

EMPIRICALLY-DERIVED CLASSIFICATION OF COAGULATION DISORDERS IN 224 PATIENTS

Nina Santavirta,* Hjordis Björvell,* Svetlana Solovieva,^o Seppo Santavirta,* Kari Hurskainen,^o Yrjö T. Konttinen^{@^}

*Center of Caring Sciences North, Department of Medicine, Karolinska Institute, Stockholm, Sweden; ^oOrthopedic Hospital of the Invalid Foundation, Helsinki, Finland; *Department of Orthopedics and Traumatology, Helsinki University Central Hospital, Finland, [@]Institute of Biomedicine, Department of Anatomy, Helsinki University, Finland, [^]Department of Medicine, Helsinki University Central Hospital, Helsinki, Finland

ABSTRACT

Background. It is not known whether the current molecular classification of blood coagulation disorders into severe (0-1%), moderate (1-5%) and mild (5-40% factor activity remaining) corresponds to the actual clinical situation or is in the patients best interest.

Methods. A questionnaire-based study of 244 patients. Principal factor analysis was used to create a set of variables for classification, which was performed using K-means algorithm. The main variables were use of prophylactic treatment during the last five years and during the last 12 months, home treatment, bleeding, surgery, antibody inhibitors, use of cold medication, pain, use of analgesics, functional disability and physical activity level.

Results. The first five variables of the main outcome measures loaded to a factor reflecting bleeding (bleeding factor) and the last four to a pain factor; both factors produced a 3-cluster solution with severe, moderate and mild bleeding or pain. Overlap between the molecular, bleeding and pain classifications was not extensive. Only 16% of 81 patients with severe coagulation factor deficiency had severe musculoskeletal pain and disability. Furthermore, only 28.6% of the patients with severe von Willebrand's disease actually had a severe bleeding disorder.

Conclusions. Molecular classification does not correlate very well with the severity of disease as reflected in bleeding and pain. This is due to better prognosis for patients on modern medical management. Appropriate patient classification is a basis for defining and managing patients' clinical problems.

Key words: hemophilia, pain, disability, cluster analysis

Hereditary disorders of blood coagulation (broadly termed hemophilias) are usually due to a deficiency or abnormality of a single clotting factor. The three most common deficiencies are hemophilia A (factor VIII deficiency), hemophilia B (factor IX deficiency) and von Willebrand's disease (caused by a deficiency or dysfunction of von Willebrand's factor).¹ Depending upon residual activity, a distinction can be made between severe (0-1% of normal activity), moderate (1-5%) and mild

(5-40%) hemophilia.² In classical hemophilia spontaneous and repeated bleeding episodes are common in the knee, elbow and ankle joints, soft tissues and the central nervous system, although patients with mild hemophilia may not be aware of having a coagulation disorder due to the absence of spontaneous hemorrhages. In von Willebrand's disease, spontaneous hemorrhage, hematuria and hemarthrosis are rare.³ Pain may occur in association with soft-tissue or intra-articular bleeding and, more

Correspondence: Nina Santavirta, W. Aaltosentie 9, FIN-0057 Helsinki, Finland.

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importantly, in true hemophilias, due to hemophilic arthropathy.⁴

It is not known how well the conventional molecular classification corresponds to the actual clinical situation today, when prophylactic and therapeutic administration of coagulation factors is common.⁵ New issues, like the development of antibody inhibitors as a result of multiple infusions, have also arisen. Therefore patients classified according to their molecular deficiency were re-analyzed for and re-classified, using cluster analysis,⁶⁻⁸ according to various relevant clinical factors, in order to find the degree of correlation between the molecular and clinical classifications. Knowledge of the true outcome may help clinicians to focus treatment on relevant targets.

Subjects and Methods

Subjects

Postal questionnaires were sent to 398 hemophilia patients drawn from the register of the Finnish Red Cross Blood Transfusion Service. Of the 398, 76.1% (303) returned the form. Children aged 0-15 years were excluded, leaving 224 patients, 173 men and 51 women, who were classified as follows: severe type A (n=60), severe type B (n=7), moderate type A (n=27), moderate or mild type B (n=19), mild type A (n=20), severe type III von Willebrand (n=15), moderate type II von Willebrand (n=65) and factor XIII deficiency (n=11). Most women had severe or moderate von Willebrand's disease or factor XIII deficiency. The mean age of the patients was 41.4 years (range 16-84 years).

Pain

Pain was assessed by a 10 cm double-anchored visual analogue scale. The mean severity of pain was 3.2 (maximum pain 10); 93 patients did not use any analgetic medication, 117 used analgesics occasionally and 14 patients used analgesics daily.

Functional disability

The Stanford Arthritis Center Health Assessment Questionnaire (HAQ)^{9,10} includes two or

three questions regarding each of eight areas of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip and activities. Functional disability is expressed as an index (FDI, range 0-2.8). The mean FDI was 0.4.

Physical activity level

Physical activity level was measured by a five-grade scale from 1 (= no difficulties at all) to 5 = (difficulties even at rest). The mean physical activity level was 2.2±1.1 (range 1-5).

Modes of treatment

The patients had used prophylactic treatment (800-1000 units) 20±33 times/per year (range 0-200) during the last five years, and 21.9±40.3 times (range 0-270) during the last 12 months; 115 (51.3%) patients had not used prophylactic treatment at all during the last 12 months; 15 (6.7%) patients had used prophylactic treatment more than 99 times during the previous year. Eighteen (8%) patients had developed antibodies to clotting factors; 15 (6.7%) patients used prophylactic treatment continuously and 88 (39.3%), occasionally. Cold medication had been used 65±19 times (range 0-99) during the previous year and not at all by 167 (74.6%) patients. Six (2.7%) patients used cold treatment 99 times during the last year, and 79 (35.3%) patients also used Cyklokapron or Caprilon; 88 (37.5%) patients used home treatment. Bleeding during the last 12 months was reported by 136 (60.7%) patients. It occurred in joints 12.8±21.8 times (range 0-119) and in soft tissue 3.5±7.9 times (range 0-63). The number of patients who had been operated on for bleeding at least once during their lifetime was 69 (30.8%).

Statistical analysis

Principal factor analysis was used to generate the set of variables for classification. The K-means algorithm was used to perform the classification. K-means iterative partitioning algorithm was carried out to sharpen cluster assignments based on the similarity of cases to cluster centroids. Assignment of a case to a cluster is dependent on which center is closest to the case in Euclidian distance. The data was standard-

ized before the cluster procedure to control for scaling differences. Multivariate distances were calculated using Ward's method to minimize the error of the sum of squares.¹¹

The consistency of our results was tested by different methods of clustering, and linear discriminant function analysis was used to check the discriminant validity of cluster solutions.⁷ The Wilks' test and pairwise test were used to evaluate the equality of group means. The BMDP Data Processing Program 1993 was used for elaborating the data.

Results

In order to find groups that were as similar as possible (with the least variance within groups) according to the clinical features of hemophilia, the following set of variables was chosen to categorize different groups: average use of prophylactic treatment in the last five years, average use of prophylactic treatment in the last 12 months, use of cold medication, home treatment, bleeding, operations, antibody inhibitors, pain, use of analgesics, FDI-index and physical activity level. Cronbach's α for the variables used to categorize different groups (use of prophylactic treatment in the last five years and in the last 12 months; home treatment; bleeding; surgery; antibody inhibitors; use of cold medication; pain; use of analgesics; FDI; physical activity) was 0.7740, and 0.8135 if patients with antibody inhibitors were excluded.

A strong intercorrelation was found among the variables chosen, which were therefore investigated further by principal factor analysis. After factor rotation two distinct, uncorrelated factors were produced: the first 5 variables loaded to *bleeding factor*, whereas pain, use of analgesics, FDI and physical activity loaded to *pain factor*. Use of cold medication, involving mostly patients with antibody inhibitors, loaded to both factors and was therefore excluded from further analysis.

The common way of categorizing hemophilia is to do so according to the degree of clotting factor deficiency. In the present study this molecular classification basis was included, but instead of using it as a categorizing variable, new

groups were created based on the two factors (see above), which describe the health status of the patients.

Using the K-means algorithm we obtained a 3-cluster solution based on both factors. One of the aims in cluster analysis is to minimize the distance between cases and the centroid within each cluster. In the *bleeding factor* classification these distances were 1.5, 0.9, 0.5, and in the *pain factor* classification 1.2, 1.2 and 0.7.

To check the external stability of our data, the error rate and the percentage of misclassified cases were analyzed using linear discriminant function analysis. In the *bleeding factor* classification, the error rate was 3.2% and the percentage of misclassified cases was 2.9%. The same figures for the *pain factor* were 3.9% and 5%, respectively.

According to Wilks' test and the pairwise test a very significant difference between group means was found in both classifications ($p < 0.0005$).

Comparison of the conventional molecular with the new clinical classification (Table 1) showed large variation in the groups originally classified as severe type B hemophilia, severe type III and moderate von Willebrand disease, and factor XIII deficiency. According to the new classification 35 (58.4%) of the patients with severe type A hemophilia belonged to the severe bleeding group, but only seven (11.7%) had severe pain and disability. Four (57.1%) of the patients with severe type B hemophilia belonged to the severe bleeding group, but only one (14.3%) had severe pain and disability. None of the patients with severe type A or B hemophilia were classified in the mild bleeding group. In moderate type A hemophilia, 15 (55.5%) patients were loaded to the moderate bleeding group, but seven (25.9%) had severe bleeding features. Twelve (60%) patients with mild type A hemophilia were loaded to the mild and 8 (40%) to the moderate bleeding group. Patients with moderate and mild type B hemophilia belonged to the moderate or mild bleeding groups (13/5, respectively), and one patient was loaded to the severe bleeding group. Only four (28.6%) of the 14 with severe von Willebrand deficiency and none of eleven with severe factor XIII deficiency belonged to the group with

Table 1. Distribution of 224 hemophilia patients after classification. Values are frequencies/percentages.

Molecular classification	Severe bleeding			Moderate bleeding			Mild bleeding			Patients with antibody inhibitors N= 18 (8%)			
	Severe pain	Moderate pain	Mild pain	Severe pain	Moderate pain	Mild pain	Severe pain	Moderate pain	Mild pain	Severe pain	Moderate pain	Mild pain	
	N=51 (22.8%) ¹ N=74 (33.0%) N=81 (36.2%)												
	N=9 (4.1%) ² N=25 (11.3%) N=17 (7.7%) N=8 (3.6%) N=30 (13.6%) N=35 (15.8%) N=5 (2.3%) N=11 (5%) N=63 (28.5%) N=3 (1.4%) N=9 (4.1%) N=6 (2.7%)												
Severe type A hemophilia (N=60)	7/11.7 ³	18/30.0	10/16.7	1/1.7	5/8.3	8/13.3	0/0.0	0/0.0	0/0.0	0/0.0	3/5.0	7/11.7	1/1.7
Severe type B hemophilia (N=7)	1/14.3	2/28.6	1/14.3	0/0.0	2/28.6	1/14.3	0/0.0	0/0.0	0/0.0	0/0.0	0/0.0	0/0.0	0/0.0
Moderate type A hemophilia (N=27)	1/3.7	3/11.1	3/11.1	2/7.4	9/33.3	4/14.8	2/7.4	0/0.0	0/0.0	2/7.4	0/0.0	0/0.0	1/3.7
Moderate & mild type B hemophilia (N=19)	0/0.0	0/0.0	1/5.3	1/5.3	4/21.1	8/42.8	1/5.3	0/0.0	0/0.0	4/21.1	0/0.0	0/0.0	0/0.0
Mild type A hemophilia (N=20)	0/0.0	0/0.0	0/0.0	1/0.0	1/5.0	6/30.0	0/0.0	2/10.0	0/0.0	10/50.0	0/0.0	0/0.0	0/0.0
Severe type III von Willebrand (N=14) [*]	0/0.0	2/14.3	2/14.3	1/5.0	3/21.4	1/7.1	0/0.0	2/14.3	0/0.0	2/14.3	0/0.0	1/7.1	0/0.0
Moderate von Willebrand (N=6) ^{**}	0/0.0	0/0.0	0/0.0	1/7.1	6/9.5	5/7.9	2/3.2	6/9.5	39/61.9	0/0.0	1/1.6	3/4.8	
Factor XIII deficiency (N=11)	0/0.0	0/0.0	0/0.0	1/1.6	0/0.0	2/18.2	0/0.0	1/9.1	6/54.5	0/0.0	0/0.0	1/9.1	

*one case is missing; **two cases are missing; ¹percentages indicate the proportion of all the patients versus patients belonging to the severe bleeding group; ²percentages indicate the proportion of all the patients versus the patients with severe bleeding/severe pain; ³percentages indicate the proportion of patients belonging to the crossed cluster group versus patients belonging to the molecular classification group. Boldface indicates the highest proportion of patients belonging to the crossed cluster groups versus patients with different types of coagulation disorders.

severe bleeding features. The highest ratio of these patients was found in the moderate bleeding/moderate pain group and in the mild bleeding/mild pain group, respectively. Most (74.6%) of the moderate von Willebrand patients were classified in the mild *bleeding factor* group. Half of the patients with antibody inhibitors were classified in the moderate and 3 (5%) to the severe pain group (Table 1).

Patients in the severe *bleeding factor* group used a lot of prophylactic treatment and this amount had increased during the last 12 months; 98% of the patients had home treatment. In the moderate *bleeding factor* group, only 29 (39%) out of 74 had home treatment, 19 (25.7%) had been operated on, and all but one patient had experienced bleeding during the previous year. In the moderate *bleeding factor* group, the patients used prophylactic treatment significantly less often ($p < 0.0005$) than those in the severe group, and the amount of medication had decreased during the last 12 months. In the *mild bleeding factor* group, none of the patients had experienced bleeding, but they still used some amount of prophylactic treatment; only nine (11.1%) of them had been operated on. Patients with severe bleeding characteristics used home treatment significantly more often ($p < 0.0005$) than those belonging to the other groups (Table 2a).

Patients in the severe *pain factor* group had the highest disability and pain indexes. Fourteen (56%) used analgesics daily and only two patients (8%) did not use analgesics at all. In the moderate group, the disability index was moderate, but the patients still experienced significant pain. Patients in this group did not use analgesics very frequently. Patients who had very low disability and pain indexes belonged to the mild *pain factor* group, with 70 (57.9%) of them not using analgesics at all (Table 2b).

In all bleeding groups the relationship between age, pain and disability showed the same tendency. With increasing age pain and disability also increased. One exception was found in the group of patients with mild bleeding and moderate pain. Most of the subjects in this group (6 of 11) had moderate von Willebrand's disease (Table 2a).

Discussion

Cluster analysis is an effective method for defining distinct subgroups of patients with similar features. In this respect cluster analysis is more flexible than other statistical methods. A review of the recent literature shows that cluster analysis has been applied in a growing number of clinical studies,¹²⁻¹⁵ but this approach had not been used to classify hemophilia until now.

We distinguished three groups of patients with different clinical disease severity on the basis of two factors (*bleeding factor, pain factor*). According to Vogt and Nagel,¹³ cluster analysis is a very powerful tool, but only if the validity of the outcome clusters is carefully considered. In our study the validity of the solution was first checked by other clustering methods. We tested the outcome clusters by using fixed centroids for each cluster. The result did not significantly change the cluster solution. Only a few cases changed position in the clusters. The Euclidian distance from each case to the centroid of the cluster did not decrease. This shows that our cluster solution had a high degree of internal stability. Secondly, we used linear discriminant function analyses to test the validity. Results showed that the external stability of our cluster solution was also very satisfactory.

In this study we stress the necessity of classifying patients with blood coagulation disorders from two points of view: the clinical picture expressed by the pain factor and the coagulation defect expressed by the bleeding factor; the severity of the two is not necessarily the same in a given patient. The majority of patients after clustering were located in the moderate-mild groups. This may be due to modern therapeutic approaches which alleviate the symptoms of the disease.^{5,16}

Pain did not correspond to the original classification according to degree of deficiency of the clotting factor.

Corresponding results have been found in other types of musculoskeletal diseases like rheumatoid arthritis, osteoarthritic and chronic low-back pain disorders.¹⁷⁻²⁰ Clinical evidence shows that there is no one-to-one relationship between damage or disease and pain. Some patients with severe disease function well, while

Table 2a. Age distribution and clinical aspects of the cluster analysis groups. Values are mean±SEM except for operations and home treatment, which are presented as frequencies (with percentages in parentheses).

	Age ¹	Prophylactic treatment/ per last 5 years ²	Prophylactic treatment/ per last 12 months ²	Frequency of bleeding in joints ³	Frequency of bleeding in soft tissue ³	Operations ⁴ yes/no	Home treatment ^{**} use/do not use	Use of cold medication ⁵
Severe bleeding	N=51 38.2±13.5 (16-63)	65.4±3.8 (10-99)	77.1±7.1 (10-270)	41.6±4.1 (4-199)	9.6±1.9 (0-63)	35/16 (65%/35%)	50/1 (98%/2%)	18.0±4.5 (0-99)
Severe pain and disability	N=9 46.7±11.5 (24-60)	61.0±12.1 (20-99)	96.7±28.6 (21-270)	45.6±11.1 (4-199)	21.3±8.0 (3-63)	8/1 (89%/11%)	9/0 (100%/0%)	27.6±13.9 (0-99)
Moderate pain and disability	N=25 40.6±13.9 (16-63)	62.9±5.7 (10-99)	68.4±8.6 (10-200)	45.6±6.3 (9-111)	6.5±1.3 (0-20)	16/9 (64%/36%)	24/1 (96%/4%)	22.2±6.9 (0-99)
Mild pain and disability	N=17 30.2±9.6 (17-53)	71.3±5.0 (40-99)	79.8±7.6 (40-150)	33.0±5.0 (5-78)	7.5±2.5 (0-29)	11/6 (65%/35%)	17/0 (100%/0%)	6.7±4.3 (0-70)
Moderate bleeding [*]	N=73 42.9±16.0 (17-79)	13.0±2.3 (0-99)	10.4±2.1 (0-100)	7.6±1.1 (0-48)	2.9±0.5 (0-20)	19/54 (26%/74%)	31/43 (42%/58%)	3.8±1.2 (0-60)
Severe pain and disability	N=8 55.1±6.9 (43-64)	23.8±13.7 (0-90)	21.9±13.4 (0-100)	4.8±1.4 (1-11)	2.4±1.2 (0-10)	3/5 (38%/62%)	3/5 (38%/62%)	10.1±8.3 (0-60)
Moderate pain and disability	N=30 47.9±13.8 (19-66)	12.3±2.7 (0-51)	8.7±2.4 (0-51)	12.3±2.2 (0-48)	3.8±1.0 (0-20)	8/22 (27%/73%)	10/20 (33%/66%)	5.9±2.2 (0-50)
Mild pain and disability	N=35 34.8±14.3 (17-79)	12.1±3.6 (0-99)	9.8±2.5 (0-50)	4.7±1.1 (0-23)	2.3±0.7 (0-20)	8/27 (23%/77%)	16/18 (47%/53%)	0.8±0.5 (0-16)
Mild bleeding ^{**}	N=79 43.2±16.1 (16-83)	1.8±0.8 (0-50)	1.3±0.8 (0-60)	0.0±0.0 (0-0)	0.0±0.0 (0-0)	9/70 (11%/89%)	3/78 (4%/96%)	0.4±0.2 (0-15)
Severe pain and disability	N=5 57.2±10.6 (39-65)	8.8±5.6 (0-30)	0.4±0.4 (0-2)	0.0±0.0 (0-0)	0.0±0.0 (0-0)	2/3 (40%/60%)	0/5 (0%/100%)	0.0±0.0 (0-0)
Moderate pain and disability	N=11 60.3±16.1 (22-83)	0.5±0.4 (0-5)	0.2±0.2 (0-2)	0.0±0.0 (0-0)	0.0±0.0 (0-0)	1/10 (9%/91%)	0/11 (0%/100%)	0.0±0.0 (0-0)
Mild pain and disability	N=63 38.3±13.0 (16-67)	1.5±0.9 (0-50)	1.6±1.0 (0-60)	0.0±0.0 (0-0)	0.0±0.0 (0-0)	6/57 (10%/90%)	3/59 (5%/95%)	0.5±0.3 (0-15)
Patients with antibody inhibitors	N=18 35.4±11.8 (16-53)	ND	ND	11.6±3.0 (0-47)	4.4±1.4 (0-17)	5/13 (28%/72%)	0/18 (0%/100%)	13.2±5.9 (0-99)
Severe pain and disability	N=3 42.7±15.3 (25-52)	ND	ND	14.7±7.5 (0-25)	1.3±0.9 (0-3)	2/1 (67%/33%)	0/3 (0%/100%)	2.3±1.5 (0-5)
Moderate pain and disability	N=9 36.0±11.1 (16-53)	ND	ND	14.9±4.8 (0-47)	6.2±2.1 (0-17)	3/6 (33%/67%)	0/9 (0%/100%)	22.2±10.8 (0-99)
Mild pain and disability	N=6 28.8±9.9 (19-40)	ND	ND	5.2±3.3 (0-17)	3.2±2.8 (0-17)	0/6 (0%/100%)	1/5 (17%/83%)	5.0±5.0 (0-30)

*one case is missing; **2 cases are missing; 1 years, Mean±SD; 2 in doses of 800-1000 units; 3 number of bleeding incidents during the last 12 months; 4 operations for joint and soft tissue bleeding during patients lifetime; 5 number of times during last 12 months; ND: not done.

Table 2b. Clinical aspects of the cluster analysis groups. Values are mean±SEM except for treatment and analgesics, which are presented as frequencies (with percentages in parentheses).

		FDI ¹	VAS ²	PAL ³	Analgesics do not use/ occasionally/daily
Severe bleeding	N=51	0.8±0.1 ^{ab} (0.0-2.8)	4.6±0.4 ^b (0.0-10.0)	2.8±0.1 ^{ab} (1.0-5.0)	13/34/4 25%/67%/8%
Severe pain and disability	n=9	1.7±0.3 (0.4-2.8)	6.3±0.8 (2.0-10.0)	3.9±0.3 (2.0-5.0)	1/4/4 12%/44%/44%
Moderate pain and disability	N=25	0.8±0.1 (0.1-1.6)	5.2±0.5 (0.0-10.0)	3.0±0.1 (2.0-4.0)	5/20/0 20%/80%/0%
Mild pain and disability	N=17	0.1±0.05 (0.0-0.6)	2.8±0.4 ^e (1.0-7.0)	1.8±0.1 (1.0-3.0)	7/10/0 41%/59%/0%
Moderate bleeding [*]	N=74	0.4±0.1 ^a (0.0-1.9)	3.7±0.3 ^d (0.0-10.0)	2.2±0.1 ^{ad} (1.0-4.0)	30/39/4 41%/53%/6%
Severe pain and disability	N=8	1.2±0.2 (0.4-1.9)	6.3±0.5 (5.0-8.0)	3.6±0.2 (3.0-4.0)	1/3/4 13%/37%/50%
Moderate pain and disability	N=30	0.6±0.1 (0.0-1.5)	5.4±0.4 (1.0-10.0)	2.8±0.1 (1.0-4.0)	10/20/0 33%/67%/0%
Mild pain and disability	N=35	0.04±0.02 (0.0-0.4)	1.8±0.3 (0.0-7.0)	1.4±0.1 (1.0-2.0)	19/16/0 54%/46%/0%
Mild bleeding ^{**}	N=81	0.2±0.1 ^{bc} (0.0-2.4)	1.6±0.3 ^{bcd} (0.0-9.0)	1.7±0.1 ^{bcd} (1.0-5.0)	46/30/3 58%/38%/4%
Severe pain and disability	N=5	1.3±0.3 (0.8-2.4)	6.2±0.6 (5.0-8.0)	3.1±0.5 (2.0-5.0)	0/2/3 0%/40%/60%
Moderate pain and disability	N=11	0.8±0.2 (0.0-1.9)	4.2±1.0 (1.0-9.0)	3.2±0.2 (2.0-4.0)	5/6/0 45%/55%/0%
Mild pain and disability	N=63	0.04±0.02 (0.0-0.6)	0.8±0.2 ^e (0.0-5.0)	1.3±0.1 (1.0-4.0)	41/22/0 65%/35%/0%
Patients with antibody inhibitors	N=18	0.5±0.1 ^c (0.0-2.0)	4.0±0.7 ^c (0.0-4.0)	2.6±0.3 ^c (1.0-5.0)	4/11/3 22%/61%/17%
Severe pain and disability	N=3	1.1±0.5 (0.4-2.0)	7.3±0.7 (6.0-8.0)	4.3±0.3 (4.0-5.0)	0/0/3 0%/0%/100%
Moderate pain and disability	N=9	0.6±0.2 (0.0-1.4)	5.0±0.7 (2.0-7.0)	2.8±0.1 (2.0-3.0)	1/8/0 11%/89%/0%
Mild pain and disability	N=6	0.1±0.06 (0.0-0.4)	0.8±0.5 (0.0-3.0)	1.5±0.2 (1.0-2.0)	3/3/0 50%/50%/0%

*one case is missing; **two cases are missing; ¹functional disability index; ²visual analogue scale; ³physical activity level.

Comparison between different groups of bleeding severity regarding VAS, FDI and PAL was performed by Kruskal-Wallis test; ^abetween severe bleeding and moderate bleeding groups, $p < 0.05$; ^bbetween severe bleeding and mild bleeding groups, $p < 0.05$; ^cbetween mild bleeding group and patients with antibody inhibitors, $p < 0.05$; ^dbetween moderate bleeding and mild bleeding groups, $p < 0.05$; ^ebetween severe bleeding/mild pain and mild bleeding/mild pain groups, $p < 0.05$.

others are quite impaired; perhaps this can be explained by various psychological mechanisms.

After the clustering, most of the patients with severe types of coagulation disorders experienced moderate pain, while those with moderate coagulation disorders experienced moderate or mild pain. In the moderate bleeding group, the frequency of bleeding in joints was higher for

patients in the moderate pain group than for the ones in the severe group (Table 2a), and the pain index was also quite high for this group of patients (Table 2b). However, regarding the level of functional disability and physical activity, these patients reported less disability than those in the severe pain group. One possible explanation is that these patients experience acute pain

with bleeding but not chronic pain due to hemophilic arthropathy. The *pain factor* reflects chronic more than acute pain because of the combination of pain and functional disability. This shows clearly that the *pain factor* does not strongly relate to the *bleeding factor*. The severity of pain and disability is not dependent on the severity of bleeding. This indicates that the multivariate relationships between pain and bleeding are complicated. The classification also revealed that increasing usage of prophylactic treatment during last 5 years reduced the severity of pain and disability in patients with severe bleeding (Table 2a and 2b). This tendency was not found in the other bleeding groups. In treating hemophilia patients it seems to be important to pay attention to both aspects of the disease: the bleeding features and the pain and disability.

According to our results, the strongest predictors for assigning patients to the appropriate diagnostic groups concerning pain and disability are the use of prophylactic treatment and home therapy. These two variable seems to enhance self-care abilities which moderate the management of the disease.

Another important result in our study was the distribution of patients with von Willebrand's disease into different disease subsets after clustering. Because of the molecular complexity and clinical variability of the disease, laboratory diagnosis is not always simple and straightforward.³ Spontaneous hemorrhage, hematuria, and hemarthrosis are rare.³ Patients with severe von Willebrand's disease did not exhibit severe symptoms. Patients with antibody inhibitors showed a very large variance within the new cluster groups, although most of them (11 out of 18) belonged to the group with severe type A hemophilia (Table 1).²¹

Our results indicate that pain and bleeding seem to be the main items that determine the clinical severity of a coagulation disorder. These functional qualities appear to be more important for the clinical classification of hemophilia than the type and grade of coagulation factor defect.

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