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ORIGINAL RESEARCH

Effectiveness of Prophylactic Coagulation Factor Replacement Therapy in Patients with Severe Hemophilia A in Taiwan – A Population-Based Study

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Purpose: Taiwan launched reimbursement of prophylactic coagulation factor replacement therapy (CFRT) for patients with severe hemophilia type A (severe PWHA) in 2014. However, since then, the effectiveness of prophylactic CFRT in real-world practice has not been evaluated thoroughly. This study aimed to evaluate the effectiveness of prophylactic CFRT in severe PWHA cases on the outcome of bleeding risks.

Patients and Methods: We included male, severe PWHA cases from a nationwide, population-based database in Taiwan. Given that the database lacked details of the dosing regimen for prophylactic CFRT, we applied group-based trajectory modeling using the proportion of days covered (PDC) by CFRT from 2014 to 2015 in order to classify patients. A high PDC level corresponded to a greater proportion of time under CFRT, thus implying that the patient was probably receiving prophylactic therapy. We followed up patients from January 01, 2016 until occurrence of any bleeding events, death or December 31st 2017.

Results: We identified a total of 420 severe PWHA and classified them into high- (n = 88), medium- (n = 181) and low- (n = 151) PDC groups. The mean (±SD) PDC values of the three groups were 0.78 (±0.1), 0.40 (±0.1) and 0.12 (±0.1), respectively. Using Cox regression models with propensity score adjustment, we found patients with medium- (hazard ratio: 0.69; 95% CI: 0.56–0.89) or high-PDC (0.45; 0.36–0.68) under CFRT had reduced risks of any bleeding, compared to the low PDC group.

Conclusion: The findings demonstrated the effectiveness of prophylactic CFRT in the prevention of bleeding events in real-life severe PWHA.

Keywords: hemophilia, coagulation factor replacement therapy, prophylaxis, proportion of days covered

Background

Hemophilia A is a congenital bleeding disorder characterized by deficiency of blood coagulation factor VIII (FVIII). The severity of disease is related to the degree of FVIII deficiency. Severely ill patients most commonly experience bleeding into the joints, muscles, and other organs. To prevent bleeding, coagulation factors can be replenished by injecting exogenous coagulation factor concentrate into a vein. The infusion aids in maintaining the factor level within the normal range, which promotes normal blood coagulation. This is called prophylactic coagulation factor replacement therapy (CFRT). Prophylaxis with CFRT has been recommended by the World Federation of Hemophilia (WFH) as the standard care for patients with severe hemophilia A.[1] Compared to episodic treatment or on-demand therapy, prophylactic CFRT provides benefits in preventing hemarthroses and arthropathy.[1–3] Clinical controlled trials show that when initiated at an early age, prophylactic therapy is associated with more than 80% reduction in the risk of joint damage, as determined by

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magnetic resonance imaging, as well as a decrease in hemarthroses and any type of bleeding events.[4–6] Prophylaxis also provides other long-term benefits such as preventing intracranial hemorrhage[7] and reducing functional limitations and disability, thereby reducing utilization of health care resources and improving patients' quality of life.[8]

Nevertheless, most patients rely on financial support from their insurance or government programs to cover the high costs of prophylactic CFRT.[9–11] In 2014, seeking to balance clinical efficacy in preventing joint damage with the health care budget impact, the National Health Insurance Administration of Taiwan started to reimburse the cost of prophylactic CFRT for patients with severe hemophilia A (severe PWHA).[12] A previous study from Taiwan indicated that while the initiation of reimbursement for prophylactic CFRT in severe PWHA increased the total medical costs with the increased use of factor therapy, non-factor costs were decreased, suggesting that the growth of prophylactic factor therapy might reduce clinical complications of severe PWHA.[13] To date, numerous studies have evaluated the real-world effectiveness of prophylactic CFRT. However, some of them are of cross-sectional design which limits their ability to infer any causal relationship between prophylactic CFRT and bleeding outcomes,[14,15] while others included only a single institution and may have been of limited sample size with relatively low generalizability to the population.[16–18]

Therefore, this study aimed to undertake a large population-based evaluation of the effectiveness of prophylactic CFRT in severe PWHA in a real-world setting. Specifically, we adopted group-based trajectory modeling (GBTM) to classify patients into groups based on their probability of undergoing prophylactic CFRT, as indicated by the proportion of days covered (PDC) by CFRT, and we investigated the association between different CFRT trajectories and risks of bleeding and arthropathy.

Methods

Design and Data Source

This was a retrospective cohort study utilizing claims data from 2013 to 2017 from the National Health Insurance Database (NHID) from Health and Welfare Data Science Center in Taiwan.[19] The NHID is a population-based claims database covering more than 99% of the entire population of Taiwan (approximately 23 million individuals). The NHID's datasets comprise medical records containing disease diagnoses and medication prescriptions from outpatient, inpatient and emergency departments. To protect data privacy, encrypted personal identification numbers were used to interlink between different datasets. To obtain more valid clinical information and follow-up data, we linked the NHID to the Cause of Death Registry and the Catastrophic Illness Certificates (CIC) database to acquire information on death records and more valid hemophilia diagnoses. This study was conducted in accordance with the ethical standards of the Institutional Review Board and the Declaration of Helsinki. Research ethics approval was given by the IRB of National Cheng Kung University Hospital (ID B-ER-108-390), whereby the IRB waived the written informed patient consent requirement due to the retrospective nature of the study design and because all individual identifiers were encrypted and thus not personally identifiable.

Study Population

We included male patients with severe hemophilia A with at least one record of FVIII treatment from 2014 to 2015. Hemophilia A was identified through the International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification diagnosis codes (ICD-9-CM 286.0; ICD-10-CM D66) in the patients' CICs. Because patients with CICs were able to waive certain copayments, all diagnoses in the CIC database were required to have been validated by experts from the National Health Insurance Administration. The NHID contained no laboratory examination results that could have served to classify patients' hemophilia A severity; therefore, in order to increase the positive predictive value when identifying true severe PWHA, we referred to previous studies[20–22] that investigated the health resource utilization of severe PWHA and defined patients with at least 6 outpatient visits including CFRT prescriptions per year during the study period as having severe hemophilia A. We found that the proportion of the so defined severe patients was approximately 55% among all PWHA (data not shown), which was consistent with a previous report from Taiwan.[23]

Classification of Patients by Proportion of Days Covered (PDC)

Given the NHID's lack of details on the dosing regimen for prophylactic CFRT, we calculated the PDC by FVIII as an indicator to classify patients. The PDC level reflected how long a patient persisted with FVIII therapy within a pre-specified period. A PDC level of 1 indicated that the patient was under CFRT every day during the specified period, while a PDC level of 0.1 indicated that the patient was under CFRT for only 10% of the days within the specified time. A higher PDC level represented a greater proportion of time under FVIII therapy, thus implying that the patient was more likely to be receiving prophylactic therapy. By contrast, a lower PDC level meant that the patient maintained FVIII therapy only briefly or that the patient received relatively high doses of factors for a short period of time, ie for episodic treatment. For each patient, we retrieved all records of FVIII prescriptions from 2014 to 2015 and calculated the PDC for every quarter.

Group-Based Trajectory Modeling (GBTM)

To describe real-world usage patterns of CFRT, we applied GBTM to classify patients based on their PDC with CFRT. GBTM is a data-driven method that identifies and categorizes clusters of individuals with similar developmental trajectories (ie, treatment patterns presented as different PDC groups in this study).[24–26] We used a censored normal distribution statistical model that applied maximum likelihood estimation to identify groups of trajectories which were summarized by a finite polynomial function of time.[24–26] After pre-specifying a number of trajectory groups, the probability of a specific group membership was estimated for each subject and all subjects were then assigned to the group for which they had the highest probability. In this study, we fitted several 2- or 3-group models with polynomials of varying degree in each group because larger numbers of groups would have been affected more by the smaller and imbalanced sample sizes between strata. To select the best model, we applied the Bayesian information criterion (BIC) as a major criterion, together with the following, suggested by Nagin[27] to select the best model: (1) sufficient number of patients in each group (>5% in each group); (2) an average posterior probability value >0.7 for each group; (3) the odds of correct classification >5 for each group; (4) close correspondence between probability of membership in each group and proportion of individuals assigned to each group; and (5) reasonably narrow confidence intervals.

Outcomes and Follow-Up

We started following up patients from January 1st 2016 to the occurrence of outcome events, death or the end of the study period (Dec 31st 2017), whichever came first. The primary outcome was any bleeding event or an increase in the dose of FVIII by 20% over the preceding month. The secondary outcomes included major bleeding and hospitalization due to arthropathy. Major bleeding events included hemarthrosis, intracerebral/intracranial hemorrhage, gastrointestinal hemorrhage and bleedings from other organ systems that resulted in hospitalization. Any records of synovectomy, arthrodesis, arthroplasty or joint replacement implemented during hospitalization were used to identify arthropathy. The details of definitions and diagnosis codes of the outcomes are presented in the Supplementary Data. Schematic presentation of the study design and patient follow-up is given in Figure 1.

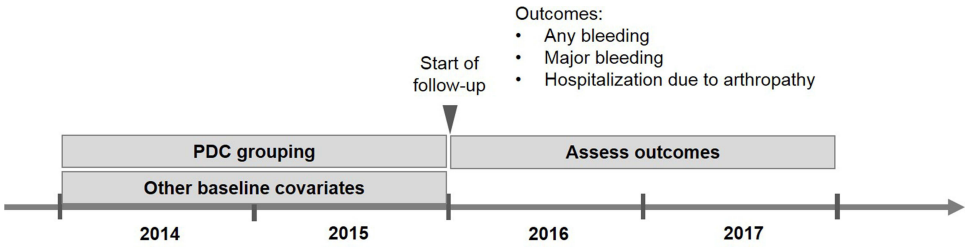

Figure 1 Scheme of exposure grouping and outcome follow-up.
Abbreviation: PDC, proportion of days covered.

Covariates

We selected patients' covariates based on clinicians' opinions and previous literature,[8,28] and included risk factors for bleeding that were likely to be confounders. The covariates included patients' demographics (age at the start of follow-up, and sex), comorbidities (cancer, hypertension, gastrointestinal hemorrhage, liver failure, arthropathy, synovitis, osteoporosis, bleeding history) and concurrent medications (bypass agents, non-steroid anti-inflammatory drugs, tranexamic acid and corticosteroid).

Statistical Analysis

We described continuous variables as mean with standard deviation (SD) and categorical variables as patient numbers with percentages. ANOVA, chi-square test and Fisher's exact test were used to detect significant differences in characteristics between groups. For control of potential confounders, we applied propensity score method using inverse probability of treatment weighting (IPTW) with stabilized weight method.[29] The propensity score was the probability of assignment to a group generated by multinomial logistic regression model conditional on all covariates listed in Table 1. The propensity score with IPTW allows for a comparison between groups based on the average treatment effect in the entire population and has been increasingly applied in pharmacoepidemiological studies.[30,31] We performed Cox regression model to calculate hazard ratios with 95% confidence intervals (CIs) to compare the risks of outcome events between different groups. We used Kaplan–Meier curves for the survival analysis to illustrate the risk of outcome events among groups. For all statistical tests, a p value less than 0.05 was considered statistically significant. All analyses were conducted using SAS v9.4.

Results

Characteristics and PDC Trajectories of Severe PWHA

From 2014 to 2017, we identified a total of 420 severe PWHA. By applying the GBTM, we finally identified three trajectories for PDC with FVIII therapy for these patients (Figure 2). These trajectories were classified as groups with high-, medium- and low-PDCs, whereby the high- and low-PDC groups yielded a consistent trend over the period, while

Table 1 Characteristics of Patients with Severe Hemophilia Type A

	Total		Different PDC-Level Groups					
			Low		Medium		High	
	n	%	n	%	n	%	n	%
N	420		151	(36.0)	181	(43.1)	88	(21.0)
PDC (mean±SD) [a]	0.4±0.3		0.12±0.1		0.40±0.1		0.78±0.1	
Age (mean±SD)[a]	29.3±16.1		32.4±15.7		29.3±16.3		24.1±15.3	
Comorbidities:								
Cancer	17	4.0%	<10[b]	-	11	6.1%	<10[b]	-
Hypertension	57	13.6%	25	16.6%	24	13.3%	8	9.1%
Gastrointestinal hemorrhage	20	4.8%	7	4.6%	9	5.0%	4	4.5%
Liver failure	114	27.1%	47	31.1%	49	27.1%	18	20.5%
Arthropathy	336	80.0%	124	82.1%	147	81.2%	65	73.9%
Synovitis	28	6.7%	<10[b]	-	<10[b]	-	<10[b]	-
Osteoporosis	24	5.7%	<10[b]	-	<10[b]	-	<10[b]	-
Medication History:								
Bypass agent[a]	16	4%	<10[b]	-	<10[b]	-	<10[b]	-
NSAID	300	71.4%	100	66.2%	133	73.5%	67	76.1%
Tranexamic acid	150	35.7%	55	36.4%	58	32.0%	37	42.0%
Corticosteroid	157	37.4%	57	37.7%	62	34.3%	38	43.2%

Notes: [a]Indicated p<0.05 for comparison between groups. [b]Due to data privacy, variables with too few numbers were not allowed to report.
Abbreviations: NSAID, Non-Steroidal Anti-Inflammatory Drug; PDC, proportion of days covered.

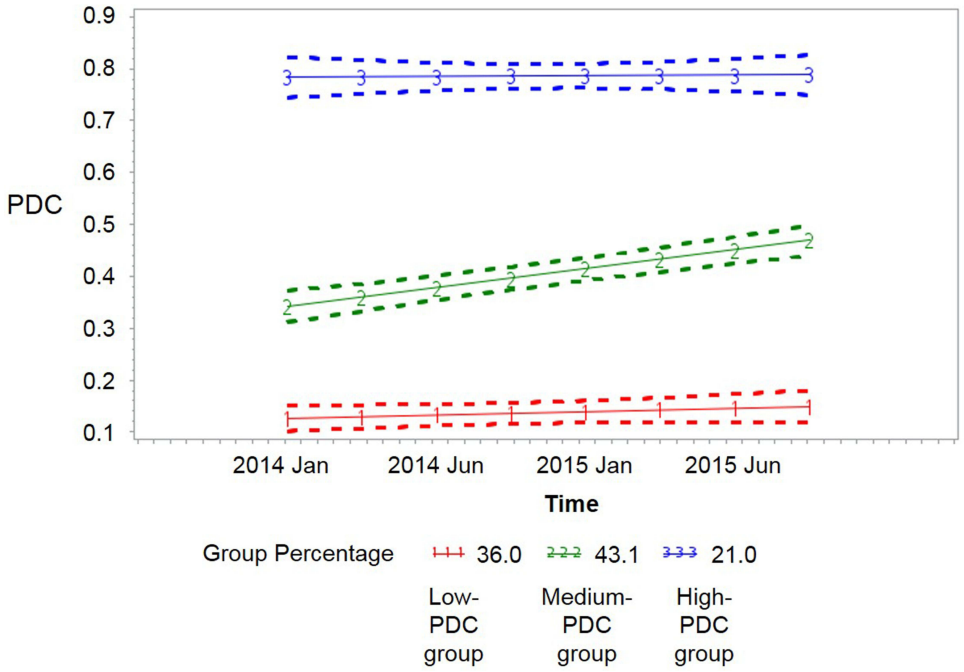

Figure 2 Trajectories of proportion of days covered by FVIII therapy in patients with severe hemophilia type A from 2014 to 2015.

the PDC of the medium group increased gradually from 0.3 to more than 0.4. One hundred and fifty-one (36.0%), 181 (43.1%) and 88 (21.0%) patients were grouped into the high-, medium-, and low-PDC groups, respectively, according to their use of FVIII therapy (Table 1). The high-, medium-, and low-PDC groups' mean (± standard deviation; SD) ages were 24.1 ± 15.3, 29.3 ± 16.3 and 32.4 ± 15.7, respectively, with the lower PDC group being relatively older, and their mean (±SD) PDCs were 0.78 ± 0.1, 0.40 ± 0.1 and 0.12 ± 0.1, respectively. For the high PDC group, a value of 0.78 meant that during the period from 2014 to 2015, 78% of days, on average, were covered by the use of FVIII therapy. With regard to comorbidities, three groups of patients had similar rates of gastrointestinal hemorrhage (approximately 5%), liver failure (21 to 31%) and arthropathy (74 to 82%). Other characteristics are presented in Table 1.

Trajectories with Different PDCs and Bleeding Outcomes

From 2016 to 2017, a total of 335 episodes of any bleeding events were detected (Table 2). Patients in the high-, medium- and low-PDC groups experienced 57, 143 and 135 episodes of bleeding events, respectively, resulting in incidence rates of 18.2, 28.6 and 47.7 per thousand patient-years, respectively. When compared to the low PDC group, the high- and medium-PDC groups had significantly lower odds (high- vs low-PDC group: odds ratio (OR): 0.45, 95% confidence interval (CI): 0.33–0.61; medium- vs low-PDC group: OR: 0.69, 95% CI: 0.55–0.87) of experiencing any bleeding event. A total of 14 major bleeding events and 18 hospitalizations due to arthropathy occurred during the study period. The incidence rates for high-, medium- and low-PDC groups were 0.38, 0.70 and 0.45 per thousand patient-years for major bleeding events and 0.80, 0.80 and 0.60 per thousand patient-years for hospitalization due to arthropathy, respectively. When compared to the low PDC group, the hazard ratios showed no statistical difference for the high- and medium-PDC groups (Table 2).

Discussion

This was the first study to demonstrate the effectiveness of CFRT in preventing bleeding events in real-world severe PWHA in Taiwan. We applied GBTM and identified 3 patterns of utilization based on PDC with CFRT. These included a consistently high PDC, a gradually increasing medium PDC, and a consistently low PDC. The group with high PDC could represent patients undergoing prophylactic CFRT, ie receiving long-term coverage with CFRT during a pre-specified period. The groups with medium- and low-PDCs could represent those intermittently undergoing prophylactic

Table 2 Risks of Bleeding Outcomes

	Total	Different PDC-Level Groups		
		Low	Medium	High
Any bleeding				
Event number	335	135	143	57
Incidence rate[a]	30.5	47.7	28.6	18.2
HR (95% CI)		Ref.	0.69 (0.56, 0.89)[b]	0.45 (0.36, 0.68)[b]
			p = 0.0032	p <0.0001
		-	Ref.	0.6 (0.52, 0.95)[c]
				p = 0.0217
Major bleeding				
Event number	14	<5	8	<5
Incidence rate[a]	0.6	0.45	0.7	0.38
HR (95% CI)		Ref.	2.48 (0.68, 10.28)[b]	1.13 (0.15, 7.38)[b]
			p = 0.1582	p = 0.9669
		-	Ref.	0.89 (0.07, 2.11)[c]
				P = 0.2764
Hospitalization due to arthropathy				
Event number	18	5	9	4
Incidence rate[a]	0.7	0.6	0.8	0.8
HR (95% CI)		Ref.	1.13 (0.23, 1.40)[b]	1.13 (0.15, 1.75)[b]
			p = 0.2186	p = 0.2834
		-	Ref.	1.13 (0.25, 3.22)[c]
				p = 0.8638

Notes: [a]Incidence rates were presented as number of episodes per 1000 patient-year. [b]Pairwise comparison was conducted taken the low-PDC level group as reference. [c]Pairwise comparison was conducted taken the medium-PDC level group as reference.

Abbreviations: HR, hazard ratio; PDC, proportion of days covered.

CFRT or not at all. Compared to the low PDC group, the high- and medium-PDC groups were duration-dependently associated with lower risks of any bleeding event, supporting the real-world effectiveness of prophylactic CFRT.

In this study, we found that patients with higher PDC were associated with 55% lower incidence and hazard for any bleeding event, compared to those with low PDC. In addition, our results manifested a duration-dependent benefit with the higher PDC group showing a lower incidence rate in any bleeding. This finding suggested that patients receiving routine or longer duration of prophylactic CFRT were at a lower risk of bleeding events requiring treatment doses of coagulation factor. This benefit of lower bleeding risk has been demonstrated before in clinical trials comparing prophylaxis with on-demand treatment, showing that prophylactic CFRT reduces risk of total hemorrhage by more than 70%, keeping the mean annual bleeding rate at lower than 4 episodes per patient.[5,32–34] Observational studies have also shown similar results, namely that prophylaxis can reduce any bleeding events.[8,18,35] Nagae et al[18] and Ay et al[35] have demonstrated in their studies that coagulation factor prophylaxis reduces the annual bleeding event rate to lower than 5 events per patient.

Dose counts as one of the most important factors for the effectiveness of the therapy. Although it was not investigated and cannot be precisely measured in this study, the dosing regimen reimbursed in Taiwan was 15 to 35 IU FVIII/kg, one to three times per week.[36] Under most circumstances, this would correspond to an intermediate-dose prophylaxis, following the WFH guideline.[1] Our study results revealed the real-world effectiveness of such intermediate-dose prophylactic CFRT in reducing any bleeding risk for PWHA. The clinical benefits of intermediate-dose prophylaxis have also been proven in a study conducted in China,[17] showing that compared to on-demand treatment, intermediate-dose FVIII prophylaxis is associated with fewer bleeding events and joint bleedings and with better preservation of joint structure and function. Other studies suggest that, compared to high-dose prophylaxis, intermediate-dose prophylaxis

achieves comparable quality of life but offers a smaller reduction in risks of bleeding and hemophilic arthropathy, at 60% of the total cost.[37,38] Overall, this suggests that the intermediate dose CFRT reimbursed in Taiwan could be considered cost-effective in reducing risk of any bleeding in PWHA.

Contrary to some clinical studies, the risks of major bleeding events including joint bleeds and arthropathy that resulted in hospitalization were found to be insignificantly different between the groups in our study.[14,15,28,39] This might have been due to the very small event numbers observed across all PDC-level groups. These very low numbers could be attributed to the high health resource accessibility and overall fine health care in Taiwan. Although CFRT was not reimbursed until 2014, it had been funded since 2005 from a governmental special funding program for those predominantly needing on-demand treatment or secondary prophylaxis. Therefore, most PWHA were already under fair care even before the reimbursement of prophylactic CFRT and as a result, the event rate of severe adverse outcomes was anticipated to be low. Another reason for the small numbers of events was the relatively short-term follow-up in this study, which was limited by data availability at the time of analysis. Given these limited numbers of events, our study was possibly underpowered to detect differences in arthropathy outcomes between groups. Other studies that indicated joint benefits had an average follow-up of 5 years or longer, increasing their probability of detecting more outcomes.[5,14,32,33,39]

The study had several strengths. First, it utilized population-based data to conduct the analysis and thus was representative of the whole PWHA population in Taiwan. This could complement and support the results found in other smaller-sampled observational studies.[17,18,35] Second, this study applied GBTM to describe the patterns of CFRT. In the past, various research utilizing administrative claims data has tried to identify patients undergoing prophylactic CFRT using many different criteria, such as restricting to a minimum number of FVIII prescriptions during a prespecified period or using days of supply data.[21,40] However, the real-world utilization of factor therapy has resisted a perfect classification into either prophylaxis or on-demand treatment. In our approach, it was important to understand how PWHA had been treated with CFRT over time and how these treatment patterns corresponded to subsequent clinical prognosis. The application of the data-driven method, ie, GBTM, enabled us to identify the hidden clusters of patients who shared similar factor therapy utilization patterns. As a result, we did not need to group these patients a priori and were able to follow them for further comparison. Third, we applied propensity scoring with inverse probability of treatment weighting to control for potential confounders that were imbalanced between groups while maintaining all patients in the analysis and not compromising sample size.

One big challenge of this study was that although prescriptions could be identified from the database, details of the actual coagulation factor regimen were unknown. However, we applied PDC as an index to identify patients potentially undergoing prophylactic CFRT. A high PDC implied a long duration of FVIII coverage and thus it was reasonable to assume with high probability that the patient was under prophylactic CFRT. The high PDC group identified in our study had a mean PDC of approximately 0.8, meaning the patients were under CFRT for 80% of the study period. This corresponded well with the 2012 WFH guideline for prophylaxis whereby the duration covered by CFRT be 85% of the year, as well as with some studies[13,40] that used PDC > 0.7 as a cut-off to distinguish prophylaxis from on-demand treatment. Another limitation was the lack of laboratory data, resulting in potential misclassification of the study groups. Specifically, we were more likely to have included some non-severe PWHA in the low PDC group than in the other two groups. To address this, we adopted and modified the algorithm for identifying severe PWHA used in other database studies[20–22] and we found that the overall proportion of severe PWHA cases identified was consistent with the epidemiological data in Taiwan. Nevertheless, we may have underestimated the effectiveness of prophylactic CFRT because the reference group (low PDC group) may have had a lower baseline bleeding risk than expected. This would imply that the actual effectiveness of prophylactic CFRT in the higher PDC groups was even greater. Therefore, we believe that the impact of this misclassification was negligible. Another limitation was our inability to assess the influence of self-paid prescriptions or over-the-counter medications. However, since PWHA are a special patient category who are exempt from co-payments for health care and medications under the national health insurance program in Taiwan,

these patients were unlikely to have purchased other drugs outside of the national health care system. Therefore, the impact was expected to be minimal.

Conclusion

Patients with severe hemophilia A revealed three patterns of coagulation factor therapy based on PDC levels: consistently high, medium with gradually increasing trend, and consistently low PDCs. The high PDC group could be considered as patients undergoing prophylactic CFRT. Compared to the group with low PDC, both the medium- and the high-PDC groups may carry a reduced risk of any bleeding event. The results suggested that under the reimbursement program in Taiwan, the prophylactic CFRT was effective in preventing total hemorrhages in severe PWHA cases.

Abbreviations

CFRT, Coagulation factor replacement therapy; CI, Confidence interval; CIC, Catastrophic Illness Certificates; FVIII, Coagulation factor VIII; GBTM, Group-based trajectory modeling; NHID, National Health Insurance Database; PDC, Proportion of days covered; PWHA, Patients with hemophilia A; SD, Standard deviation; WFH, World Foundation of Hemophilia.

Data Sharing Statement

Data are not available due to legal restrictions for privacy protection of susceptible populations under the regulations of Taiwan.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the ethical standards of the Institutional Review Board and the Declaration of Helsinki. Research ethics approval was given by the IRB of National Cheng Kung University Hospital (ID B-ER-108-390), whereby the IRB waived the written informed patient consent requirement due to the retrospective nature of the study design and because all individual identifiers were encrypted and thus not personally identifiable.

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Author Contributions

All authors made a significant contribution to the work reported, whether in conception, study design, execution, acquisition of data, analysis or interpretation. They took part in drafting, revising or critically reviewing the article; they all gave final approval of the version to be published and agreed on the journal to which to submit the article. All authors have agreed to be held accountable for all aspects of the work.

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Disclosure

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