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Original article

Characterizing hospital pathways for the care of acquired hemophilia in France using comprehensive national health data

Caractérisation du parcours hospitalier et des traitements anti-hémorragiques des patients avec hémophilie acquise suivant les données du PMSI (programme de médicalisation des systèmes d'information)

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Abstract

Purpose

Acquired hemophilia (AH) is a rare, serious bleeding disorder most often associated with older age and life-threatening complications. The patient care pathway for AH is complex because of the different types of bleeding, the presence of comorbidities, and the heterogeneity of medical specialists who care for these patients.

Methods

This observational study used the French national PMSI (*Programme de médicalisation des systèmes d'information*) database to characterize patients with AH in real-life practice and analyze their hospital pathway. In total, 180 patients with AH were identified over a 5-year study period (January 2010 to December 2014), based on three criteria: bypassing agent use, International Classification of Diseases, 10th revision code allocation, and aged over 65 years. Comparison of the incidence rate of AH versus registry data validated the PMSI as an epidemiological database.

Results

Rituximab was prescribed more often (60/180; 33.3%) than expected following guidelines and was associated in half of cases to early infections (32/60; 53.3%), surgery procedures were frequently performed during the year before AH onset (29/159; 18.2%), which may suggest a triggering effect, extended hospital stays (median: 20 days) and mortality remaining high (66/180; 36.7%) that occurred mainly during the first month after AH diagnosis. Median costs and number of injections were comparable between recombinant activated factor VII and plasma-derived activated prothrombin complex concentrate.

Conclusion

These findings could inform future medico-economic approaches in this AH population (duration of stays, bypassing agents, rituximab use, comorbidities, hospitalizations with infections).

Keywords: Antibodies; Chronic disease; Epidemiology; Factor VII; Hemophilia; Public health

1 Introduction

Acquired hemophilia (AH) is a rare, serious bleeding disorder with an incidence of around 1.5 affected individuals per million inhabitants/year, which is probably underestimated [1,2]. The incidence of AH increases with age, from 0.3 per million in those aged < 65 years to 15 per million in those aged > 85 years [1]. Although the morbidity and mortality associated with bleeding episodes have been reduced with bypassing agents, AH can cause severe life-threatening bleeding complications [3], especially in patients aged > 76 years [4].

Management of AH is done almost exclusively in hospitals and remains primarily based on expert opinion [5,6] in the absence of prospective studies. The patient pathway is highly complex due to the different types of bleeding (typically bruising, muscle, gastrointestinal, urogenital and retroperitoneal bleeding) [3], the presence of comorbidities such as cancer or autoimmune diseases, and the heterogeneity of medical specialists who care for these patients. The consequence is delayed diagnosis and management by specialists.

The French PMSI (*Programme de médicalisation des systèmes d'information*) is a national hospital discharge summary database that provides access to anonymized data on all short-, medium- and long-term stays in public and private hospitals in surgical or medical settings [7]. Initially designed to manage and finance healthcare in France, the PMSI is also an interesting tool for public health and epidemiological purposes, enabling access to medical, demographic, quantified and standardized data.

The current study investigated whether the PMSI could be used as an alternative to registry data to characterize patients with AH in real-life practice and analyzed patients' hospital pathway from their first stay associated with bypassing agent use.

2 Methods

2.1 PMSI

The PMSI collects data on demographics, reason for admission, associated diseases, comorbidities (including thromboembolic complications and infectious diseases), complications, surgical/interventional procedures and in-hospital duration for all hospitalized patients in France [7,8]. Transfusions and use of costly medications for AH, including factor VIII concentrate, bypassing agents and rituximab, are recorded. Diagnoses are coded at the hospital discharges using the International Classification of Diseases, 10th revision (ICD-10) [9] for each stay and entered as: primary diagnosis (main admission reason); related diagnoses (disease context of primary diagnosis); associated diagnoses (complications/comorbidities).

The severity of hospital stays is allocated to one of four grades according to age, primary diagnosis, comorbidities and general patient status (1 = lowest severity; 4 = highest severity).

2.2 Patient selection

Data on patients with AH from January 2010 to December 2014 were extracted during 2016. Permission to extract and analyze the database was obtained from the French Data Protection Authority (Commission nationale de l'informatique et des libertés [CNIL]).

Since AH is not allocated a specific ICD-10 code in France, a combination of three selection criteria was used to identify patients with AH: patients treated for the first time with a bypassing agent (recombinant activated factor VII [rFVIIa] and/or plasma-derived activated prothrombin complex concentrate [pd-aPCC]); patients assigned during the hospital stay to an ICD-10 code corresponding to bleeding conditions that can include AH: (a) "Hereditary factor VIII deficiency" (D66) as the primary, related or associated diagnosis; (b) "Acquired deficiency in clotting factor" (D68.4) as the primary or related diagnosis; or (c) "Bleeding disorders due to circulating anticoagulants" (D68.3) as the primary or related diagnosis; these codes were selected because they are used in the four investigators' centers (Caen, Montpellier, Rennes and Rouen) for coding patients with AH. Patients were aged \geq 65 years, to limit the selection of patients with inherited bleeding conditions and to better target the elderly AH demographic.

To validate this methodology and use of the PMSI as an epidemiologic database, a post hoc comparison of the incidence of patients over 65 years of age and with AH treated with bypassing agents was performed versus national and international registries [1,4,10]. On the other hand, the number of patients selected by the PMSI hospitalized in the university hospitals of Caen, Montpellier, Rennes, and Rouen was compared with the number of patients who had a confirmed diagnosis of AH by the Bethesda titration method in the same university hospitals and during the same period.

2.3 Data collection

Demographic data comprised age, gender, diagnostic coding, transfusions, types of surgery (major- and minor-intermediate [11]), tumors and thromboembolic complications in the previous year or during the first hospital stay for AH, and comorbidities such as autoimmune diseases preceding/during the first hospital stay.

Data on the patient pathway comprised the site of AH diagnosis, number of hospital stays, use of bypassing agents and immunosuppressive treatment (rituximab [evaluated in 2010–2012 and 2013–2014]), infectious and thrombotic complications and mortality (Online material Supplemental Table).

2.4 Data analysis

Results were analyzed for all stays: quantitative data are expressed as mean, median, quartiles and range; qualitative results are presented as frequency. Statistical tests included the Fisher's exact test and calculated 95% confidence intervals (CIs).

3 Results

3.1 Patient population

In total, 180 patients with AH were identified during the 5-year study period (Table 1). Overall median patient age was 82 years (range, 65–100 years) (Fig. 1).

Table 1 Distribution of *ICD-10* diagnostic codes at initial diagnosis.

alt-text: Table 1

Diagnostic codes	<i>n</i>	%
Total patients	180	100
Patients with only one code (151/180, 84%)		
D66	68	37.8
(Female/male)	(30/38)	(44.1/55.9)
D68.3	18	10.0
D68.4	65	36.1
Patients with associated codes (29/180, 16%)		
D68.3 + D68.4	9	5.0
D66 + D68.3	3	1.7
D66 + D68.4	15	8.3
D66 + D68.3 + D68.4	2	1.1

ICD-10: international classification of diseases, 10th revision. ICD-10 codes are systematically annotated at hospital discharges for each hospital stay. Among patients > 65-years-old who received at least one bypassing agent, analyzed ICD-10 codes were D66 for “Hereditary factor VIII deficiency”; D68.3: bleeding disorders due to circulating anticoagulants; D68.4: Acquired deficiency in clotting factor.

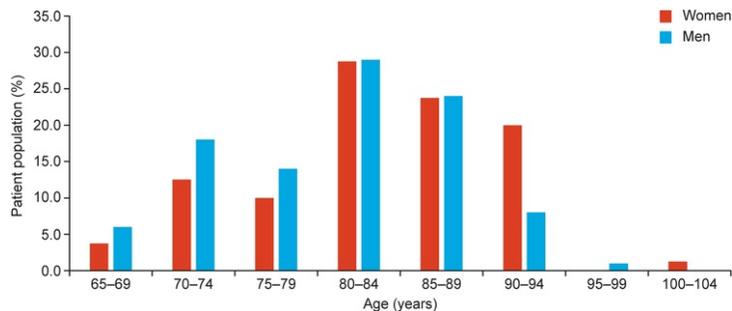


Fig. 1 Distribution of patient ages at first AH diagnosis, according to gender. AH: acquired hemophilia.

3.2 Confirmation of methodology

To confirm our methodology, we compared the incidence of patients with AH treated with a bypassing agent with incidence rates derived from published registries [4,14]. Based on these incidence rates, 500-600 cases of AH would be expected over a 5-year period in France. The difference between this and the cases identified in the PMSI (180) can be explained by our study's exclusion of women of childbearing potential, patients < 65 years, and patients not receiving bypassing agents. According to EACH2 and SACHA [4,10], these patients represent ~10% (50 patients), 7-17% (35-84 patients aged 40-65 years), and 41-61% (200-300 patients) of the total AH population, respectively. Taking this into consideration, 112-180 patients with AH would be expected over a 5-year period (25-40/year) in the registries. If the UK surveillance study [1] is also considered, 112-204 patients with AH would be expected in the same period (25-50/year). Our study population is therefore consistent with registry data and supports the methodology used. On the other hand, the number of patients selected by the PMSI in 4 test university hospitals (Caen, Montpellier, Rennes and Rouen) was the same as that of diagnosed patients in same the hospitals and during the same period.

3.3 Sites of AH diagnosis

Patients were first assigned diagnostic codes for AH in university hospital centers (UHCs; 123 [68.3%] patients), general hospital centers (GHCs; 55 [30.6%]), or private clinics (2 [1.1%]). Among those coded in a UHC, 24 (19.5%) were referred from a GHC, while five (9.1%) coded in a GHC came from another establishment. Overall, 78 (43.3%) patients were referred by an emergency unit; this proportion was lower for UHCs (45 [36.6%]) than for GHCs (33 [60.0%]), suggesting that direct entry to a specialized department for diagnosis occurred more frequently at UHCs than GHCs.

3.4 Number of hospital stays

The mean number of hospital stays per patient was 6.1 (range, 1-41); mean number of stays per patient treated with a bypassing agent was 1.4 (range, 1-13), ranging from 1 stay for 134 patients [74.4%], 2 stays for 30 [16.7%], 3 stays for 11 [6.1%]) and ≥ 4 stays for five [3%].

3.5 Comorbidities

Analysis of comorbidities (summarized in Table 2) focused on the first code assigned to comorbidities or surgery in a 1-year period (thromboembolic events and surgery) or in a 6-month period (cancer) before AH diagnosis (including when AH was diagnosed), regardless of any other code attributed to the same comorbidity during the remainder of the patient pathway. For the 21 patients diagnosed with AH during the first 6 months of 2010, no data on comorbidities or surgery were collected prior to first hospital stay. Autoimmune diseases were identified as occurring before the first hospital stay for AH or when patients received a code for an autoimmune disease during their first stay.

Table 2 Comorbidities, surgeries and thrombotic events before or at the time of the acquired hemophilia diagnosis.

alt-text: Table 2

	Patients, <i>n</i> (%) <i>n</i> = 159	Details
Comorbidities related to AH		
Cancer during the 6 months before or during AH diagnosis	38 (23.9%)	29 solid tumors ^b (18.2%)

		9 malignant hemopathies ^c (5%)
Autoimmune disease before or during the diagnosis	11 (6.1%) ^a	7 rheumatoid arthritis (3.3%) 3 bullous pemphigoids (1.7%) 1 mixed connective tissue disease (0.6%)
Considered idiopathic	131 (72.8%)	
Thrombotic events		
During the year before or during AH diagnosis	10 (6.3%)	4 strokes (2.5%) 2 MIs (1.3%) 4 venous thromboses (2.5%)
Surgeries		
During the year before or during AH diagnosis	29 (18.2%)	9 major surgery (5.7%) 20 minor surgery (12.8%)
During the 6 months before or during AH diagnosis	17 (10.7%)	6 major surgery (3.8%) 11 minor surgery (6.9%)

AH: acquired hemophilia; MI: myocardial infarction.

^a $n = 180$ patients.

^b Cancers included: bladder cancer (11 patients; 37.9%), prostate cancer (seven patients; 24.1%), colorectal cancer (four patients; 13.8%), kidney cancer (two patients; 6.9%), malignant melanoma (two patients), lung cancer (one patient; 3.4%) breast cancer (one patient), pancreatic cancer (one patient) ear, nose, and throat/laryngeal tumor (one patient), and lower limb cancer—origin not specified (one patient).

^c Malignant hemopathies included: chronic lymphocytic leukemia (four patients; 44.4%), diffuse large B cell lymphoma (two patients; 22.2%), acute myeloid leukemia (one patient; 11.1%), non-Hodgkin malignant lymphoma (one patient) and one unspecified malignant immune proliferative disease.

In total, 38 patients (23.9%) had an “active” malignancy in the 6-month period before AH diagnosis. Of these, 29 (76.3%) patients had solid tumors (primary/metastatic), 12 (41.4%) of whom were assigned an initial diagnostic code in the 6 months preceding AH diagnosis; the remaining 17 (58.6%) received an initial code during the stay when AH was diagnosed. The other nine patients had malignant hemopathy; in six of these, diagnosis was made when AH was diagnosed. Eleven (6.1%) in total had autoimmune diseases, rheumatoid arthritis being the most common (7/11 patients, 63.6%).

Twenty-nine of 159 patients (18.2%) underwent surgery in the year before AH diagnosis, including 17 within 6 months (10.7%) and eight within 3 months (5.0%) (Table 2). A total of 10 patients presented a thrombotic event during the year before or during the AH diagnosis.

3.6 Transfusions

Transfusion was needed in 61/256 (23.8%) stays associated with bypassing agent use. Another 26 (15.4%) patients received transfusions within 3 months preceding the diagnosis; one of these underwent surgery and transfusion during the same stay.

3.7 Severity of hospital stays associated with bypassing agents

Of the 256 stays associated with bypassing agents, 56.6% had a severity level of 3-4 (mean severity level/patient: 2.8). This analysis included 123 patients ≥ 75 years, whose age generally places them at a higher severity level. However, even among patients aged 65-74 years ($n = 35$), 38.0% of hospital stays with bypassing agents were allocated a severity level of 3-4 (mean severity level/patient: 2.4).

3.8 Bypassing treatments

In total, 256 stays were associated with bypassing agent use and analyzed for the 180 patients included. More hospital stays associated with bypassing agents were recorded with rFVIIa alone ($n = 144$ [56.3%]) than pd-aPCC alone (84 [32.8%]); both bypassing agents were used during the same stay on 16 (6.3%) occasions (Table 3). Twelve stays (4.7%) were managed with both FVIII and one bypassing agent.

Table 3 Number and duration of hospital stays for acquired hemophilia associated with bypassing agents treatments.

alt-text: Table 3

	rFVIIa as monotherapy	pd-aPCC as monotherapy	rFVIIa + pd-aPCC during same stay	Total
Total number of first stays with AH diagnosis	104	65	11	180
Total number of stays for AH	149	91	16	256
Duration of stays, days				
Mean (SD)	20.4 (16.1)	26.4 (19.5)	42.4 (19.3)	23.9 (18.4)
Median (Q1–Q3) [Min–max]	17.5 (8–27) [0.5–83]	23 (13–35) [0.5–112]	41 (29–53) [14–73]	20 (11–32) [0.5–112]

AH: acquired hemophilia; pd-aPCC: plasma-derived activated prothrombin complex concentrate; Q: quarter; rFVIIa: recombinant activated factor VII; SD: standard deviation. The indicated durations are for hospital stays during which the bypassing agents were used. However, they do not indicate the duration of by-passing agents' treatments. During the first stay, rFVIIa was used in 104 (57.8%) and pd-aPCC in 65 patients (36.1%); both bypassing agents were used in the other 11 (6.1%) cases (Table 3). pd-aPCC was used more frequently in UHCs (86.2%) than GHCs (13.8%), but differences in rFVIIa use between centers were less pronounced (54.8% vs. 43.3%). Both median cost and number of injections of the two agents were comparable: based on a unit dose of 5.4 mg (90 µg/kg) for rFVIIa and 4500 U (75 U/kg) for pd-aPCC for a 60-kg adult, the estimated median number of injections/patient was 6.6 for rFVIIa and 6.4 for pd-aPCC. Table 4 summarizes the bypassing agents' dosages.

Most patients (159/180 [88.3%]) were treated with the same bypassing agent as monotherapy throughout their care pathway. Ten (5.6%) switched during the pathway: six (3.3%) from rFVIIa to pd-aPCC and four (2.2%) from pd-aPCC to rFVIIa. Eleven received both bypassing agents during the same hospital stay; of these, only one required another stay, when he received rFVIIa.

Median duration of stay was 20 days (Quarter [Q]1–Q3; 11–32 days). Median durations for rFVIIa (104 stays) or pd-aPCC (65 stays) as monotherapy were 17.5 days (Q1–Q3: 8–27 days) and 23 days (Q1–Q3: 13–35 days), respectively. For patients who received both (11 stays), median duration of hospitalization was 41 days (Q1–Q3: 29–53 days). On the other hand, the median cost of treatments using of the two by-passing agents were comparable (no significant difference) (Table 4).

Table 4 Consumption of bypassing agents during all the hospital stays.

alt-text: Table 4

	rFVIIa	pd-aPCC	rFVIIa	pd-aPCC
	As monotherapy		With the 2 bypassing agents during the same stay	
Dosages per stay				
Total	19,944 mg	4725.50 kU	4397 mg	1461.5 kU
Mean (SD)	133.8 mg (211.7)	51.93 kU (64.67)	274.8 mg (281.5)	91.34 kU (72.35)
Median (Q1–Q3) [Min–max]	36 mg (14–158) [1–1262]	29 kU (10–69) [1–435]	147 mg (87–457) [17–844]	77.50 kU (43.75–122.00) [5–243]
Cost ^a per stay, k€				
Median (Q1–Q3)	20.25 (7.88–88.86)	24.22 (8.40–57.62)	159.28	

AH: acquired hemophilia; FVIII: factor VIII; pd-aPCC: plasma-derived activated prothrombin complex concentrate; rFVIIa: recombinant activated factor VII; SD: standard deviation; U: units; UC: units consumed.

^a The total doses of rFVIIa and pd-aPCC used in monotherapy were 19,994 mg and 4,725,500 U, respectively. 1 mg rFVIIa = €562.4 and 1 pd-aPCC U = €0.835 (costs correct as of January 1, 2019).

3.9 Thrombotic complications post-diagnosis

Twenty-two (12.2%) patients were coded for thromboembolic complications during or after the first stay: nine with stroke, four with myocardial infarction, seven with deep vein thrombosis, and two with pulmonary embolism. None had a history of thromboembolic disease in the 12 months before AH diagnosis.

Eleven of 22 were coded for thrombotic incidents (seven arterial, four venous) within the first 3 months after the first hospital stay for AH (6.1% of all patients diagnosed with AH and 8.3% of those still alive at 3 months). Of 104 receiving rFVIIa monotherapy during the first AH stay, five (4.8%) experienced a thromboembolic complication; of 65 patients receiving pd-aPCC as monotherapy during the first stay, two (3.1%) had thromboembolic complications (a non-significant difference).

3.10 Mortality

Overall, the cumulative incidence of mortality at 1 year of follow-up after the AH diagnosis was 33.3% (60/180). Most deaths (48 [72.7%]) occurred during the first 3 months after diagnosis/relapse; 36 (54.5%) occurred within the first month. Twenty-nine (16.1%) patients died during hospital stays associated with a bypassing agent. Two (3.0%) deaths occurred between 1 and 2 years and four (6.1%) after 2 years. Causes of death could not be determined.

3.11 Rituximab use

Rituximab was administered to 60 (33.3%) patients, 44 (73.3%) of whom received it during their first hospital stay. The remaining 16 initiated rituximab at a median of 1.5 months (range, 0.5-9 months) after first AH stay.

Of 94 patients between 2010 and 2012, 35 (36.5%) received rituximab during ≥ 1 hospital stay. Eighty-four patients were included between 2013 and 2014, 25 (29.8%) of whom were treated with rituximab during at least one stay. For both evaluation periods, rituximab was prescribed more frequently during the first stay than subsequent stays, but this difference was greater in the second evaluation period (68.6% vs. 32.4% of patients from 2010 to 2012 and 80.0% vs. 20.0% from 2013 to 2014).

3.12 Infectious complications

Eighty-two (45.6%) patients were coded for an acute infectious complication, thirty-two (17.8%) of whom received rituximab, while 50 (27.8%) did not. In order to exclude complications due to immunosuppressive treatments possibly prescribed before Rituximab uses, the analysis of infections associated with Rituximab, was performed in the only 44 patients receiving Rituximab during their first stay for AH diagnosis. Rituximab-treated patients experienced more infections in the 6 months after the first injection (20/44 [45.5%]) than those who did never receive rituximab (34/120 [28.3%]; odds ratio 2.11 [95% CI: 1.03-4.31]; $P=0.04$).

4 Discussion

This is the first study focusing on global care of AH through analyzing pre-diagnosis anamnestic data and post-diagnosis follow-up data to inform use of transfusions, bypassing agents and rituximab. Our key findings indicate that 68.3% of care pathways were associated with UHCs and therefore involved specialized departments, hospitalizations were frequent irrespective of cause, 25.6% of patients using bypassing agents had more than one hospitalization, 56.6% of stays with bypassing agents had a severity level of 3-4 and infectious complications were probably underestimated.

Other notable findings included the high rate of rituximab use. The observed trend toward increased rituximab use is not in accordance with expert recommendations or study data [5,6,12-15] and suggests it is being used too widely in France for AH. There is no prospective published study on rituximab use in this setting, but the potential risk of infectious complications in elderly patients should not be overlooked [16,17]. Our data and other studies suggest that the infectious risk with rituximab in elderly patients should be considered similar to other immunosuppressive drugs. However, in our study, the latter group was probably heterogeneous with different types of immunosuppressive drugs alone or combined, such as corticosteroids and cyclophosphamide. On the other hand, we cannot exclude a selection bias concerning the side effects observed with Rituximab. It is indeed possible that all our patients with severe acquired hemophilia were considered at high risk of complications. Clinicians might have so preferred Rituximab to cyclophosphamide. Finally, in order to minimize the influence of other immunosuppressive treatments, infectious complications were analyzed in patients receiving Rituximab during their first stay for AH. This sub-group had significantly more infections than other patients having never received Rituximab. The prospective, randomized CREHA study (Outcome of Acquired Hemophilia With Steroid Combined With Cyclophosphamide Versus Steroid Combined With Rituximab; NCT01808911) will provide additional and more robust informations from a large population of patients with AH.

The median duration of the first AH-associated hospital stay was 20 days, indicating the severity of the disorder and perhaps reflecting delays in diagnosis. Hospital stay was extended up to 41 days where both bypassing agents were needed during the same stay. Over half of hospital stays that used bypassing agents had a severity level of 3-4, again emphasizing that AH is a serious condition. Our study also identified a high mortality rate (36.7%), especially in the first month after the first stay linked to AH diagnosis. This likely reflects the use of selection criteria that focused on patients aged ≥ 65 years with severe AH and comorbidities who were treated with bypassing agents. Although this mortality rate is similar to that in national and international registries (EACH2: 26.3%; SACHA: 32.9%; British: 43.0%) and GTH-AH (33.3%) [1,4,10,18], it is probably underestimated, since it does not include deaths occurring outside public/private hospitals.

As hospital pharmacists in France are required to notify each use of rFVIIa or pd-aPCC in order to be reimbursed, PMSI data reflect real-life use. Approximately 75% of patients had only one hospital stay with a bypassing agent, showing that this first-intention treatment combined with immunosuppression is usually effective. Repeat treatments were generally with the same agent; only 5.5% of patients switched during the care pathway. In contrast to previous reports [4,10], both median cost and number of injections of the two bypassing agents were comparable.

The risk of thrombotic events was higher after diagnosis than before; however, as in EACH2 [4], the risk did not appear associated with bypassing agents and may be attributable to prolonged hospitalization and the presence of abnormal laboratory parameters, such as the rapidly increased FVIII levels following inhibitor eradication [5,6]. The incidence of venous thromboembolic complications was perhaps underestimated in our study because their treatment does not necessarily require hospitalization.

Our methodology cannot guarantee inclusion of all AH patients in the PMSI because there is no specific AH code in France. On the other hand, by selecting patients older than 65 years, postpartum HA was excluded from this study. The formal exclusion of low patient numbers with congenital mild hemophilia who had developed alloantibodies is also not certain, as it is not possible to distinguish allo- from auto-antibodies in this population. Nevertheless, all hospital pathways extracted corresponded to elderly patients treated with a bypassing agent at the first stay. It was also not possible to collect data for asymptomatic AH patients who had only a laboratory diagnosis. Similarly, the study did not capture patients with AH without severe bleeding who did not require bypassing agent treatment. Finally, data on comorbidities were not exhaustive for patients recruited during the first or last 6 months of the study period.

5 Conclusions

Analysis of the PMSI represents a valid methodology, albeit with some bias, for assessing the incidence of AH treated with bypassing agents. Based on the PMSI data, we provide, for the first time, information on the hospital pathway for severe forms of AH, including patient demographics, severity and duration of hospitalization, presence of comorbidities and use of bypassing and some immunosuppressive treatments (rituximab) in the real-life hospital setting. These findings could inform future medico-economic approaches in this population (duration of stays, bypassing agents, rituximab use, comorbidities, hospitalizations with infections).

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Disclosure of interest

Benoît Guillet is a consultant and speaker at scientific events for Novo Nordisk and Shire (now Takeda), and an investigator in an observational study in acquired hemophilia for Novo Nordisk. Achille Aouba is a speaker at scientific events and an investigator in an observational study in acquired hemophilia for Novo Nordisk. Jeanne-Yvonne Borg is a consultant for Novo Nordisk and Takeda, and a speaker at scientific events and an investigator in an observational study in acquired hemophilia for Novo Nordisk. Jean F. Schved is a consultant and an investigator in an observational study in acquired hemophilia for Novo Nordisk, and a consultant and speaker at scientific events for Takeda. Hervé Lévesque is a consultant and speaker at scientific events for Novo Nordisk and Takeda and an investigator in an observational study in acquired hemophilia for Novo Nordisk. Funding for this project was provided by Novo Nordisk A/S.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.revmed.2021.07.003>.

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Online material Supplementary data

[Multimedia Component 1](#)