EXPLORING TEMPORAL PATTERNS OF CLOTTING FACTOR USE AND ASSOCIATED HEALTHCARE UTILIZATION IN HEMOPHILIA

Zheng-Yi Zhou, PhD[1], Christina X. Chen, PhD[2], Michael B. Nichol, PhD[3],
[1,2]Analysis Group, Inc., [1]New York, NY, [2]Boston, MA; [3]School of Pharmacy, University of Southern California, Los Angeles, CA, USA

USC School of Pharmacy

USC University of Southern California

INTRODUCTION

- The World Federation of Hemophilia and the National Hemophilia Foundation recommend initiation of prophylaxis at an early age prior to onset of frequent bleeding.
- For hemophilia patients, the choice to manage bleeds with episodic or prophylactic clotting factor replacement therapy and differences among subgroups with unique factor use patterns may have a significant impact on health and economic outcomes.
- There is lack of research on how the clotting factor use patterns impact the health outcomes in hemophilia patients.

OBJECTIVE

- To characterize clotting factor use patterns over time by using group-based trajectory models (GBTMs) and to assess the economic outcomes associated with trajectory subgroups.

METHODS

- **Data Source:** We analyzed Medicaid claims data from 6 states (California, Florida, Iowa, Kansas, Missouri, and New Jersey) during 1998 to 2012.
- **Study Sample**
  - The study included males aged 2-64 years with at least one diagnosis of hemophilia A (ICD-9 code: 286.0x) or B (ICD-9 code: 286.1x), recorded clotting factor use, and at least 36 months of consecutive enrollment.
  - Patients were excluded if they had at least two medical visits with diagnosis of Von Willebrand disease (ICD-9 code: 286.4x) or had at least one claim of bypassing agent during the entire eligibility period suggesting history of inhibitors.
- **Variables Definition**
  - ***Index date:*** the start date of eligibility was defined as the index date and the study period was the 36 months following the index date.
  - ***Proportion of months covered (PMC):*** monthly clotting factor prescriptions filled for 36 months were identified; then PMC was calculated as the number of months with clotting factor dispensed divided by 36 months of follow-up.
  - ***Severity* of hemophilia**: less severe patients were those who used desmopression, a medication prescribed only for mild or moderate hemophilia.
  - ***Hemophilia Related Comorbidities***, such as hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infection were determined by ICD-9 codes or NDC codes for the associated treatment from the entire available claims data.
  - ***Non-hemophilia Related Comorbidities*** were identified using ICD-9 codes from post 12-month index date and consisted of the Charlson Comorbidity Index (CCI).
  - ***Healthcare Utilization and Costs***
    - Measurements included inpatient, emergency room and outpatient visits during each year of the 36-month study period.
    - Healthcare costs captured the reimbursement amounts from Medicaid to healthcare providers and were adjusted to 2012 US dollars using the medical care component of the Consumer Price Index.
- **Statistical Analysis**
  - A semi-parametric, GBTM, was used to classify patients to one trajectory group of clotting factor use patterns by their observed clotting factor use over 36 months.
  - Within each trajectory group of clotting factor use pattern, all patient characteristics and outcomes were examined descriptively using means and standard deviations for continuous variables, and frequency counts and percentages for categorical variables.
  - Multivariate regression models were performed to assess the impact of high probability of clotting factors use on healthcare utilization and costs, adjusting for demographics, index year, insurance type as of the index date, hemophilia-related comorbidities, and modified CCI.
  - Count variables (including the number of medical service visits and length of hospital stay) were analyzed using negative binomial regression models.

TABLE 1. PATIENTS CHARACTERISTICS

Variable[a]	Overall (n = 1035)	Clotting Factor Use Pattern[b] Group 1 (n = 262)	Group 2 (n = 220)	Group 3 (n =76)	Group 4 (n =142)	Group 5 (n = 183)	Group 6 (n = 152)	*P*-value[c]
PMC, mean [SD]	0.4 (0.3)	0.0 (0.0)	0.2 (0.1)	0.5 (0.1)	0.4 (0.1)	0.7 (0.1)	0.9 (0.1)	<0.0001
Hemophilia type								0.004
Hemophilia A	841 (81.26)	215 (82.06)	159 (72.27)	64 (84.21)	115 (80.99)	157 (85.79)	131 (86.18)	
Hemophilia B	194 (18.74)	47 (17.94)	61 (27.73)	12 (15.79)	27 (19.01)	26 (14.21)	21 (13.82)	
Insurance type FFS	706 (68.21)	170 (64.89)	151 (68.64)	54 (71.05)	103 (72.54)	133 (72.68)	95 (62.50)	0.23
Age, mean [SD]	15.6 (14.0)	15.9 (14.8)	17.1 (15.5)	18.2 (14.7)	17.3 (15.0)	14.3 (11.2)	11.5 (10.5)	0.01
Race/ethnicity								0.04
White	440 (42.51)	121 (46.18)	103 (46.82)	33 (43.42)	63 (44.37)	72 (39.34)	48 (31.58)	
Black	140 (13.53)	40 (15.27)	33 (15.00)	14 (18.42)	25 (17.61)	16 (8.74)	12 (7.89)	
Hispanic	246 (23.77)	67 (25.57)	50 (22.73)	15 (19.74)	29 (20.42)	37 (20.22)	48 (31.58)	
Other	209 (20.19)	34 (12.98)	34 (15.45)	14 (18.42)	25 (17.61)	58 (31.69)	44 (28.95)	
State								0.004
California	368 (35.56)	75 (28.63)	77 (35.00)	43 (30.28)	72 (39.34)	22 (28.95)	79 (51.97)	
Florida	295 (28.50)	65 (24.81)	44 (20.00)	50 (35.21)	63 (34.43)	31 (40.79)	42 (27.63)	
Iowa	72 (6.96)	36 (13.74)	18 (8.18)	6 (4.23)	8 (4.37)	2 (2.63)	2 (1.32)	
Kansas	35 (3.38)	18 (6.87)	9 (4.09)	2 (1.41)	4 (2.19)	0 (0.00)	2 (1.32)	
Missouri	162 (15.65)	42 (16.03)	39 (17.73)	26 (18.31)	26 (14.21)	8 (10.53)	21 (13.82)	
New Jersey	103 (9.95)	26 (9.92)	33 (15.00)	15 (10.56)	10 (5.46)	13 (17.11)	6 (3.95)	
Hemophilia-related comorbidities								0.03
HIV	147 (14.20)	29 (11.07)	29 (13.18)	18 (23.68)	29 (20.42)	32 (17.49)	10 (6.58)	
HCV	275 (26.57)	63 (24.05)	53 (24.09)	28 (36.84)	43 (30.28)	58 (31.69)	30 (19.74)	
CCI score[e], mean[SD]	0.8 (2.0)	0.5 (1.4)	0.8 (2.0)	1.4 (2.5)	1.1 (2.2)	1.1 (2.4)	0.5 (1.4)	0.0008
Hemophilia severity: Mild condition	131 (12.66)	83 (31.68)	32 (14.55)	2 (2.63)	5 (3.52)	4 (2.19)	5 (3.29)	<0.0001

Abbreviations: PMC=proportion of months covered; SD=standard deviation; FFS=Fee for service; HCV=hepatitis C virus; HIV=human immunodeficiency virus; CCI=Charlson Comorbidity Index. **Note**: Data were presented as number (column percentage) excepted when noted for mean (SD).
[a.] The demographic and clinical characteristics were measured during the 365-day period (first year) following the index date. HIV and HCV infections were identified during the whole eligibility period. [b.] Clotting factor use patterns were identified using group-based trajectory analysis which recursively grouped together patients with similar temporal adherence patterns; the 6-group model was presented. [c.] Statistical comparisons were conducted using Chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables.

TABLE 2. HEALTHCARE RESOURCE UTILIZATION

Healthcare Utilization Variable[a]	Incidence Rate Ratio [95%CI][b] [Group 1]/[Group 6]	[Group 2]/[Group 6]	[Group 3]/[Group 6]	[Group 4]/[Group 6]	[Group 5]/[Group 6]
All-cause ER visit					
Year 1	0.6 [0.4 ,0.8]**	1.6 [1.0 ,2.4]*	1.6 [1.0 ,2.6]*	1.6 [1.1 ,2.5]*	1.7 [1.1 ,2.5]*
Year 2	0.7 [0.5 ,1.1]	1.8 [1.2 ,2.5]**	1.1 [0.7 ,1.7]	2.1 [1.5 ,3.1]***	1.9 [1.3 ,2.8]**
Year 3	0.9 [0.6 ,1.3]	2.2 [1.5 ,3.3]***	1.6 [0.9 ,2.5]	2.1 [1.4 ,3.1]**	1.5 [1.0 ,2.3]
All-cause IP visit					
Year 1	0.6 [0.4 ,0.8]**	0.5 [0.3 ,0.9]*	1.2 [0.6 ,2.3]	0.6 [0.3 ,1.1]	1.0 [0.6 ,1.8]
Year 2	0.5 [0.3 ,0.9]*	0.8 [0.5 ,1.4]	1.4 [0.8 ,2.5]	0.8 [0.4 ,1.4]	1.7 [1.1 ,2.7]*
Year 3	0.5 [0.3 ,0.8]**	0.8 [0.5 ,1.3]	1.4 [0.8 ,2.5]	1.2 [0.7 ,1.9]	1.2 [0.7 ,1.9]
All-cause OP visit					
Year 1	0.4 [0.3 ,0.5]***	0.5 [0.4 ,0.6]***	0.9 [0.8 ,1.1]	0.7 [0.6 ,0.8]**	0.8 [0.7 ,0.9]**
Year 2	0.5 [0.4 ,0.6]***	0.7 [0.6 ,0.9]**	0.9 [0.7 ,1.1]	0.9 [0.8 ,1.1]	1.0 [0.8 ,1.1]
Year 3	0.6 [0.5 ,0.7]***	0.9 [0.7 ,1.1]	1.0 [0.7 ,1.3]	1.2 [1.0 ,1.5]	1.2 [1.0 ,1.4]
Bleeding related ER/IP visit					
Year 1	0.6 [0.4 ,1.1]	1.9 [1.0 ,3.5]*	2.2 [1.1 ,4.4]*	2.2 [1.2 ,4.0]**	1.8 [1.1 ,3.0]*
Year 2	0.9 [0.6 ,1.5]	2.6 [1.6 ,4.3]***	1.2 [0.7 ,2.3]	3.3 [2.0 ,5.5]***	1.8 [1.1 ,3.0]*
Year 3	0.7 [0.4 ,1.3]	2.3 [1.4 ,3.9]**	1.6 [0.8 ,3.2]	2.1 [1.3 ,3.6]**	1.2 [0.7 ,2.0]

Abbreviations: ER=emergency room; IP=inpatient; OP=outpatient; CI=confidence interval. **Notes**: Significance at 0.05 level = *, 0.01 = **, 0.001 = ***
[a] Healthcare resource utilization was measured during each year of the 36-month study period. [b] Incidence rate ratios (IRRs) and p-values were calculated from negative binomial model with generalized estimating equation. All models were controlled for age, hemophilia type, geographic region, index year, insurance type, CCI, and comorbidities (HIV or HCV infections). IRRs>1 indicate an increased risk or incidence rates for patients in clotting factor use pattern trajectory subgroup 1-5 compared with those in subgroup 6.

RESULTS

- Table 1 describes patient characteristics stratified by the trajectory groups of clotting factor use.
- Figure 1 displays the six-group adherence trajectory model. The predicted probability of monthly factor used in each group is plotted with solid lines. The observed proportion of individuals in each group that had monthly factor used is plotted with dotted lines. The proportion of each group is displayed at the right.
- A six-group model best represented included patients (n=1,035): Group 1) had <5% mean probability of monthly factor use (proportion of study sample: 25.3%); 2) had 10%-20% mean probability of monthly factor use (21.3%); 3) switched from high (mean: 74%) to low (mean: 20%) probability of factor use (7.3%); 4) had low (mean: 28%) probability of factor use at beginning and slowly increased to 60% (13.7%); 5) switched from 60% probability of use to high of 80% probability of use (17.7%); 6) consistently 90% probability of use (14.7%) (Figure 1).
- After adjusting for baseline characteristics, patients in Group 6 had significantly fewer bleeding-related ER visits or hospitalizations compared with those in Group 2 or 4 (year 1 to 3 adjusted incidence rate ratio ranged 1.9-3.3, all p-values <0.05) (Table 2).
- Patients annual costs without inhibitor averaged $107,420 per patient (SD: $145,915; median: $51,564), of which 93% attributed to clotting factor costs (Figure 2).

FIGURE 1. TRAJECTORY MODEL

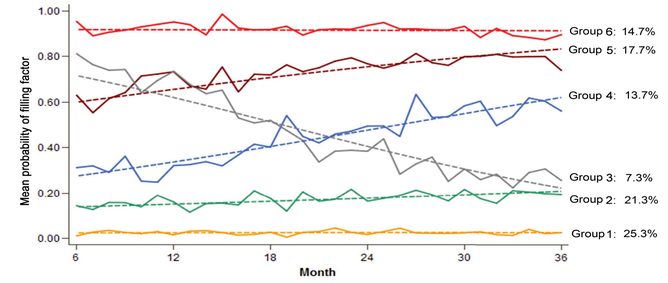
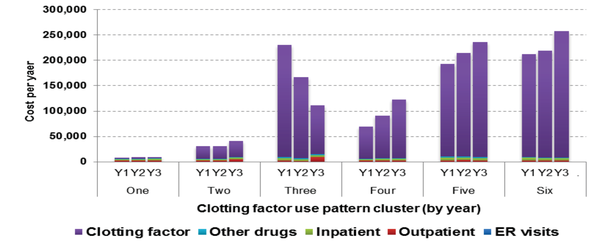


FIGURE 2. TOTAL HEALTHCARE COSTS ($)



CONCLUSIONS

- Healthcare utilization and costs differed among patient subgroups with distinct temporal patterns of clotting factor use.
- The finding on variations between individuals will be helpful for clinicians and payers to design personalized treatment regimens for hemophilia patients.

ACKNOWLEDGMENT

- Dr. Christina Chen was a Pre-Doctoral Fellow in Health Economics with Biogen and the University of Southern California at the time this work was completed.
- The authors thank the Hemophilia Utilization Group Study Steering Committee members (Randall G. Curtis, MBA, Marion A. Koerper, MD, Brenda Riske, MS, MBA, MPA, Megan M. Ullman, MA, MPH, Judith R. Baker, DrPH, MHSA) for providing editorial and project support.
- Corresponding author: Michael B. Nichol, Ph.D (mnichol@usc.edu)