

Essentials

- The impact of inhibitors on surgical outcomes in hemophilia A and B is yet to be fully explored.
- We assessed 1492 surgeries for hemostasis control, complications, and surgical plan deviations.
- Inhibitors were associated with reduced bleeding control and increase in surgery plan changes.
- Complications were not significantly different based on the presence or absence of inhibitors.

1 | INTRODUCTION

The development of neutralizing antibodies to clotting factor therapy with factor VIII in hemophilia A (HA) or factor IX in hemophilia B (HB) is a major treatment-related complication, which results in the inability to achieve hemostasis with standard clotting factor therapies [1,2]. The incidence of these antibodies, also known as inhibitors, is higher in severe disease compared to moderate or mild disease. The lifetime risk of inhibitor development ranges from 25% to 40% in severe HA, while in moderate to mild disease, the cumulative lifetime risk is 5% to 15% [3,4]. Inhibitor development occurs less frequently in HB and is almost exclusively seen in severe disease with a lifetime risk ranging from 1% to 10% [1,4–6].

In addition to disease severity, other risk factors associated with inhibitor development include multiple genetic and nongenetic factors, such as age and regimen intensity at first exposure, type of treatment regimen (prophylaxis or on-demand), and the presence of immune danger signals, such as surgery, trauma, or infection [7,8]. Polymorphisms in genes involved in the immune response and factor concentrate type have also been implicated as contributors to inhibitor development [9–11].

Based on peak inhibitor titers, inhibitors are classified into low-responding inhibitors (LRIs) or high-responding inhibitors (HRIs). LRIs have antibody titers persistently ≤5 Bethesda units (BU)/mL despite repeat exposure to clotting factor therapies, while HRIs have inhibitor titers of >5 BU/mL at any time [12–15]. Inhibitors to factor VIII concentrates in HA can be eradicated by the process of immune tolerance induction (ITI) involving frequent and regular exposure to factor concentrates over a long period of time (several months to years) [12,16]. An overall success rate of 70% to 85% has been reported with this process in HA, with patients being able to achieve hemostasis by regular clotting factor concentrate afterward [16,17].

In HB, although inhibitor development is less common, inhibitors may also be associated with anaphylactoid reactions to factor IX replacement therapy and nephrosis with ITI [18]. This has limited the use and overall success of ITI in patients with HB. Other treatment options such as plasmapheresis to lower inhibitors and desensitization to suppress the development of reactions to allow for ITI have been reported [18–20].

Cases with persistent high-titer inhibitors require the use of bypassing agents (BPAs), such as factor eight inhibitor bypass activity, anti-inhibitor coagulant complex (FEIBA, Baxter) [21], and recombinant human factor VIIa (NovoSeven, Novo Nordisk A/S) [22].

The presence of inhibitors impacts the achievement of hemostatic control, thereby complicating surgical interventions [23]. Before 1990, surgeries in patients with inhibitors were uncommon and often emergent. However, since then, substantial surgical experience has accumulated in this population [24,25]. With improvements in therapy options, used in combination with careful planning, surgeries are now often performed safely in persons with hemophilia with inhibitors [24].

The safety and effectiveness of BPAs in achieving perioperative hemostasis have been studied in persons with hemophilia with inhibitors. These studies have reported achievement of perioperative hemostatic control in 70% to 100% of surgical procedures with either FEIBA [26,27] or recombinant human factor VIIa [28,29]. Postoperative complications have been reported in up to 15% of procedures with reported complications including transient wound hematomas, wound infections, and mortality [27,29].

While perioperative hemostasis and complications have been assessed in persons with hemophilia with inhibitors, there were no comparisons of perioperative outcomes across similar procedures and similar patient populations based on inhibitor status.

Therefore, we aimed to assess the impact of inhibitors on the achievement of perioperative hemostasis, development of complications, and the need to alter presurgical plans, which could be related to the development of hemostatic and nonhemostatic complications.

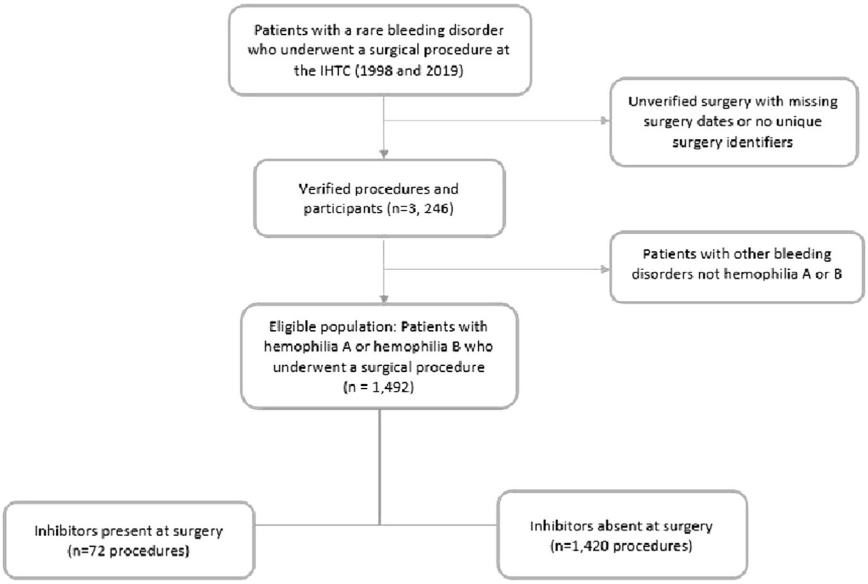
2 | METHODS

Using data captured in the Indiana Hemophilia & Thrombosis Center (IHTC) surgical database, we conducted a retrospective cohort study according to guidance provided in the Strengthening the Reporting of Observational Studies in Epidemiology checklist [30].

2.1 | Data source

The IHTC surgical database was designed to facilitate surgical care plan development and assessment of surgical outcomes in persons with hemophilia and rare bleeding disorders. This database was

FIGURE 1 Study flow chart: inhibitors in hemophilia and surgical outcomes. IHTC, Indiana Hemophilia & Thrombosis Center.



created in 2006 and contains data collected retrospectively from electronic medical records from 1998 to 2006, after which data have been collected prospectively. Data on demographics, diagnoses, procedures, and surgical outcomes are captured with special features tracking if surgical plans were followed as originally written before surgery. Description of this database and its creation, contents, and scope are provided elsewhere [24].

Data collection, storage, access, analysis, and reporting are conducted in compliance with Health Insurance Portability and Accountability Act guidelines with individual patient and surgery data deidentified [31]. Data used for this study were considered exempt by the Institutional Research Ethics Board of relevant institutions.

2.2 | Participants

All patients with a primary diagnosis of HA or HB verified to have undergone a surgical procedure were eligible for study inclusion. Surgeries in patients with von Willebrand disease and other bleeding disorders were excluded. Surgery entries with missing surgery dates or no unique surgery identifiers were also excluded. A flowchart of study eligibility is provided in Figure 1.

2.3 | Study variables

Inhibitors were assessed as present or absent at the time of surgery, with surgeries involving inhibitors categorized into LRIs if preoperative inhibitor titers are ≤5 BU/mL despite repeat exposure to clotting factor therapies; HRIs if preoperative inhibitor titers are >5 BU/mL at any time; and a third category with inhibitor titers not tested before surgery due to the presence of historical persistent inhibitors, with BPAs being used as the hemostatic agent.

Achievement of adequate perioperative hemostatic control was assessed as the primary outcome [1]. Hemostatic control was defined as "adequate" if excellent or good and "inadequate" if fair, poor, or none based on World Federation of Hemophilia guidelines for minimal perioperative blood loss and blood component transfusions comparable to the population without hemophilia [13]. Secondary outcomes assessed included both hemostatic and nonhemostatic complications (eg, infections, fever, allergic reactions, thromboembolism), and presurgical plan deviations. Data on postoperative complications were collected within a 2-week follow-up period, with data collected by chart reviews, by telephone contact, and from information from the clinical discharge summary. Follow-up longer than 2 weeks was also captured from patients' self-report.

Patients' characteristics at the time of surgery (eg, age, weight, sex, hemophilia type, and hemophilia severity) as well as procedural characteristics (eg, planning type [planned or emergent], surgery type [major or minor], setting [inpatient or outpatient], data collection period [retrospective or prospective], and antifibrinolytics recommendation) were identified as potential confounders and were controlled for in the analysis. Surgical procedures were classified into major or minor based on a combination of the level of surgical invasiveness (defined by general or spinal anesthetic requirement, need for respiratory assistance, and penetration of a major body cavity), clinical judgment, and World Federation of Hemophilia guideline recommendations for planned number of consecutive perioperative days of hemostatic support [32,33].

2.4 | Statistical analysis

Patient and procedural characteristics were summarized using mean, SD, median, and range for continuous variables and frequencies and percentages for categorical data. Continuous variables were compared by *t*-test for normally distributed variables and Mann–

TABLE 1 Description of surgeries in patients with factor VIII and IX deficiency with and without inhibitors.

Patient and procedural characteristics	Procedures 1492 (100%)	Inhibitors present 72 (4.8%)	Inhibitors absent 1420 (95.2%)	*P* value
Age				
Adult	1032 (69.2)	40 (55.6)	992 (69.9)	.020
Pediatric	423 (28.4)	28 (38.9)	395 (27.8)	
Weight at surgery (kg)				
Mean (SD)	75.3 (33.0)	98.2 (32.6)	74.2 (32.6)	<.001
Median (range)	80.2 (3.2-160.7)	99.0 (16.9-131.9)	79.2 (3.2-160.7)	
Sex				
Male	1361 (91.2)	72 (100.0)	1289 (90.8)	.002
Female	131 (8.8)	0 (0.0)	131 (9.2)	
Diagnosis				
Hemophilia A	1012 (67.8)	39 (54.2)	973 (68.5)	.011
Hemophilia B	480 (32.2)	33 (45.8)	447 (31.5)	
Planning type[a]				
Emergent	85 (5.7)	10 (13.9)	75 (5.3)	.001
Planned	408 (27.3)	26 (36.1)	382 (26.9)	
Unreported	999 (67.0)	36 (50.0)	963 (67.8)	
Severity of factor deficiency				
Mild	532 (36.0)	1 (1.4)	531 (37.7)	<.001
Moderate	292 (19.7)	0 (0.0)	292 (20.7)	
Severe	656 (44.3)	71 (98.6)	585 (41.6)	
Antifibrinolytics recommended				
No	1051 (70.4)	45 (62.5)	1006 (70.8)	.130
Yes	441 (29.6)	27 (37.5)	414 (29.2)	
Setting				
Inpatient	891 (61.1)	63 (92.6)	828 (59.5)	<.001
Outpatient	568 (38.9)	5 (7.4)	563 (40.5)	
Data collection period				
1998-2006, historic	597 (40.0)	32 (44.4)	565 (39.8)	.432
2006-2019, prospective	895 (60.0)	40 (55.6)	855 (60.2)	
Hemostatic agent used				
Clotting factor replacement	953 (63.9)	5 (6.9)	948 (66.8)	<.001
Bypassing agent	45 (3.0)	44 (61.1)	1 (0.1)	
Other[b]	494 (33.1)	23 (31.9)	471 (33.2)	
Procedure type				
Major	540 (36.2)	27 (37.5)	513 (36.1)	.813
Minimally invasive	952 (63.8)	45 (62.5)	907 (63.9)	

Unless indicated otherwise, data are presented as frequencies and percentages.
[a]Complete cases only (*N* = 493). The variable for surgery planning type was added to the database at a later date.
[b]Other hemostatic agents included desmopressin, antifibrinolytic agent, and aminocaproic acid.

Whitney U-test for nonnormally distributed variables. Categorical variables were compared using chi-square and Fisher's exact tests. Associations between inhibitor status and perioperative hemostatic control, complications, and plan deviations were examined by generalized estimating equations using a negative binomial distribution with a log link function to estimate relative risks (RRs) and 95% CIs.

Potential confounders identified a priori based on clinical judgment such as age, hemophilia diagnosis, surgery planning type, surgery setting (inpatient/outpatient), data collection period, and hemostatic agent used were adjusted for in the model. The quasi-likelihood under the independence model criterion was used in checking the model with the best fit [34], with the model with the smaller value having a better fit. In subgroup analysis, perioperative outcomes were assessed based on inhibitor titer categories.

Complete case analysis was done in the primary analysis. The nature and degree of missingness were explored to identify if missing data were at random, not at random, or completely at random. Missing data were addressed in a sensitivity analysis using multiple imputation by Markov Chain Monte Carlo method. Five complete datasets were created, and the results represent the mean of the imputed datasets. All analyses were performed using SAS Software 9.4 version (SAS Institute Inc).

3 | RESULTS

3.1 | Description of surgeries in persons with HA and HB

Within the 22-year study period (1998-2019), 1492 surgical procedures were performed in 539 persons with hemophilia at IHTC. The distribution of surgeries across the study period is provided in the Supplementary Figure. The majority of the population were adults (69.2%); were male (91.2%), had HA (67.8%), had severe disease (44.3%), and underwent a minor procedure (63.8%). Most procedures were performed in the inpatient setting, and majority were performed in the prospective data collection period (2006-2019).

A total of 72 (4.8%) procedures were performed in 20 (3.7%) patients with inhibitors. HRIs accounted for 37.5% (27/72), LRIs accounted for 18.1% (13/72), and inhibitor titer at the surgery time was untested in 44.4% (32/72) of patients who had historically persistent inhibitors.

In the 33% (493/1492) of surgeries with available data for surgery planning type (planned vs emergency), more surgeries were planned overall, in contrast to emergency procedures (27.3% vs 5.7%; P = .001). Procedures with missing data for the planning type (planned vs emergent) were categorized to a third level in analyses. Surgeries involving inhibitors were absent in females and in patients with moderate factor deficiency. The one surgery in a patient with mild HA with an inhibitor was considered an outlier as including this case in analysis will produce statistically imprecise estimates. Description of procedures based on the presence/absence of inhibitors is provided in Table 1, and the description based on hemophilia type and inhibitor subcategories is provided in Supplementary Table 1.

3.2 | Perioperative hemostasis, complications, and deviations from presurgical plans

Adequate hemostasis was achieved in 88.7% of all procedures. The RR of inadequate perioperative hemostasis was higher in procedures involving inhibitors than in procedures without inhibitors (RR, 4.10; 95% CI, 2.89-5.83; $P < .001$). Controlling for age, diagnosis, inpatient vs outpatient setting, data collection period, hemostatic agent used, and surgical planning type (emergency vs planned), the adjusted relative risk (adjRR) of inadequate perioperative hemostasis was 3.78-fold higher in procedures involving inhibitors (adjRR, 3.78; 95% CI, 1.89-7.56; $P < .001$). Factors associated with inadequate perioperative hemostasis included emergency surgeries (RR, 1.88; 95% CI, 1.04-3.41; P = .037) vs planned surgeries, and inpatient surgeries (RR, 3.02; 95% CI, 1.25-7.23; P = .014) (Table 2, Figure 2). Findings from multivariable analyses are presented in Supplementary Tables 2 to 4.

TABLE 2 Perioperative hemostasis, complications, and surgical plan deviations based on inhibitor status.

Outcomes	Procedures 656 (100%)	Inhibitors absent 585 (89.2%)	Inhibitors present 71 (10.8%)	RR (95% CI)	*P* value	adjRR (95% CI)	*P* value
Perioperative hemostasis							
Adequate	533 (88.7)	491 (91.4)	42 (65.6)	Ref		Ref	
Inadequate	68 (11.3)	46 (8.6)	22 (34.4)	4.10 (2.89-5.83)	<.001	3.78 (1.89-7.56)	<.001
Complications							
None	493 (83.7)	452 (85.4)	41 (68.3)				
Yes	96 (16.3)	77 (14.6)	19 (31.7)	2.13 (1.38-3.30)	<.001	1.25 (0.63-2.49)	.526
Original plan							
Followed	359 (57.3)	340 (60.5)	19 (29.2)				
Altered	268 (42.7)	222 (39.5)	46 (70.8)	1.77 (1.43-2.21)	<.001	1.47 (1.12-1.93)	.005

adjRR, adjusted relative risk; Ref, reference group; RR, relative risk.

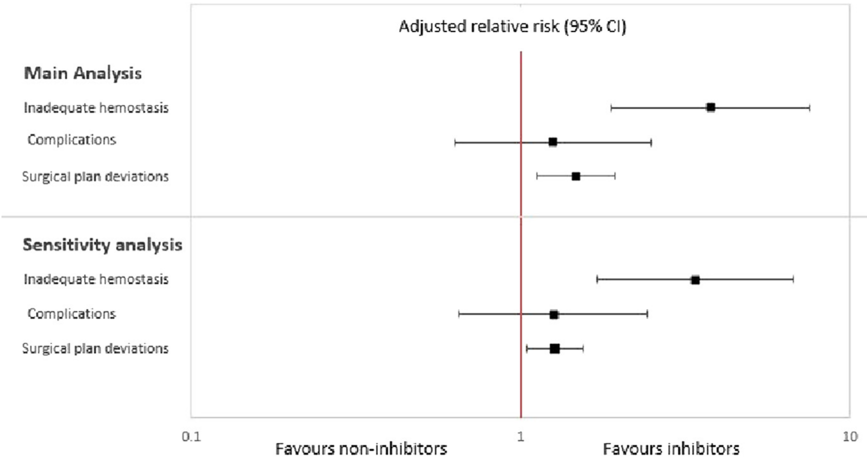


FIGURE 2 Perioperative outcomes in persons with hemophilia based on inhibitor status.

Complications, which included both hemostatic complications such as venous thromboembolism and nonhemostatic complications such as infections and myocardial infarction, occurred more frequently in procedures involving inhibitors compared to noninhibitor surgeries (31.7% vs 14.6%; adjRR, 1.25; 95% CI, 0.63-2.49; P = .526). However, this was not statistically different between surgeries involving inhibitors or not. Overall, 96 (16.3%) procedures reported complications, which included bleeding (n = 28), fever (n = 22), thrombosis (n = 5), anemia (n = 6), development of inhibitors (n = 6), infections (n = 14), and pain (n = 22). Descriptions of reported complications are provided in Supplementary Table 5. Inpatient surgeries were associated with higher rates of complication compared to outpatient procedures (adjRR, 4.86; 95% CI, 1.86-12.69; P = .001). Procedures performed in the prospective data collection period have lower frequency of complications compared to those performed in the retrospective data collection period (adjRR, 0.5; 95% CI, 0.32-1.92; P < .001).

Deviations from surgical plans also occurred more frequently in procedures involving inhibitors (70.8% vs 39.5%; adjRR, 1.47; 95% CI, 1.12-1.93; P = .005). Inpatient surgeries were associated with higher rates of surgical plan deviations compared to outpatient procedures (adjRR, 1.45; 95% CI, 1.02-2.07; P = .041), and procedures performed during the prospective data collection period have higher rates of surgical plan deviations compared with those performed during the retrospective data collection period (adjRR, 1.52; 95% CI, 1.21-1.92; P < .0011).

3.3 | Subgroup analysis

Inadequate hemostasis, complications, and surgical plan deviations were not significantly different in surgeries with LRIs vs HRIs or surgeries involving persistent HRIs vs HRIs (Table 3).

3.4 | Sensitivity analysis around missing data

The degree of missingness was 10.8%, 12.6%, and 7.4% in models assessing hemostasis, complications, and plan deviations, respectively, with outcome variables missing at a frequency of 8.4%, 10.2%, and 4.4% in each model. Using 5 imputed datasets created by Markov Chain Monte Carlo simulations, our findings were consistent with the complete case analysis (Supplementary Table 6).

4 | DISCUSSION

The development of inhibitors poses a threat to the effectiveness of clotting factor replacement therapy as well as the successful perioperative management of persons with hemophilia undergoing surgery.

TABLE 3 Subgroup analysis.

Outcomes	Procedures 656 (100%)	adjRR (95% CI)	P value
Inadequate perioperative hemostasis			
High-responding inhibitors	26 (4.0)	Ref	Ref
Low-responding inhibitors	13 (2.0)	0.99 (0.47-2.10)	.981
Persistent inhibitors	32 (4.9)	0.77 (0.30-1.99)	.587
Inhibitors absent	585 (89.2)	0.26 (0.12-0.55)	<.001
Complications			
High-responding inhibitors	26 (4.0)	Ref	Ref
Low-responding inhibitors	13 (2.0)	0.99 (0.29-3.40)	.985
Persistent inhibitors	32 (4.9)	1.47 (0.45-4.75)	.533
Inhibitors absent	585 (89.2)	0.83 (0.38-1.81)	.640
Surgical plan altered			
High-responding inhibitors	26 (4.0)	Ref	Ref
Low-responding inhibitors	13 (2.0)	0.78 (0.56-1.10)	.159
Persistent inhibitors	32 (4.9)	0.82 (0.59-1.14)	.243
Inhibitors absent	585 (89.2)	0.62 (0.47-0.81)	<.001

adjRR, adjusted relative risk; Ref, reference group.

In our assessment of 1492 surgeries in persons with hemophilia, presence of inhibitors at the time of surgery was associated with the development of adverse clinical outcomes, including increased risk of inadequate perioperative hemostasis, comparable complication risk, and an increased risk of presurgical plan deviation.

In our study population, there were twice as many patients with HA as there were patients with HB (69.6% vs 30.4%), which is different from the estimated 6:1 prevalence ratio of HA to HB in previous studies [35,36]. This relatively higher prevalence of HB compared to HA in our study population (2:1 in contrast to 6:1) is likely reflective of the population with hemophilia at the IHTC who required a surgery. However, our findings are consistent with population-based surveillance data published by the Indiana Hemophilia Surveillance Project across Indiana and the United States, which shows a 64.8% vs 35.2% prevalence of HA compared to HB [37]. Overall prevalence of inhibitors in the population (3.7%) is also lower compared to estimates in published studies, with 5% to 7% of inhibitors unresolved after ITI [1,38]. This could be attributed to an aggressive early approach to ITI treatment for inhibitors at the IHTC.

Based on a 10-year study of postoperative complications following dental extractions in patients with inherited bleeding disorders, 18.9% (10/53) of the procedures reported postoperative bleeding. This was further complicated by the development of inhibitors, especially in mild hemophilia [39]. This is similar to the 16.3% (96/656) prevalence of complications in assessed procedures in our study, which included 26 (1.7%) dental procedures [24]. Achievement of perioperative hemostasis reported in our study (65.6% to 91.4%) is also similar to rates found in previous studies (78% and 94.4%) [27,28].

Deviation from the presurgical plan has been shown to be associated with increased risk of adverse intraoperative events in major abdominal surgery [40]. However, our study is the first to report presurgical plan deviations specifically in persons with HA or HB in relation to inhibitor status.

Limitations of our study include missing data on variables such as surgery planning type, which was included later after database inception. With surgery planning type identified to be an independent risk factor for complications and surgical plan deviations in our analysis, further studies are required to determine the role of surgery planning type on the evaluated perioperative outcomes. However, missing data were addressed in further sensitivity analysis. Surgeries involving inhibitors were absent in females and surgeries in moderate and mild factor deficiency were excluded in further analysis. Therefore, our study findings may not be generalizable to female patients and patients with mild or moderate disease.

In our study, we also identified the absence of standard definitions for classifying surgeries into major or minor surgeries in patients with rare bleeding disorders [32,33]. Further research should be considered in establishing criteria for the classification of surgeries in persons with hemophilia and other genetic bleeding disorders.

With advancements in the management of hemostasis over the study period, for example, introduction of non–clotting factor therapies (eg, emicizumab, fitusiran, concizumab, and marstacimab) [41–44], evaluation of perioperative hemostasis in relation to specific hemostatic agents, as well as time trends in relation to preavailability and postavailability of newer treatment alternatives, would be crucial and would be considered in future analyses.

In conclusion, with higher risks of adverse perioperative outcomes in procedures involving inhibitors, more treatment approaches that prioritize prevention and aggressive eradication of inhibitors in persons with hemophilia are needed. Also, as part of ongoing quality improvement, especially in the surgical care of people with rare bleeding disorders, tracking and surveillance for perioperative outcomes in each hemophilia treatment center and nationally should be emphasized to achieve best practice and best treatment and surgical outcomes.

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AUTHOR CONTRIBUTIONS

O.O.O., A.D.S., and A.I. designed and conceptualized the study. O.O.O., T.M., and C.H. performed data curation. O.O.O. and L.Mbuagbaw performed data analysis. C.H., L.Mbuagbaw, and T.M. performed data validation. O.O.O., A.D.S., A.I., C.N., C.H., J.-E.T., D.M., C.H., and L.Mbuagbaw performed investigation. O.O.O. developed the methodology. O.O.O., A.D.S., and A.I. were resposible for project adminiatration. A.D.S., A.I., J.-E.T., L.Mbuagbaw, and D.M. supervised the study. O.O.O. wrote the original draft of the manuscript. All authors reviewed and edited the manuscript.

RELATIONSHIP DISCLOSURE

A.I. is currently employed at McMaster University and received research grants paid directly to the institution from Bayer, BioMarin, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Sobi, and Takeda. L.Malec received consultancy fees from CSL Behring, Genentech, HEMA Biologics, Pfizer, and Takeda and consultancy fees and research funding from Sanofi. D.M. received research grants paid directly to the institution from Bayer, Pfizer, Novo Nordisk, Sanofi, Spark, and Octapharma; received personal fees outside the submitted work from Sanofi, Sobi, Novo Nordisk, Bayer, Pfizer, and Octapharma for participation in advisory boards, lectures, and preparation of educational material; and reports employment at McMaster University. A.D.S. received clinical research support from Novo Nordisk, Genentech, Sanofi, Kedrion, Agios, Takeda, Pfizer, and Sigilon; received consulting fees from Kedrion Biopharma and Sigilon; received speakers bureau fees from Novo Nordisk and Genetech; received presentation fees from Sanofi; participated in the advisory board of Takeda, Roche, Sanofi, Sigilon, BioMarin, Novo Nordisk, and Genentech; is a Blood Products Advisory Committee (BPAC)-member of the Food and Drug Administration; and is on the Board of Directors of the Novo Nordisk Hemophilia Foundation. The other authors declare no relevant conflict of interest in the design, conduct, and writing of this manuscript.

DATA AVAILABILITY

Access to deidentified data is available by contacting the Indiana Hemophilia & Thrombosis Center at ashapiro@ihtc.org.

TWITTER

Omotola O. Olasupo @oo_olasupo
Lynn Malec @malecly
Lawrence Mbuagbaw @lmbuagbaw
Alfonso Iorio @AlfonsoIorio

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SUPPLEMENTARY MATERIAL

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