Received: 28 August 2025 | Revised: 29 December 2025 | Accepted: 8 January 2026

https://doi.org/10.1016/j.rpth.2026.103356

ORIGINAL ARTICLE

Country-level prediction of blood type distribution in hemophilia A in support of factor VIII consumption

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Handling Editor: Dr A Tosetto

Abstract

Background: Hemophilia A is an inherited bleeding disorder resulting from a lack of factor (F)VIII. Patients with blood type O show faster decay in their FVIII pharmacokinetics and may require higher usage of factor concentrate. Although country-level blood type distribution among persons with hemophilia A is not well characterized, its alignment with the general population may offer a useful basis for prediction.

Objectives: This study compared FVIII usage across blood types and assessed whether the distribution of blood types differs between general population and persons with hemophilia A.

Methods: Data were extracted from the WAPPS-Hemo research database for the hemophilia A cohort and from an online source for the general population. Factor VIII pharmacokinetics and usage differences were assessed using analysis of variance. Poisson log-linear regression models described crosscountry counts of blood types. Congruence between blood type distributions of persons with hemophilia A and general populations was assessed by likelihood ratio test.

Results: Factor VIII pharmacokinetics and usage was significantly different in patients with blood type O. Likelihood ratio test comparison showed no significant difference between both cohorts, with Poisson regression describing reasonably well the count and distribution across blood types.

Conclusion: Patients with blood type O were found to require more FVIII on average. Predicting blood type distributions in persons with hemophilia A is enabled by their statistical similarity to the general population, potentially supporting country-level management of FVIII accessibility. Since South and Latin American countries showed a higher blood type O incidence, persons with hemophilia A from these populations may require a higher FVIII usage.

KEYWORDS
ABO blood-group system, hemophilia A, pharmacokinetics

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Essentials

- Patients with blood type O show shorter terminal half-life and higher factor VIII usage on average.
- Blood type is not significantly different between persons with hemophilia A and general population.
- Blood type distribution in persons with hemophilia A can be predicted from that in general population.
- Factor VIII needs may be increased in countries with high blood type O incidence.

1 | INTRODUCTION

Hemophilia A is an inherited bleeding disorder resulting from a lack in clotting factor (F)VIII. The standard treatment for hemophilia A is prophylactic FVIII replacement therapy consisting of regular infusions of plasma-derived or recombinant FVIII. The interval between infusions and the amounts infused are primarily dependent on an individual's pharmacokinetic (PK) profile.

Blood type O is known to affect the PK of FVIII [1–3] and maybe associated with higher usage of FVIII. Indeed, FVIII PK is correlated with von Willebrand factor (VWF) levels regardless of the factor concentrate [1,2,4]. However, VWF levels are lower in persons with hemophilia A with blood type O than those in persons with other blood types [1,2]. This led to blood type O being identified as a significant covariate describing interpatient variability in FVIII population PK models, associated with faster clearance and shorter terminal half-life in blood type O populations [1–3]. On average, patients with blood type O showed a 1.4-hour significantly shorter FVIII terminal half-life [3].

Blood type is a key factor for treatment management at a population level, which may vary across countries. Specifically, dosing recommendations or assessment of potential benefits when switching to new interventions could be refined using blood type O incidence. However, due to the geographical variations within blood type distributions, this could lead to updating factor stocking recommendations to be highly localized.

The distribution of ABO blood type among persons with hemophilia remains unknown. The FVIII gene whose mutation is responsible for hemophilia FVIII deficiency or impairment is located on the X chromosome [5] while blood type results from the ABO gene located on the ninth chromosome [6]. This does not imply that the ABO blood type distribution would be different in patients with hemophilia compared with that in the general population. This study aims to assess whether blood type distributions in hemophilia A is different from blood type distributions in the general population. To this end, crosscountry blood type distributions using the Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo; www.wapps-hemo.org/) website, which has collected blood type in a substantial number of persons with hemophilia, capturing the ABO blood type distributions in populations with hemophilia worldwide, was tested against crosscountry ABO blood type distributions in the general population (as reported in literature) [7].

If blood type distributions across countries are not different between general population and persons with hemophilia A, count and proportion of persons with hemophilia A with blood type O, who tend to require more FVIII products, could be estimated from the general population. This could lead to improvements in the management and procurement of more appropriate factor and nonfactor stocking levels based on local blood type distributions, which may be relevant during tender processes.

2 | METHODS

2.1 | Populations

Data for population with hemophilia A were extracted from the WAPPS-Hemo research database on July 25, 2025, and included 11,783 unique persons with hemophilia A aged from 1 month to 92 years. Blood type was known in 6117 of these patients (51.9%). Patients for whom blood type was not known were excluded from the subsequent analyses. Patients with all severity types were included, meaning endogenous FVIII levels ranged from <0.01 to 0.40 IU/mL. Factor VIII concentrate, terminal half-life, current treatment plan (as recorded from the WAPPS-Hemo clinical calculator), and VWF levels were extracted from the WAPPS-Hemo databases to assess the effect of blood type on these variables. The final WAPPS-Hemo dataset summarized the count of patients per blood type and country.

Data for the general population was sourced online from the World Population Review website, which provides a country-specific compendium of overall population percentages for different blood types [7]. To simplify the process of data collection for the general population, this unique source was selected because it compiles distributions for most countries represented in the WAPPS-Hemo database.

2.2 | Statistical analysis

Distributions of VWF levels, estimated terminal half-life, and factor usage from current treatment plan along with blood types were graphically analyzed using boxplots and statistically using analysis of variance (ANOVA).

A Poisson log-linear regression modeling approach was used to test for the significance of the association between blood type (A, B, AB, and O) and data source (general vs hemophilia A cohorts) while controlling for country [8]. This approach consisted of conducting a likelihood ratio test (LRT) between 2 Poisson log-linear regression models that used the count of individuals in each blood group and data source combination as dependent variables [8]. The LRT test aims to assess whether the description of the data as fitted by the regression model is significantly better. The LRT test involved a model that included, and another one that excluded, an interaction term between blood type and data source, while accounting for country as a categorical covariate. This interaction term was assumed to be significant if the P value was <.05. A significant interaction would mean that persons with hemophilia have a different blood type distribution compared with the general population. Two main assumptions were used to select the terms to include/exclude in the models used in the LRT test: (i) blood group is different across countries, which supported the inclusion of the interaction term between blood type and country; and (ii) incidence of hemophilia A is consistent across countries [9], which supported the omission of an interaction between source and country and a 3-way interaction term between source, blood type and country.

The goodness of fit of the models was evaluated based on an overdispersion test to rule out model misspecification of the Poisson distribution, plots of observed vs predicted counts and percentages, as well as plots for standardized Pearson residuals [8]. Model estimation was conducted using R version 4.4.1, through the glm() function from the stats package. Graphical analyses were carried out with the ggplot2 R package (R Core Team).

3 | RESULTS

3.1 | Populations

The summary of the WAPPS-Hemo data subset that included patients with known blood type is shown Table 1, where VWF levels were known for 1874 patients. Blood type distributions according to country are presented in Table 2 for both general and hemophilia A cohorts. Overall, WAPPS-Hemo blood type data were available in 54 countries; however, for half of the countries, <50 patients with known blood type were available. From Table 2, South and Latin American countries demonstrated significantly higher proportions of people with blood type O in both general and hemophilia A cohorts with 54.7% and 61.3%, respectively, while the rest of the world demonstrated 37.5% and 40.8% of people with blood type O in general and hemophilia A cohorts, respectively. This result is supported by Figure 1, where proportions of patients with designated blood types were colored by region. For blood type O, South and Latin American countries were clustered on the top right of the figure, which demonstrated a higher proportion of patients with blood type O in these countries.

3.2 | Statistical analysis

Table 1 summarizes the median and first (Q1) and third quartiles (Q3) for VWF levels, estimated terminal half-life, and FVIII usage across concentrate and blood types. Patients with blood type O demonstrated significantly lower VWF levels as illustrated in Figure 2 and Table 1 (median, 0.87 IU/mL) than those with blood types A, B, or AB (median, 1.17, 1.19, and 1.30 IU/mL, respectively; $P < .01$). For each FVIII concentrate except Afstyla and Altuviiio, ANOVA resulted in a significantly shorter terminal half-life in patients with blood type O ($P < .01$) as illustrated in Figure 2 and Table 1. Factor usage corresponds to the weekly amount of FVIII to be infused if the current treatment plan is observed. Figure 2 boxplots and Table 1 show that usage tended to be higher in patients with blood type O for most FVIII concentrates. Since there were less available data regarding treatment plan, this pattern was found significant with ANOVA only for SHL recombinant FVIII concentrates, with an average usage of 9.5 IU/kg/wk higher in patients with blood type O ($P = .028$); for Adynovate, with an average usage of 8.4 IU/kg/wk higher in patients with blood type O ($P = .043$)l and for Eloctate, with an average usage of 11.3 IU/kg/wk higher in patients with blood type O ($P < .01$).

When comparing the distribution of blood type between the hemophilia and general cohorts, the statistical test for the interaction term between blood types and source indicated no evidence, suggesting that blood type distributions differ between general and hemophilia A cohorts. Results for the corresponding LRT are presented in Table 3, while the estimated models used for this test can be found in Appendix B.

The evaluation of the Poisson regression model, presented in Figures 1 and 3, showed an excellent goodness of fit in terms of count as well as an acceptable goodness of fit in terms of proportions per blood type across countries and data sources. The goodness-of-fit assessment was supported with (coefficient of determination) R^2 values of 0.983, 0.990, 0.964, and 0.900 for blood types O, A, B, and AB, respectively in the hemophilia A cohort. Goodness-of-fit assessments resulted satisfactory, which supported the conclusions based on the model (Supplementary Tables A1 and A2 and Supplementary Figure A1 in Appendix A).

Since the distribution of blood types A, B, AB, and O among individuals with hemophilia A showed no evidence of statistical difference from that of the general population, we can use the general population data to estimate the proportion of blood type O within the hemophilia A population (P_{Hemo}). The 95% CI for P_{Hemo} can be calculated using the following formula (which is based on the asymptotic sampling distribution of a sample proportion under the Central Limit Theorem):

$$P_{Hemo} = P \pm \frac{1.96}{\sqrt{N}}\sqrt{P(100-P)},$$

where P represents the percentage of individuals with a specific blood type in the general population and N represents the count of persons with hemophilia A. The number of individuals with a specific blood type in the hemophilia cohort N_{Hemo} may be deduced as follows:

$$N_{Hemo} = N * P_{Hemo}/100.$$

TABLE 1 Summary of VWF, estimated terminal half-life, and factor usage across blood types.

	Blood type O	Blood type A	Blood type B	Blood type AB
VWF (IU/mL)	0.87 (0.70-1.13); 776	1.17 (0.94-1.48); 650	1.19 (0.98-1.49); 326	1.30 (1.09-1.70); 122
SHL recombinant FVIII				
Terminal half-**life (h)**	9.7 (7.8-12.2); 969	11.9 (9.5-14.7); 727	11.6 (9.5-14.3); 341	12.1 (10.1-15.0); 136
Usage (IU/kg/wk)	97.2 (77.5-111.1); 34	90.5 (74.3-126.8); 35	87.5 (70.6-129.6); 17	65.7 (65.0-109.2); 7
SHL plasma-derived FVIII				
Terminal half-life (h)	9.7 (8.0-12.3); 330	11.6 (8.9-14.6); 238	11.1 (9.4-13.7); 133	13.2 (10.6-15.9); 45
Usage (IU/kg/wk)	87.5 (86.6-102.5); 27	87.5 (87.5-107.8); 32	95.5 (87.5-117.0); 17	87.5 (76.0-128.1); 3
SHL BDD FVIII				
Terminal half-**life (h)**	8.8 (7.0-10.8); 333	10.9 (9.1-13.8); 259	10.5 (8.3-13.1); 97	11.0 (8.9-13.0); 29
Usage (IU/kg/wk)	88.1 (75.5-108.5); 20	87.5 (76.6-118.1); 31	87.5 (71.0-96.8); 13	85.8 (81.8-119.1); 6
Afstyla				
Terminal half-**life (h)**	12.6 (10.4-15.5); 56	14.0 (10.9-17.9); 30	16.8 (15.1-21.2); 12	14.1 (10.3-18.6); 7
Usage (IU/kg/wk)	78.6 (73.3-86.0); 6	63.9 (56.9-70.3); 2	129.6 (109.3-140.2); 3	NA; 0
Adynovate				
Terminal half-**life (h)**	13.0 (10.9-15.8); 252	16.1 (13.6-19.6); 219	15.8 (12.7-18.4); 86	18.4 (13.9-21.5); 28
Usage (IU/kg/wk)	86.4 (67.1-108.5); 51	80.5 (68.0-98.9); 44	58.4 (44.0-82.4); 15	57.0 (54.8-70.6); 8
Eloctate				
Terminal half-**life (h)**	13.9 (11.6-17.7); 554	17.0 (13.7-20.6); 514	17.6 (14.6-21.2); 184	18.9 (15.5-22.8); 65
Usage (IU/kg/wk)	84.7 (65.2-97.6); 89	76.1 (57.2-95.7); 107	84.3 (57.6-100.0); 44	80.6 (65.6-97.1); 19
Esperoct				
Terminal half-**life (h)**	15.4 (12.9-21.1); 65	18.6 (15.5-21.7); 76	19.4 (16.9-22.0); 27	20.5 (19.6-22.3); 9
Usage (IU/kg/wk)	70.0 (60.8-86.4); 15	77.8 (65.9-87.5); 25	72.9 (59.1-86.9); 11	61.2 (49.6-91.4); 3
Jivi				
Terminal half-**life (h)**	14.0 (11.9-16.2); 78	17.1 (14.1-21.0); 79	19.2 (14.4-22.0); 26	20.9 (17.9-22.7); 12
Usage (IU/kg/wk)	86.7 (64.0-92.5); 10	73.7 (69.6-98.3); 14	77.3 (64.5-95.6); 7	65.1 (65.1-65.1); 1
Altuviiio				
Terminal half-**life (h)**	49.5 (45.7-52.4); 47	49.0 (46.2-54.7); 27	49.8 (46.1-54.7); 20	54.0 (51.4-57.1); 4
Usage (IU/kg/wk)	50.0 (47.6-63.0); 7	49.1 (46.2-49.8); 7	51.5 (50.0-51.7); 5	45.0 (42.5-47.5); 2

Values are median (Q1-Q3); *n*.
NA, not applicable.

4 | DISCUSSION

Our analyses supported the hypothesis that FVIII PK and usage are different in patients with blood type O. They also supported the congruence of blood type distributions between hemophilia A and general population cohorts, with results stemming from real-world data collected within the WAPPS-Hemo database.

This analysis assumed that blood type would affect PK and usage through its correlation with VWF levels. Because of such correlation, we hypothesized that blood type O proportion in a population correlates with lower distribution of VWF levels in that same population. Difference in VWF levels may lead to differences in PK and usage for some factor concentrates but would not affect, for example, Altuviiio or emicizumab PK and potentially usage. In that regard, the anticipated effect of blood type on PK across most factor concentrates [3] was supported by our study (Figure 2 and Table 1); nevertheless, this effect did not explain the existing individual variability to a great extent (the remaining variability was ∼30%). Thus, estimation of individual PK is still necessary for FVIII replacement therapy, regardless of an individual's blood type. This analysis is not valuable to inform about PK-tailored treatment but valuable at the population or national scale regarding the assessment of factor and nonfactor resources. Since presence of blood type O is associated with a 1.4-hour average decrease in terminal half-life for both standard and extended

TABLE 2 Comparison of blood type distributions between general population and persons with hemophilia A populations split by country.

	Hemophilia A (covered by WAPPS-Hemo)					General				
Country	Population	O (%)	A (%)	B (%)	AB (%)	Population	O (%)	A (%)	B (%)	AB (%)
Algeria	53	52.83	35.85	9.43	1.89	4.74×10^7	46.28	32.49	16.20	5.03
Argentina	107	63.55	31.78	3.74	0.93	4.59×10^7	54.63	34.07	8.94	2.36
Australia	104	50.00	34.62	13.46	1.92	2.70×10^7	44.12	37.25	13.73	4.90
Austria	91	31.87	45.05	16.48	6.59	9.11×10^6	36.20	44.24	14.08	5.48
Belarus	15	46.67	40.00	13.33	0.00	9.00×10^6	38.00	36.00	18.00	8.00
Belgium	51	54.90	33.33	7.84	3.92	1.18×10^7	45.00	40.00	10.00	5.00
Bosnia and Herzegovina	13	38.46	23.08	30.77	7.69	3.14×10^6	36.00	43.00	14.00	7.00
Brazil	186	52.15	36.56	9.14	2.15	2.13×10^8	45.00	42.00	10.00	3.00
Bulgaria	5	20.00	40.00	20.00	20.00	6.71×10^6	33.00	44.00	15.00	8.00
Canada	356	44.66	37.08	14.33	3.93	4.01×10^7	46.00	42.00	9.00	3.00
Chile	42	61.90	26.19	11.90	0.00	1.99×10^7	59.20	30.22	8.63	1.95
China	797	40.40	24.72	25.97	8.91	1.42×10^9	34.43	27.88	29.13	8.56
Colombia	454	64.98	26.43	7.05	1.54	5.34×10^7	66.43	23.81	7.98	1.78
Croatia	12	16.67	66.67	8.33	8.33	3.85×10^6	34.00	42.00	18.00	6.00
Czech Republic	176	42.61	36.93	14.77	5.68	1.06×10^7	32.00	42.00	18.00	8.00
Denmark	14	35.71	50.00	14.29	0.00	6.00×10^6	41.00	44.00	10.00	5.00
Estonia	13	46.15	46.15	7.69	0.00	1.34×10^6	33.80	35.30	23.70	7.20
Finland	131	32.82	37.40	15.27	14.50	5.62×10^6	33.00	41.00	18.00	8.00
France	116	42.24	46.55	6.03	5.17	6.67×10^7	43.00	45.00	9.10	2.90
Germany	636	37.89	43.24	11.01	7.86	8.41×10^7	41.00	43.00	11.00	5.00
Greece	97	45.36	38.14	11.34	5.15	9.94×10^6	44.40	37.90	13.00	4.70
Guatemala	7	42.86	28.57	28.57	0.00	NA	NA	NA	NA	NA
Hong Kong	17	47.06	23.53	29.41	0.00	7.40×10^6	43.03	25.32	25.72	5.93
Hungary	223	30.04	43.50	14.80	11.66	9.63×10^6	32.00	40.00	19.00	9.00
Indonesia	25	40.00	20.00	32.00	8.00	2.86×10^8	37.00	26.00	29.00	8.00
Ireland	77	54.55	31.17	11.69	2.60	5.31×10^6	55.00	31.00	11.00	3.00
Italy	231	47.62	38.53	12.12	1.73	5.91×10^7	46.00	42.00	9.00	3.00
Japan	81	24.69	43.21	25.93	6.17	1.23×10^8	30.05	40.00	20.00	9.95
Korea, Republic of	161	29.19	34.16	29.19	7.45	5.17×10^7	29.05	31.94	30.95	8.06
Mexico	51	70.59	21.57	5.88	1.96	1.32×10^8	61.82	27.44	8.93	1.81
Netherlands	131	49.62	40.46	9.16	0.76	1.83×10^7	45.00	43.00	9.00	3.00
New Zealand	4	100.00	0.00	0.00	0.00	5.25×10^6	49.90	37.00	11.00	2.10
Norway	53	43.40	41.51	9.43	5.66	5.62×10^6	39.00	49.00	8.00	4.00
Oman	2	0.00	50.00	50.00	0.00	NA	NA	NA	NA	NA
Peru	1	100.00	0.00	0.00	0.00	3.46×10^7	71.40	18.90	8.08	1.62
Poland	22	9.09	54.55	22.73	13.64	3.81×10^7	37.00	38.00	17.00	8.00
Portugal	91	42.86	43.96	8.79	4.40	1.04×10^7	42.30	46.60	7.70	3.40
Qatar	17	29.41	52.94	17.65	0.00	NA	NA	NA	NA	NA
Romania	2	0.00	100.00	0.00	0.00	1.89×10^7	33.00	43.00	16.00	8.00

(Continues)

TABLE 2 (Continued)

	Hemophilia A (covered by WAPPS-Hemo)					General				
Country	Population	O (%)	A (%)	B (%)	AB (%)	Population	O (%)	A (%)	B (%)	AB (%)
Russian Federation	73	34.25	38.36	17.81	9.59	1.44×10^8	42.00	35.00	20.00	3.00
Saudi Arabia	15	40.00	20.00	13.33	26.67	3.46×10^7	55.70	19.35	20.32	4.62
Slovakia	116	25.00	38.79	26.72	9.48	5.47×10^6	32.00	42.00	18.00	8.00
Slovenia	9	33.33	66.67	0.00	0.00	2.12×10^6	38.00	40.00	15.00	7.00
South Africa	7	28.57	42.86	28.57	0.00	6.47×10^7	45.00	37.00	14.00	4.00
Spain	339	41.30	41.59	11.80	5.31	4.79×10^7	44.00	43.00	10.00	3.00
Sweden	23	26.09	60.87	8.70	4.35	1.07×10^7	38.00	44.00	12.00	6.00
Switzerland	30	36.67	43.33	13.33	6.67	8.97×10^6	41.90	45.00	9.00	4.10
Taiwan	300	40.33	27.33	28.00	4.33	2.31×10^7	44.14	25.97	23.89	6.00
Thailand	17	29.41	29.41	23.53	17.65	7.16×10^7	41.00	17.00	37.00	5.00
Turkey	2	50.00	50.00	0.00	0.00	8.77×10^7	33.80	43.80	15.30	7.10
United Kingdom	101	58.42	25.74	12.87	2.97	6.96×10^7	50.00	36.46	10.42	3.13
United States	358	48.88	39.66	8.94	2.51	3.47×10^8	46.73	39.41	9.90	3.96
Uruguay	10	50.00	40.00	10.00	0.00	NA	NA	NA	NA	NA
Venezuela	49	65.31	16.33	18.37	0.00	2.85×10^7	62.30	29.70	6.00	2.00

NA, not applicable; WAPPS-Hemo, Web-Accessible Population Pharmacokinetic Service—Hemophilia.

half-life concentrates [3], more frequent infusions or higher doses may be required overall to reach same FVIII trough levels in patients with blood type O. Blood type is an optional variable collected by the WAPPS-Hemo website when registering patients as it is not a strong predictor of PK variability. This may explain such a high rate of missing values in our database. This analysis assumed that missing blood type was random across the population and not associated with patient factor usage nor country. Our analysis showed that FVIII usage in WAPPS-Hemo was significantly higher in patients with blood type O for SHL recombinant FVIII concentrates Adynovate and Eloctate. From these data, patients with blood type O may require approximately 10-IU/kg/wk more FVIII than patients with blood type A, B, or AB. Increased FVIII usage could also come from more severe bleeding phenotype in patients with blood type O due to their lower VWF levels. However, association of blood type with bleeding tendency, desired target levels according to patient's clinical status, and/or lifestyle were out of scope in this analysis. Regardless of cause, a population with a higher blood type O incidence may require significantly more FVIII for their replacement therapy.

Since there was no evidence to suggest that the distribution of blood types A, B, AB, and O among individuals with hemophilia A was different from the general population, we derived a formula to estimate the count and proportion, along with their CI, of persons with hemophilia A with blood type O within a country from the proportion known in the general population and total count of persons with hemophilia A in a country. For instance, the World Federation of Hemophilia estimates that there are 3335 individuals with hemophilia A in Colombia [10]. Then, the estimated count and percentage of persons with hemophilia A with blood type O in Colombia is as follows: N_{Hemo} = 2214 (95% CI, 2161-2268) and P_{Hemo} = 66.4% (95% CI, 64.8%-68.0%).

Omission of blood type variation within resource planning could leave the country short in terms of FVIII stocking. For instance, a conservative increase in usage of 5 IU/kg/wk for persons with blood type O (Eloctate usage was ∼10 IU/kg/wk higher in patients with blood type O) within an adult population weighing 70 kg on average would signify 12.4 million IU/y increase of FVIII in Colombia (66.4% of patients with blood type O) compared with that in Canada (46.0% of blood type O patients), while both countries have a similar number of persons with hemophilia A.

Table 2 and Figure 1 illustrate the high intercountry variability in blood type distributions. In particular, South and Latin American countries exhibited higher proportions of people with blood type O (>50%), while most countries ranged approximately 40%. In literature, some ethnic populations such as Mayans and Peruvian Indians were shown to have very high proportions of people with blood type O up to almost 100% [11]. The previous example emphasizes that such populations may require a significant FVIII usage.

The main limitation to this study resides in its data sources. On the one hand, data on the general population was obtained from an open-source web page (World Population Review [7]), which has no explicit data quality assessment or methodology documentation. We conducted several checks on the alignment of numbers provided with cited sources (Supplemental file). Numbers were aligned not necessarily identical with the cited sources, which were mainly country-dependent blood services websites whose numbers are publicly available but are subject to updates while lacking traceability. Given the extent and complexity of the required data, this source was

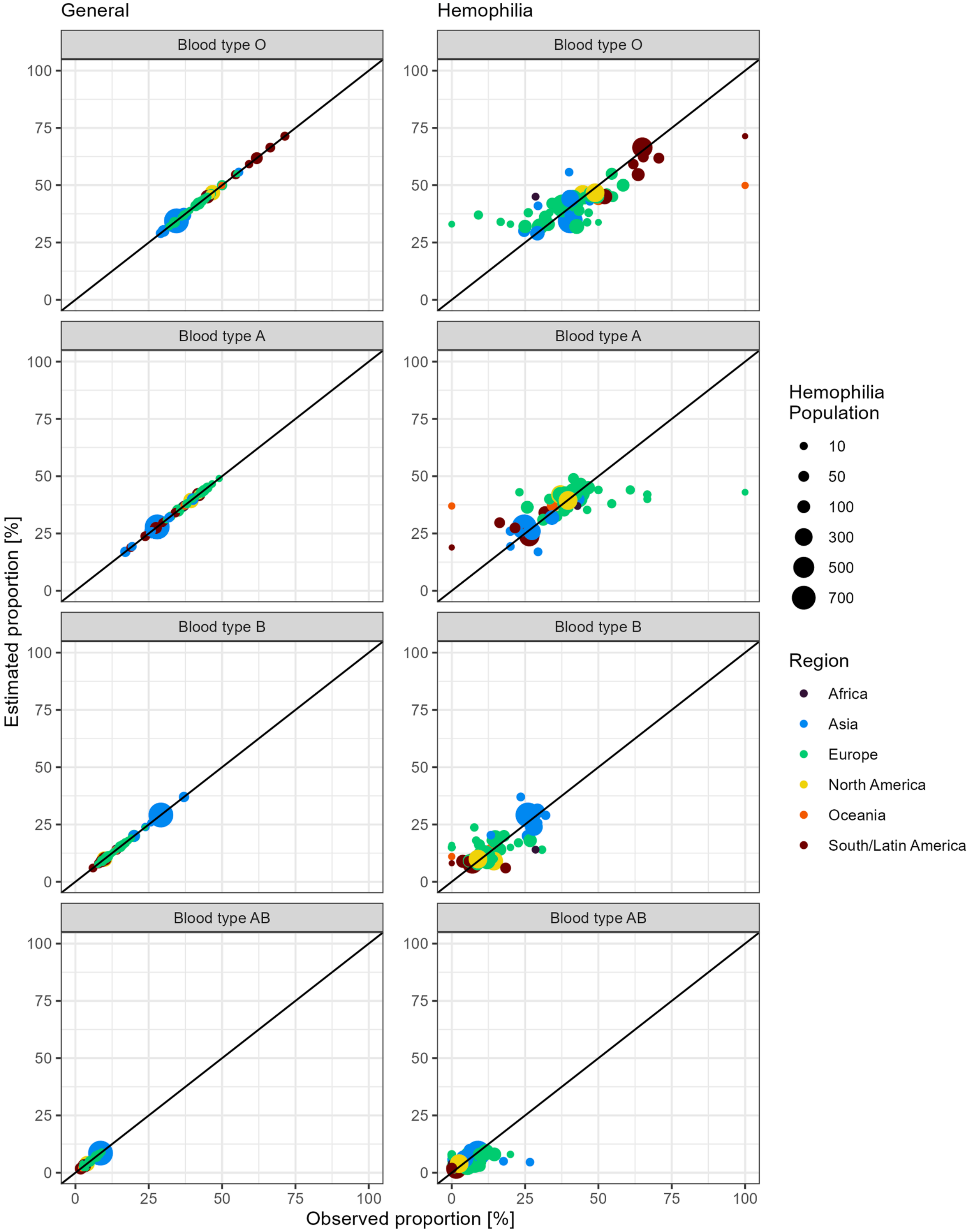

FIGURE 1 Observed vs predicted proportions across blood types split by data source and region.

selected to summarize the blood type distributions across countries, helping to achieve a standardized process of data collection that would minimize sources of variation. On the other hand, data for the hemophilia A cohort came from the WAPPS-Hemo database, which captures a subset of the overall population with hemophilia. Since many factors can affect available data on hemophilia A, such as a

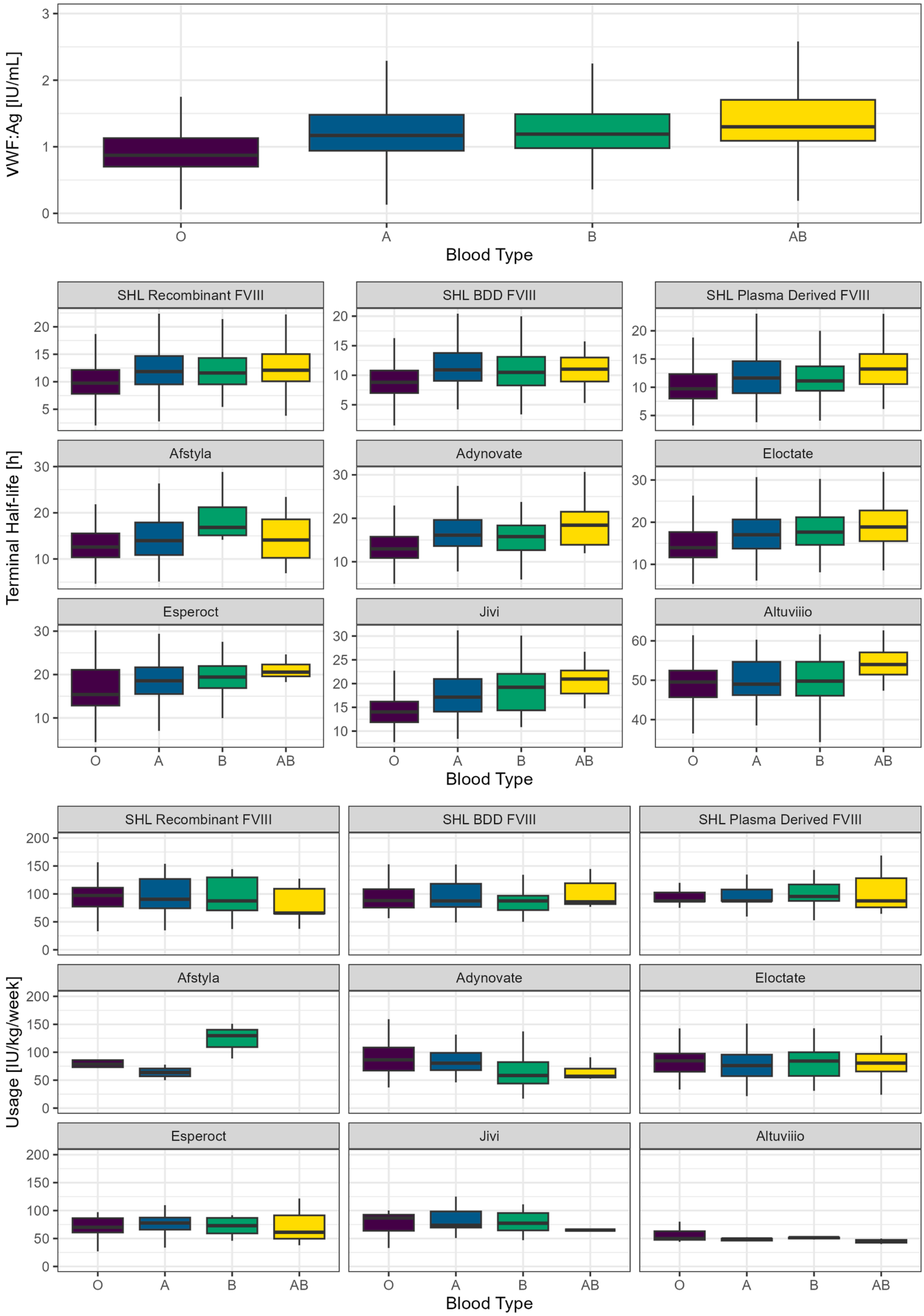

FIGURE 2 von Willebrand factor (VWF) levels, terminal half-life, and factor VIII usage according to blood types collected in Web-Accessible Population Pharmacokinetic Service—Hemophilia (WAPPS-Hemo) database.

country's economic status, health system, and geographical and financial accessibility to treatment centers [9], there is variability in data quality and size between countries represented in WAPPS-Hemo. Nonetheless, the WAPPS-Hemo database represents the largest hemophilia data repository worldwide and included 5000+ patients with known blood type used as real-world data in this study.

TABLE 3 Results of likelihood ratio test (LRT) between the regression models.

Model	Residuals: degrees of freedom	Residuals: deviance	Degrees of freedom	Deviance	LRT *P*
No interaction	200	2.171×10^2	196	3.400×10^8	NA
Interaction between blood type and source	196	2.118×10^2	4	5.308×10	.257

NA, not applicable.

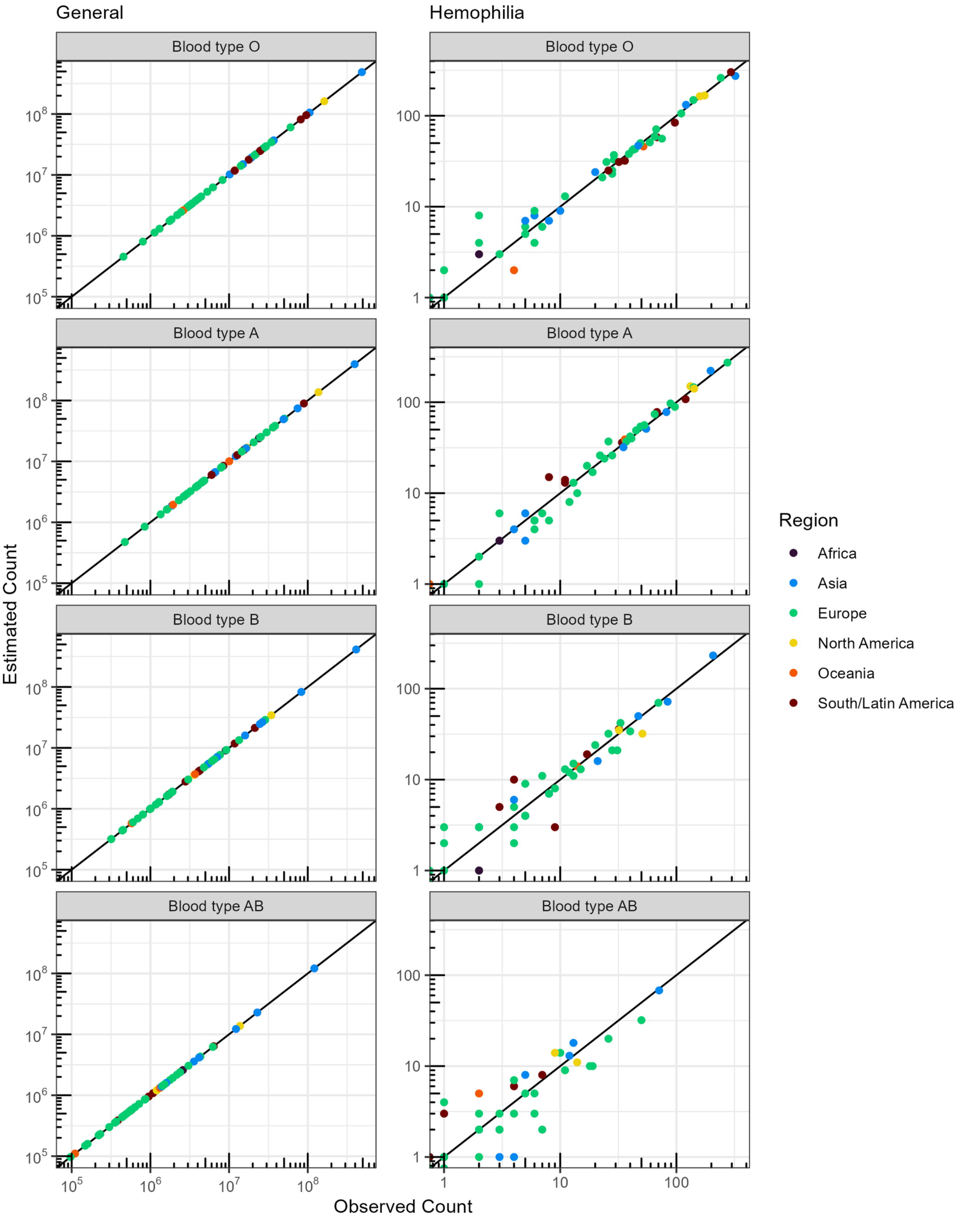

FIGURE 3 Observed vs predicted count across blood types split by data source and region.

This work has the potential to change the budget allotment of various medications as those countries with a high incidence of patients with blood type O patients, such as Colombia, would require more standard and extended half-life FVIII than a country with lower incidence, such as Canada. In these cases, there may be a budget wide cost-savings if a policy shift was made to prioritize novel therapies. For instance, prioritizing switching to efanestocog alfa or emicizumab may be of more interest, as the PK of these products does not depend on VWF and should not be influenced by blood type. This implication could also impact decision making at a country level toward the funding of gene therapy. Since its effectiveness would likely be dependent on blood type, countries with a high percentage of patietns with blood type O may not find it cost-effective.

5 | CONCLUSION

Patients with blood type O were found to require more FVIII on average across most of FVIII concentrates within the WAPPS-Hemo database. Predicting blood type distributions in the hemophilia A cohort is enabled by their statistical similarity to the general population, potentially supporting country-level management of FVIII accessibility. Since South and Latin American countries showed a higher blood type O incidence [7,11], persons with hemophilia A from these populations may require a higher FVIII usage, on average, which could have a potential impact on FVIII stocking, allocation, and funding prioritization for novel treatments.

FUNDING

The authors received no funding for this study.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

AUTHOR CONTRIBUTIONS

P.C. and S.H. contributed to the concept and design of the manuscript, analysis and interpretation of data, and critical writing or revising the intellectual content. D.H. contributed to the analysis and interpretation of data and to the critical writing or revising the intellectual content. A.I. and A.E. contributed to the critical writing and revising the intellectual content.

DATA AVAILABILITY

Hemophilia data can be requested through WAPPS-Hemo (contact: wappshemo@mcmasterhkr.com).

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SUPPLEMENTARY MATERIAL

The online version contains supplementary material available at https://doi.org/10.1016/j.rpth.2026.103356.