European Journal of Clinical and Biomedical Sciences
2023; 9(3): 28-37
http://www.sciencepublishinggroup.com/j/ejcbs
doi: 10.11648/j.ejcbs.20230903.11
ISSN: 2575-4998 (Print); ISSN: 2575-5005 (Online)

Clinical Profile and Cardiovascular Risk Factors Among Hemophilians Followed at University Clinics of Kinshasa

Gueth Kundabi[1, *], Gibency Mfulani[5], Karim Assani[1], Nina Domo[1], Aleine Budiongo[1], Jonathan Kukila[4], Eric Mukenge[4], John Senga[2], Bodi Mabiala[3], René Ngiyulu[1], Jean-Lambert Gini[1]

[1]Hematology-Oncology Service, Department of Pediatrics, Kinshasa University Clinics, Faculty of Medecine, University of Kinshasa, Kinshasa, DR Congo

[2]Cardiology Service, Department of Paediatrics, Kinshasa University Clinics, Faculty of Medecine, University of Kinshasa, Kinshasa, DR Congo

[3]Emergency Department, Department of Paediatrics, Kinshasa University Clinics, Faculty of Medecine, University of Kinshasa, Kinshasa, DR Congo

[4]Department of Hematology, Department of Medical Biology, Kinshasa University Clinics, Faculty of Medecine, University of Kinshasa, Kinshasa, DR Congo

[5]Department of Anesthesia-Resuscitation, Kinshasa University Clinics, Faculty of Medecine, University of Kinshasa, Kinshasa, DR Congo

Email address:

guethkundabi84@gmail.com (Gueth Kundabi), gibencymfulani1990@gmail.com (Gibency Mfulani), drassanik@gmail.com (Karim Assani) domonina23@gmail.com (Nina Domo), albudiongo@gmail.com (Aleine Budiongo), jonathankuksy21@gmail.com (Jonathan Kukila), eric_mukenge@yahoo.com (Eric Mukenge), selijohnes@gmail.com (John Senga), josephbodi9@gmail.com (Bodi Mabiala), relyse2000@yahoo.com (René Ngiyulu), giniehungu@gmail.com (Jean-Lambert Gini)

[*]Corresponding author

To cite this article:

Gueth Kundabi, Gibency Mfulani, Karim Assani, Nina Domo, Aleine Budiongo, Jonathan Kukila, Eric Mukenge, John Senga, Bodi Mabiala, René Ngiyulu, Jean-Lambert Gini. Clinical Profile and Cardiovascular Risk Factors Among Hemophilians Followed at University Clinics of Kinshasa. *European Journal of Clinical and Biomedical Sciences*. Vol. 9, No. 3, 2023, pp. 28-37. doi: 10.11648/j.ejcbs.20230903.11

Received: June 11, 2023; **Accepted**: July 11, 2023; **Published**: August 31, 2023

Abstract: *Background:* Hemophilia is a congenital, inherited bleeding disorder that prevents blood from clotting, causing abnormally long bleeding. It remains underdiagnosed in Africa and particularly in the Democratic Republic of Congo, where it remains poorly known to the population and health professionals. The present study aims to determine the clinical profile and cardiovascular risk factors in hemophiliacs at the University Clinics of Kinshasa. *Methods*: This is a cross-sectional study with an analytical aim, in which 155 patients (children and adults) with a haemorrhagic syndrome were included. The diagnosis of haemophilia was confirmed in thirty-six patients, all male; 22 hemophiliac patients regularly followed were matched with 24 non-hemophilic patients (control group). *Results*: hemophilia A represented 81% and hemophilia B 19%. The most represented age group was between 3 to 6 years (19%). Regarding the severity of the disease, half of the patients, or 50%, presented with severe hemophilia, the main symptom being hemarthrosis (30%). Of our total sample of hemophiliacs, we had recorded two cases of death (5.5%). Regarding cardiovascular risk factors, only the deterioration of myocardial function was found in one patient (4.5%). *Conclusion*: hemophilia is a disabling disease, which alters the quality of life of patients. Cardiovascular risk factors seem to be lower in Congolese hemophiliacs, however, ultrasound monitoring is necessary in order to prevent any pejorative evolution.

Keywords: Hemophilia, Cardiovascular Risk Factors, Clinical Profile, University Clinics of Kinshasa

1. Introduction

Hemophilia is a congenital and hereditary hemorrhagic disease, with recessive transmission, linked to the X chromosome. It is therefore men who cause the disease and women are carriers (healthy carriers) [1]. The biological diagnosis is carried by a deficiency in factor VIII for hemophilia A and factor IX for hemophilia B. The disease

affects 1 boy for every 5,000 births, with a predominance for hemophilia A than over hemophilia B. There are currently nearly 217,000 hemophiliacs in the world, of whom approximately 85% are hemophiliacs A and 15% hemophiliacs B [1, 2]. In Africa, the disease is still underdiagnosed. In 2019 only about 15% of expected cases were identified, which represents 2.8% of patients diagnosed worldwide. [2]. Several reasons may explain this under-notification of hemophilia patients: insufficient number of hematology specialists interested in this pathology and absence of adequate laboratories for the precise biological diagnosis of the disease.

The Democratic Republic of Congo (DRC), thanks to the combined efforts of the medical team of the pediatric hematology and medical biology department of the University Clinics of Kinshasa, it entered the theoretical and associative training program of the Alliance franco- African Hemophilia Treatment Association (AFATH) from 2018 to 2022. Thus, thanks to this program, the precise diagnosis of hemophilia is made possible as well as the availability of plasma coagulation concentrates (CFC) for patients suffering from this pathology. In the DRC, with an estimated population of over 100 million, we should have around 10,000 people suffering from this anomaly, according to the WHO estimate: 1 hemophiliac/5,000 male births [2]. The data concerning the incidence of cardiovascular disease risk in the literature, in children and young adults with hemophilia are very controversial [3].

Mortality due to cardiovascular pathologies in hemophilia patients would have increased by 2 to 6% between 1972 and 2001 and the prevalence of cardiovascular diseases would have doubled during the period of 2000-2007 compared to 1990-1999 [4, 5]. With equal risk factors, the occurrence of cardiovascular diseases seems to be lower in the hemophiliac population [6]. Data from cohorts suggested that hemophiliac patients have a lower mortality rate from a cardiovascular cause than in the general population, this phenomenon being probably due to their blood hypocoagulable states [6]. This suggested that hemophilia confers a protective effect against the risk of cardiovascular disease [6, 7].

However, this hypothesis has been refuted by several recent studies: Alperstein et al., showed that the incidence of hypertension and obesity were significantly higher in children with hemophilia compared to the control group and that dyslipidemia was similar in both groups [3]. In 2019, Zeynep et al in Turkey showed that the deterioration of myocardial function associated with arterial hypertension and dyslipidemia was greater in children with hemophilia, compared to the control group [6]. In 2011, Ragni et al published a five-year study in Pennsylvania. Six to 10% of hemophilia patients hospitalized over this period were for coronary disease. The risk factors, the severity of the pathology and the intra-hospital mortality, were similar to those encountered in the general population. They therefore emphasize that hemophilia does not protect against the risk of cardiovascular disease [8].

However, some risk factors are specific to hemophilia. Hemophilia patients with severe arthropathies are inclined to exercise less physical activity than their peers. This sedentary lifestyle leads to a tendency to obesity and consequently to the metabolic syndrome [9, 10]. Arthropathy-related pain motivates the taking of non-steroidal anti-inflammatory drugs which increase the risk of cardiovascular accidents. Thus, hemophiliac patients are exposed to cardiovascular risks, in the same way as their congeners or even, in certain situations, more at risk than the general population. Hence the need to know these risk factors and to better identify them, because they can be such as to darken the prognosis and life expectancy of hemophiliac patients, particularly in developing countries where the access to quality care is very limited.

In recent decades, great progress has been made in the management of hemophilia. They concern the establishment of more precise diagnostic procedures, increasingly effective and sufficient therapeutic means, even allowing prophylaxis from a young age, and finally the hope of a gene therapy which points to the 'horizon. These advances have significantly improved the life expectancy of patients with hemophilia worldwide, particularly in developed countries [4]. However, the extension of this life expectancy is currently hampered by the emergence of comorbidity [4, 6]. Thus, hematologists are today confronted with the management of these emerging pathologies, which the medical community has rarely been confronted with. It is therefore a new challenge to correctly manage hemophilia patients with comorbidities. The present study was initiated with the aim of filling the gap in epidemiological data on hemophilia by determining the frequency and cardiovascular risk factors in patients followed at the University Clinics of Kinshasa.

2. Methods

This is a cross-sectional study with an analytical aim, relating to patients suffering from hemophilia regularly followed at the University Clinics of Kinshasa, compared to a non-hemophilic control group. It covered the period from March 2018 to October 2021 and took place at the University Clinics of Kinshasa, Department of Pediatrics / Department of Hematology and Pediatric Cardiology.

The present study opted for an exhaustive sampling with consecutive recruitment of 155 patients who consulted for hemorrhagic syndrome. Among these patients, there were 22 male patients aged 6 months to 44 years with hemophilia A or B (cases) and 24 patients of the same age and sex, having consulted the hematology department for the same clinical picture., in whom the diagnosis of hemophilia has not been confirmed (control case or controls).

2.1. Data Collection Technique

This study used prospective data collection. The selected patients were followed and then submitted to a certain number of assessments. A medical file was established for each child containing all the elements collected during the

complete clinical examination (anthropometric parameters, blood pressure and haemorrhagic stigmata). A blood sample was taken in the laboratory of the Faculty of Medicine, using a semi-automated machine, and a cardiac ultrasound was performed by the cardio-pediatrician of the CUK Pediatric Cardiology Service.

The following variables were retained: socio-demographic data (age, sex, province of origin). The measurement of anthropometric parameters was made using a FAZZII SS Padana 317-20090 brand scale made in Italy in 2015 for weight measurement and a tape measure or a vertical measuring rod was used to measure the height of patients..

clinical data (family history of haemophilia or congenital haemorrhagic diseases, history of cardiovascular diseases; anthropometric parameters: weight, height; vital parameters: blood pressure, temperature; presence of limb deformities, haemorrhagic lesions (haemarthroses, hematomas, etc.); presence of bleeding events and possible complications; nature of treatment (prophylactic treatment or on demand), determination of BMI: P (Kg)/ T (m^2) was related to the WHO curve for age and sex.

The blood analyzes (hemoglobin, fasting blood sugar, total triglycerides, LDL cholesterol and HDL cholesterol) were carried out in the laboratory of the Faculty of Medicine by colorimetric method, using an automaton of the HUMANLYZER PRIMUS type. The homeostasis assessment (TCA and TQ assay as well as plasma factor VIII and IX activity assay) was carried out in the CUK hematology laboratory, using a semi-automatic coagulation analyzer. -automatic START-STAGO type.

Cardiac Doppler and tissue ultrasound was performed by a cardiopediatrician from the Pediatric Cardiology Service of the University Clinics of Kinshasa, using a Philips CX50 3.1.1 portable ultrasound device (Andover, MA, USA, 2013), wearing 2 probes of 5 and 8 mHz respectively for patients under 4 years old and over 4 years old. It made it possible to evaluate the following parameters:

1) The left ventricular systolic ejection fraction (LVEF);
2) The diastolic diameter of the interventricular septum (DdSIV);
3) The systolic diameter of the interventricular septum (DsSIV);
4) The internal diastolic diameter of the left ventricle (DDIVG);
5) The internal systolic diameter of the left ventricle (DsIVG);
6) The diastolic diameter of the posterior wall of the left ventricle (DdPVG);
7) The systolic diameter of the posterior wall of the left ventricle (DsPVG);
8) The isovolumic relaxation time (IVR): the time elapsed between the closure of the aortic valve and the opening of the mitral valve;
9) The isovolumic contraction time (TCIV): the time elapsed between the closing of the mitral valve and the opening of the aortic valve;
10) The total ejection time of the left ventricle: the time elapsed between the opening and the closing of the aortic valve;
11) The myocardial performance index (MPI) = Tei index, was calculated by the following formula:

$$\text{MPI} = \frac{TRIV+TCIV}{TET}$$

The ultrasound machine automatically gave the value of the IPM (Tei index).

MPI <0.83 was considered normal, while a value >0.83 reflected a decline in myocardial performance.

Hemophilia has been classified:

1) Severe (major) hemophilia: anti-hemophilic factor A or B deficiency is <1%.
2) Moderate hemophilia: anti-hemophilic factor deficiency varies between 1 and 5%
3) Mild hemophilia: anti-hemophilic factor deficiency is > 5% but <40%.

The IPM > 0.83 reflected a drop in myocardial performance and hypertrophy of the left ventricle: defined by a diastolic diameter of the interventricular septum (DdSIV) or diastolic diameter of the posterior wall of the left ventricle (DdPVG) > P97 (for the child) or > 1.1cm (for adults).

2.2. Data Processing and Analysis

After data collection; an initial quality control was carried out to ensure the completeness, accuracy and reliability of the data. A second consistency check of each sheet was carried out to make corrections to certain inconsistencies noted in order to guarantee the validity of the results. The data processing was done in several stages: manual analysis of the forms; entry, purification and encoding on Excel 2013 finally the analysis was carried out on SPSS version 22; the presentation of the data was done in the form of tables and figures.

The descriptive analyzes carried out are the mean ± the standard deviation for the quantitative data with a Gaussian distribution and the median with the interquartile space (IQS), for the data with a non-Gaussian distribution, the relative (%) and absolute (n) for categorical or qualitative data. Ficher's exact test was performed to compare the percentages. The Student's t test compared the means and the ANOVA test to compare the medians.

2.3. Ethical Considerations

Adherence to the study was conditional on the voluntary signature of the consent form after clear explanations given to the patient. The research protocol was validated by the ethics committee of the School of Public Health of the University of Kinshasa under the number: ESP/CE/288/2021. Confidentiality rules were respected during data processing and analysis.

3. Results

During the present study, we identified a total of 155 patients with hemorrhagic syndrome. The diagnosis of

hemophilia was confirmed in 36 patients, all male, 22 hemophiliac patients regularly followed at the CUK were matched with a control group of 24 non-hemophilic patients. The median age of the study population was 15 years, with extremes ranging from 6 months to 44 years.

The diagram below shows the flow of patients:

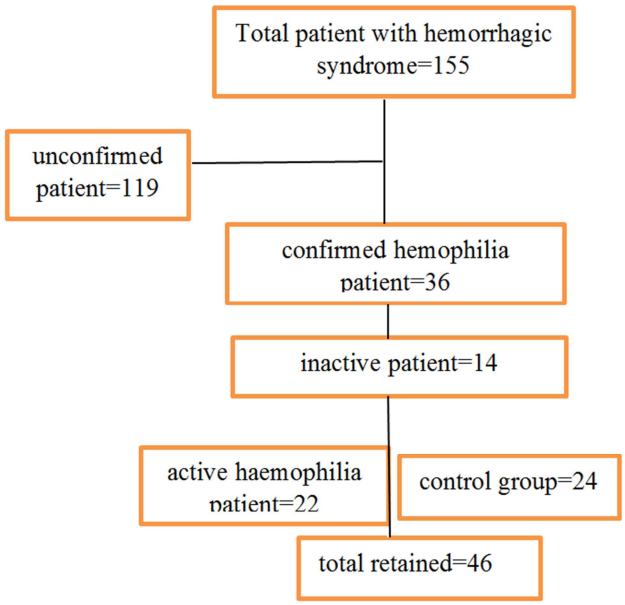

Figure 1. *Flowchart.*

3.1. Sociodemographic Characteristics of the Study Population

It emerges from this study that the most found age group was between 3 and 6 years in 19.4% of cases. The median age of the study population was 15 (6.7-26.2). Comparatively there was no age difference between hemophiliacs and non-hemophiliacs (p=0.896). Most came from the provinces of Bandundu and Kongo (Table 1).

Table 1. *Distribution of study participants (cases and controls) according to sociodemographic characteristics.*

Variables	All n=46 (%)	Case n=22 (%)	Control n=24 (%)	P-value
Age, years: Me (EIQ)	15 (6.7-26.2)	15.5 (5.5-25.7)	16.5 (9-16.5)	
6 months to 6 years	11 (23.9)	6 (27.3)	5 (20.8)	
7 to 12	11 (23.9)	5 (22.7)	6 (25)	0.896
13 to 18	6 (13)	2 (9.1)	4 (16.7)	
19 to 25	6 (13)	4 (18.2)	2 (8.3)	
>25	12 (26.1)	5 (22.7)	7 (29.2)	
Provinces of origin				
Bandundu	14 (30.4)	7 (31.8)	7 (29.2)	
Central Kongo	13 (28.3)	6 (27.3)	7 (29.2)	
mongala	5 (10.9)	0	5 (20.8)	
Upper Katanga	4 (8.7)	4 (18.2)	0	0.064
Tshopo	4 (8.7)	3 (13.6)	1 (4.2)	
Kasai	3 (6.5)	1 (4.5)	2 (8.3)	
Ituri	2 (4.3)	0	2 (8.3)	
North Kivu	1 (2,2)	1 (4.5)	0	
Measurements				
Size	145.3±31.8	142.8±35.4	147.5±28.7	0.620
Weight	42.9±22.2	39.2±22	46.2±22.2	0.291
BMI	18.5±3.9	17.3±3.1	19.5±4.3	0.051
NOT	113.6±13.4	112.7±14.2	114.4±12.8	0.673
PAD	68.5±6.4	67.1±7	69.8±5.7	0.158
Background				
Haemophilia	22 (47.8)	19 (86.4)	3 (12.5)	<0.001
Hemorrhagic disease	29 (63)	19 (86.4)	10 (41.7)	0.002
CVD	3 (6.5)	3 (13.6)	0	0.061

The BMI, PAS and PAD parameters were slightly elevated in the control group, compared to hemophiliacs, with no significant difference (P>0.05). The antecedents of haemophilia and haemorrhagic diseases were significantly more found in the haemophiliac group than the control.

3.2. Clinical Information of Hemophilia Patients in General

It emerges that 81% of patients had hemophilia A and 19% hemophilia B. Hemarthroses are the dominant clinical symptoms (30.2%).

Table 2. *Distribution of hemophiliac patients according to clinical symptoms.*

Symptoms	Hemophilia A not (%)	Hemophilia B not (%)
Hemarthroses	19 (30.2)	9 (34.6)
Limb hematomas	18 (28.6)	5 (19.2)
External bleeding	12 (19)	4 (15.4)
Chronic arthropathy	7 (11.1)	4 (15.4)
Post-circumcision bleeding	6 (9.5)	2 (7.7)
Intracranial hemorrhage	1 (1.6)	0

The circumstances and age at first diagnosis are given in Table 3. Hemarthroses were the first warning signs (36.1%) when the disease was discovered and the age at first diagnosis was in most cases cases between 3 and 6 years (19.4%).

Table 3. *Distribution of hemophiliacs according to circumstances and age at first diagnosis.*

Variables	n=36	Percentage
Diagnosis circumstances		
Hemarthroses on walking	13	36.1
Limb hematomas	9	25
Post-circumcision bleeding	6	16.7
External bleeding	5	13.9
Family screening	3	8.3
Age at first diagnosis		
6 months – 2 years	6	16.7
36 years	7	19.4
7 – 12 years old	3	16.7
13 – 18 years old	2	16.7
19 – 25 years old	5	13.8
>25 years	4	16.7

3.3. Disease Severity

The proportion of patients with severe and moderate hemophilia was 50% and 33% respectively. The annual number of hemorrhagic strokes increases with the severity of the disease, 14/18 patients with severe haemophilia (77.8) had more than 10 hemorrhagic strokes per year (table 4).

Table 4. *Distribution of hemophiliacs according to the frequency of hemorrhagic accidents and the severity of the disease.*

Frequency of accidents	Haemophilia		
	Severe	Moderate	Lightweight
<5 accidents/year	0	3 (25)	5 (83.3)
5 to 10 accidents/year	4 (22.2)	7 (58.3)	1 (16.7)
>10 accidents/year	14 (77.8)	2 (16.7)	0
Total	18 (100)	12 (100)	6 (100)

3.4. Hemophilia Care

The graphic below describes the therapeutic options in the care of patients with hemophilia. It shows that on-demand treatment was the most used (40.9%), followed by prophylactic treatment (27.3%).

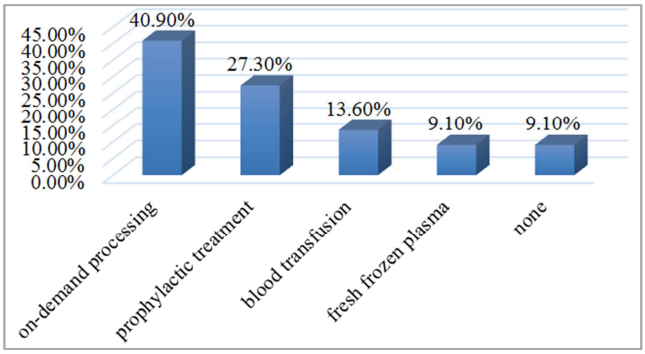

Figure 2. *Distribution of hemophiliacs according to treatment option.*

3.5. Mortality of Haemophilia Patients

It emerges from this graph, a mortality of approximately 6% of hemophiliac patients (including a death of the 1st president of the ACDH).

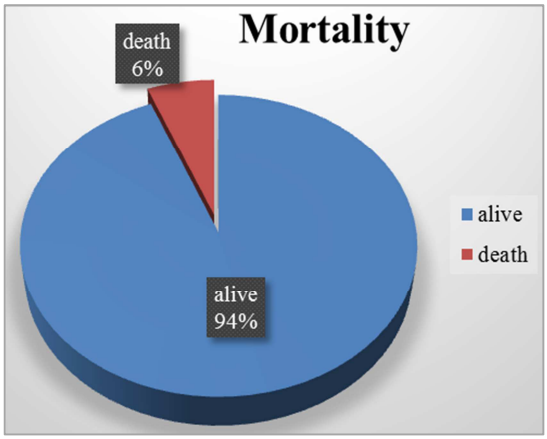

Figure 3. *Mortality of hemophilia patients.*

3.6. Biological Information of the Study Population

It appears that only hemoglobin was significantly elevated in the control group, compared to the hemophiliac group (P<0.001). Nevertheless, we noted a slight decrease in HDL-C, with a slight increase in LDL-C, but not significantly (P>0.05).

Table 5. *Distribution of participants according to biological data.*

Variables	All n=46 (%)	Case n=22 (%)	Control n=24 (%)	P-value
Hemoglobin	11.7±1.6	10.7±1.4	12.6±1	<0.001
blood sugar	66.2±13.7	68.9±15.5	63.7±11.7	0.207
Total cholesterol	103.9±19.3	103.1±18.7	104.5±20.3	0.802
HDL-C	25.7±8.5	23.7±7.5	27.5±9	0.128
LDL-C	62.8±23.8	64±22.5	61.8±25.2	0.752
Triglycerides	66.5±21.9	64.2±19.6	68.7±24.2	0.496

Table 6 describes the plasma levels of deficient coagulation factors.

It emerges that 09 patients (40.9%) had a factor VIII level between 1 to 5% (moderate hemophilia A) followed by 07 patients with a factor VIII level < 1% (severe hemophilia A (31.8%).

Table 6. *Distribution of hemophiliacs according to the level of deficient coagulation factors.*

Variables	n=22	Percentage
Factor VIII levels		
< 1%	17	47.2
1 – 5%	10	27.8
>5 - <40%	5	13.9

Variables	n=22	Percentage
Factor IX levels		
< 1%	1	2.8
1 – 5%	2	5.5
>5 - <40%	1	2.8

3.7. Ultrasound Information of the Study Population

This table shows that five patients (20.8%) in the control group presented a DdSIV greater than 1.1cm and one hemophiliac patient presented an IPM greater than 0.83 (4.5%). We found no significant difference in terms of left ventricular posterior wall dimensions and ventricular systolic ejection fraction in the two groups (P>0.05).

Table 7. *Ultrasound data of the study population.*

Variables	All n=46 (%)	Case n=22 (%)	Control n=24 (%)	P-value
DdSIV: Me (EIQ)	0.8 (0.7-0.9)	0.8 (0.6-0.9)	0.8 ± (0.7-0.9)	0.225
<0.6cm	7 (15.2)	3 (13.6)	4 (16.7)	0.063
0.6 to 1.1cm	34 (73.9)	19 (86.4)	15 (62.5)	
>1.1cm	5 (10.9)	0	5 (20.8)	

Variables	All n=46 (%)	Case n=22 (%)	Control n=24 (%)	P-value
DsSIV: Me (EIQ)	1.1 (1-1.3)	1.1 (0.9-1.3)	1.2 (1-1.3)	0.489
<0.6cm	0	0	0	0.571
0.6 to 1.1cm	21 (45.7)	11 (50)	10 (41.7)	
>1.1cm	25 (54.3)	11 (50)	14 (58.3)	
DdPVG: Me (EIQ)	0.6 (0.5-0.7)	0.5 (0.4-0.7)	0.6 (0.5-0.6)	0.306
<0.6	21 (45.7)	12 (54.5)	9 (37.5)	0.366
0.6 to 1.1cm	24 (52.2)	10 (45.5)	14 (58.3)	
>1.1cm	1 (2,2)	0	1 (4.2)	
DsPVG: Me (EIQ)	0.9 (0.7-1)	0.9 (0.7-1)	1 (0.8-1.1)	0.340
<0.6	0	0	0	0.246
0.6 to 1.1cm	21 (45.7)	12 (54.5)	9 (37.5)	
>1.1cm	25 (54.3)	10 (45.5)	15 (62.5)	
LVEF: Me (EIQ)	68.4 (65.2-71.9)	67.7 (64-71.3)	68.9 (67-72.1)	0.209
<50%	0	0	0	0.489
50 to 70%	29 (63)	15 (68.2)	14 (58.3)	
>70%	17 (37)	7 (31.8)	10 (41.7)	
IPM: Me (EIQ)	0.5 (0.5-0.6)	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.169
<0.83	45 (97.8)	21 (95.5)	24 (100)	0.291
>0.83	1 (2,2)	1 (4.5)	0	

3.8. Search for Cardiovascular Risk Factors

Table 8 shows the cardiovascular risk factors identified in this study. Only deterioration of myocardial function was found in one haemophiliac patient (4.5%). Nevertheless, 5 patients in the control group (20.8%) presented with LVH.

Table 8. *Distribution of participants according to cardiovascular risk factors.*

Variables	All n=46 (%)	Casen=22 (%)	Controln=24 (%)	P-value
hypertension	0	0	0	-
Obesity	0	0	0	
Hyperglycemia	0	0	0	
Hypercholesterolemia	0	0	0	
Hypertriglyceridaemia	0	0	0	
LVH	5 (10.9)	0	5 (20.8)	
Myocardial damage	1 (2,2)	1 (4.5)	0	

Table 9 gives the correlation between the IPM, the severity of haemophilia and the frequency of haemorrhagic accidents.

It emerges from this table that the higher the IPM, the more severe the disease and the more frequent are the annual hemorrhagic accidents. All patients with MPI greater than 0.60 had moderate (12.5%) to severe (87.5%) hemophilia with more than 10 bleeding events per year.

Table 9. *Correlation between IPM, disease severity and frequency of hemorrhagic strokes.*

Variables	IPM P	
	>0.60	<0.60
Type of hemophilia		< 0.001
Severe	7 (87.5)	0
Moderate	1 (12.5)	11 (78.6)
Lightweight	0	3 (21.4)
Bleeding acc frequency		0.005
>10 crises/year	8 (100)	0
<10 attacks/year	0	14 (100)
Total	8 (100)	14 (100)

4. Discussion

Our study set itself the general objective of determining the clinical profile and the frequency of cardiovascular risk factors in hemophiliac patients followed at the University Clinics of Kinshasa. To achieve this, we studied certain socio-demographic and anthropometric parameters; clinical and biological parameters, in particular the hemoglobin dosage, the lipogram and the plasmatic dosage of the activity of factors VIII and IX. Ultrasound analysis of the heart in tissue and Doppler mode was also performed. The cardiovascular risk factors investigated included: obesity, hypertension, hypercholesterolemia, hypertriglyceridemia, LVH and deterioration of myocardial function. Only the deterioration of myocardial function was found as a cardiovascular risk factor in hemophiliac patients. The dosage of inhibitors as well as the search for other cardiovascular risk factors (insuloresistance, microalbuminuria) were not carried out because of the limitations of material and technical resources.

4.1. Sample Size and Frequency of Hemophilia

During our study, the diagnosis of hemophilia was confirmed in 36 patients out of 155, received for hemorrhagic syndrome, which gives a frequency of 23.2%. The number of diagnosed hemophiliacs remains low. This small sample is explained by the fact that: the precise biological diagnosis of hemophilia was only introduced in the DRC recently in 2018 thanks to the partnership with the Franco-African alliance for the treatment of hemophilia (AFATH). The number of cases identified only partly reflects the epidemiological situation in

the City of Kinshasa (preliminary nature of the study).

Indeed, the number of hemophiliacs is increasing in the world, it has doubled in 12 years, from 105,494 in 2008, against 217,662 in 2020 [2]. This worldwide epidemiological growth is linked in particular to the access to precise diagnosis in several countries, made possible thanks to the humanitarian aid program of the FMH. We note for example: 156 hemophiliac patients in Cameroon, 238 in Senegal, 2282 in South Africa [2]. This is a national cohort, in countries that have a very long history with the diagnosis of haemophilia.

4.2. Sociodemographic and Clinical Characteristics of Hemophilia

Our study found that the median age of haemophilia patients was 15 years with extremes ranging from 6 months to 44 years, including 20 children (56%) and 16 adults (44%). These results are similar to those of the World Federation of Hemophilia registry, where the median age of hemophiliac patients is 20 years, with 44% children and 56% adults [2].

In our series, as in the literature [1, 11, 12], hemarthroses represent the dominant clinical symptoms (30.2%). Indeed, hemophilia remains a disease with strong articular affinity, joint bleeding remains the expressive form of the disease, whatever the region or race [1, 13]. Along with data from the literature [1, 13], the knee joint, followed by the elbow joint, was the most affected.

In our study, the most common age group at first diagnosis was 3 to 6 years (19.4%). This age group is similar to the African average where the diagnosis of hemophilia remains late. This is the case of Coulibaly et al [31] who find in their study an average age of 7 years in Senegal. As well as Maria R. et al [11], who report an average age of 5 years in Morocco. However, the average age at first diagnosis is around 8 months in the USA and 12 months in Europe [13]. The diagnosis of hemophilia therefore remains late in Africa and in countries with limited resources, for multiple reasons, among others: the problem of accessibility to the biological test and the absence of a national screening policy.

In our series, the majority of patients presented with hemophilia A (81%). These results are similar to all the studies found in the literature [1-11].

In our series, the severe, moderate and mild clinical forms represented 50%, 33% and 17% respectively. This distribution of patients according to the severity of hemophilia in our series is similar to that described by Manucci et al [10] in the United States, where severe forms represent approximately 40%, moderate forms 20%, and minor forms 40. It differs from that of Maria et al who found 23%, 47% and 30% respectively [10]. The lower frequency of mild clinical forms in our series could be explained by their lower clinical expression (few symptoms). The bias of the narrowness of our sample could also participate in this distribution of the forms of hemophilia according to their severity.

Our study showed that the annual frequency of hemorrhagic accidents increased according to the severity of the disease; about 77.8% of patients with severe hemophilia had at least 10 bleeding events per year. These results are similar to those of the World Registry of Coagulation Disorders (WCDR) and all the literature [13]. Indeed, the deeper the deficiency in coagulation factors, the more the patient is at risk of bleeding, thus darkening the functional and vital prognosis of the disease.

To treat bleeding episodes, approximately 40.9% of patients received on-demand replacement therapy. The main indications for this treatment were: hemarthroses, hematomas and exteriorized bleeding.

In our series, 27.3% of children benefited from prophylactic treatment, whereas it is close to 80% in Europe and the USA [2]. The use of this treatment is still low in countries with limited resources [12], including the DRC. Difficulties in supplying coagulation factor concentrates (CFCs) and the absence of government subsidies are the main causes of the low use of this treatment. Indeed, prophylaxis is currently the cornerstone (gold standard) of the management of hemophilia in children. It makes it possible to prevent chronic arthropathies, which are very debilitating in adulthood, and to improve the functional prognosis of the disease in the medium and long term [14, 15].

4.3. Frequency of Cardiovascular Risk Factors in Hemophiliacs

The prevalence of cardiovascular risk factors (arterial hypertension, obesity, dyslipidemia, diabetes, LVH, myocardial deterioration) in hemophiliacs remains controversial and poorly understood [6, 8]. In our study, mean systolic and diastolic arterial pressures were slightly higher (difference of 1.7mmHg for SBP and 2.7mmHg for DBP) in the control group than in the hemophiliac group, but this was not significant.

Our results are similar to those of Barnes et al. in the United Kingdom, but diverge from most studies carried out in children and young adults, which show a higher prevalence of hypertension in hemophiliacs:

1) Sharathkumar et al in the USA [16], report on a retrospective study, that the prevalence of hypertension was 57% in hemophiliacs, against 49% in the general population.
2) Rosendaal et al [17], in a study carried out in Holland, showed that the average diastolic arterial pressure (difference of 5.8 mmHg) was significantly higher in hemophiliacs and that they were 2x more often treated for hypertension than in the general population.
3) Kulkami R. et al [18], in a cohort study of moderate Canadian hemophiliacs, showed that 29% of hemophiliacs had hypertension compared to 18% in control subjects consulted for a bleeding syndrome other than hemophilia.

This high prevalence of hypertension in hemophiliacs could be due to renal failure, which seems to be higher in hemophiliacs than in the general population [18]. Apart from renal bleeding, obesity, endothelial dysfunction and acute renal obstruction secondary to treatment of bleeding with

tranexamic acid can lead to renal disease in hemophiliacs. This observation is also confirmed by Kulkami et al, who show that hospitalizations for acute or chronic kidney disease are more numerous in hemophiliacs compared to the general population and the prevalence of hypertension in hemophiliacs admitted for renal bleeding was 10% compared to 4.5% for those admitted for other reasons [18].

Obesity, one of the cardiovascular risk factors, can be a major problem in patients with hemophilia. It affects not only cardiovascular health, but also osteoarticular health [18]. In our series, the average BMI in hemophiliacs was 17.3 kg/m^2 compared to 19.5 kg/m^2 in the control group.

Our results are similar to those:

1) Rosendaal et al [17] in Holland, who report a low prevalence of overweight in hemophiliacs compared to the control group. However, the prevalence of obesity was similar in the 2 groups.
2) Wong et al [19], on a study carried out in children and adults with hemophilia, note a similar prevalence of overweight and obesity in the 2 groups.

Our results differ from those:

1) Alperstein et al [3] in Holland, who find a significantly higher prevalence of obesity in hemophiliacs compared to the control group.
2) Kulkami et al [18] in Canada reveal an average BMI in hemophiliacs of 30.2 kg/m ^{2} compared to 27.8 kg/m ^{2} in the control group.

The tendency to obesity in hemophiliacs can be explained by acute and chronic arthropathies, which limit physical activity, with a tendency to a sedentary lifestyle and therefore to overweight.

However, the tendency to thinness in hemophilia patients observed in our series could be explained by the influence of nutrition (tendency to undernourishment in developing countries) and the difference in methodology used.

Data on the prevalence of dyslipidemia in hemophiliacs are limited and controversial [17]. In our series, we found a low average HDL-C level (difference of 3.8mg/dl) and a slightly elevated average LDL-C level in hemophiliacs compared to the control group (difference of 2.2mg/dl), but this insignificantly.

These results support:

1) Zeyned et al [6], in a cross-sectional study carried out in Turkey in children with severe hemophilia, show a low level of HDL-C in hemophiliacs compared to the control group.
2) Pocoski et al [7], in a retrospective cohort study carried out in the USA, report a higher prevalence of dyslipidemia in hemophiliac patients compared to the general population.

However, these results are opposed to those of other authors in the literature, in particular;

1) Wong J. et al., in the USA [19], who found no difference in the prevalence of dyslipidemia in 1054 hemophiliacs compared to the general population.
2) Alperstein et al [3], in Holland, who report no difference in a population of hemophiliac children compared to a control group.
3) Yidiz et al [20], in Singapore, noted no difference in a population of haemophiliac children compared to a control group.

Indeed, children with severe haemophilia tend to develop dyslipidemia due to a drop in HDL-C. On the other hand, it has been reported that a low level of HDL-C, does not constitute on its own, a cardiovascular risk factor, and that the levels of other lipids and lipoproteins as well as the presence of a systemic inflammation are important., with regard to cardiovascular risks [17].

The studies published on the prevalence of diabetes in hemophiliacs show discordant results and do not make it possible to correctly estimate the importance of this cardiovascular risk factor. Nevertheless, our series showed a slightly elevated average glycaemia in hemophiliacs (difference of 5.2mg/dl), compared to the control group, but this was not significant, like most of the studies in the literature [3, 6, 18].

4.4. Left Ventricular Hypertrophy (LVH)

LHV is one of the early cardiac morphological abnormalities that can be complicated by heart failure. Its prevalence in haemophilia patients remains poorly understood, as very few studies have so far focused on this marker of cardiac damage. In our series, we did not find any cases of LVH in hemophiliacs, on the other hand 5 non-hemophilic patients (10.9%) in the control group presented with mild LVH (diastolic diameter of the interventricular septum between 1.1 to 1.3cm on echocardiography).

We did not find any correlation between this incidental discovery of LVH and other cardiovascular risk factors, including hypertension. Does hemophilia confer a protective effect against LVH? difficult to establish this assertion, given the narrowness of our sample. Our results are similar to those of Zeyned et al., in Turkey [6], who report no cases of LVH in children with severe hemophilia.

Indeed, the absence of cases of LVH in our study could be explained by the fact that our series mainly included children and young adults and that this anomaly is more common with age, i.e. in adults over 40 years old. The narrowness of our sample could also explain this hypothesis.

4.5. Deterioration of Myocardial Function

The myocardial performance index (MPI) or Tei index, assessed on cardiac ultrasound, is an overall indicator of myocardial function. Its elevation is a marker of the overall deterioration of myocardial function. The higher the IPM, the lower the left ventricular total ejection time (TETVG). Furthermore, TETVG has been shown to be recognized as a predictive marker of mortality from cardiac failure and ischemia [18].

In our series, the average IPM value was slightly increased in hemophiliacs compared to the control group (0.60 versus 0.50), but not significantly (P>0.05). However, only one haemophiliac patient (4.5%) had a pathological IPM (>0.83).

This elevation of the IPM was positively correlated with the severity of hemophilia and the annual frequency of hemorrhagic events.

In fact, this is a 25-year-old patient suffering from severe hemophilia A, with an annual frequency of hemorrhagic strokes estimated at more than 15 per year. He is on replacement therapy on demand with anti-haemophilic factor concentrates and has had chronic arthropathy of the left knee for a year, for which secondary prophylaxis has been recommended.

Our results are similar to those of most studies in the literature:

1) Zeynep et al [6], in Turkey, who find an average IPM of 0.41 in hemophiliacs, against 0.34 in the control group;
2) Staritz et al [21], in Japan, who report an IPM of 0.39 in hemophiliacs, against 0.32 in the control group.

5. Strengths and limitations of the Study

5.1. Strengths of the Study

This is the very first study carried out in the Democratic Republic of Congo, which provides a clinical and biological profile of hemophiliac patients;

1) This is the first study carried out in sub-Saharan Africa to have sought cardiovascular risk factors in patients with hemophilia;
2) It made it possible to establish the need for echographic monitoring of cardiac function in hemophiliac patients;

5.2. Study Limitations

Beyond the strengths of the study, our study nevertheless has some limitations:

1) The small size of our sample does not allow us to generalize our results at the national level and does not give enough power to the statistical tests to establish any correlations;
2) We were not able to search for other cardiovascular risk factors (microalbuminuria, insulin resistance, arterial stiffness,) for reasons of technical and material constraints.

6. Conclusion

At the end of this study, we can retain that hemophilia remains a real disease in the Democratic Republic of Congo, although underdiagnosed. Efforts must be combined with a view to early diagnosis, a guarantee of efficient management. Cardiovascular risk factors seem to be rare in Congolese hemophiliacs. Nevertheless, the overall deterioration of myocardial function, the only risk factor identified, was positively correlated with the severity of haemophilia and the frequency of haemorrhagic accidents. Hence the need for follow-up and ultrasound monitoring, in order to prevent a pejorative evolution of this cardiac anomaly.

Conflict of Interest

No conflict of interest has been declared by the authors.

Authors' Contributions

GK and JG designed, collected, interpreted, wrote and edited the manuscript. GM analyzed the data, read and corrected the article. AL, ND, JS, BM, KA and RN edited, interpreted and edited the article. EM analyzed the samples. All authors have read and approved the final version of the article.

References

[1] Schved JF. Hemophilia: physiopathology and molecular bases. Medico-surgical encyclopedia. Ed. Elsevier Masson SAS, Paris 2008: Hematology, 13-021-B10: p 1–14.

[2] Annual global survey and word bleesing disorders registry haemophilia 2020: http://shiny.wfh.org/ags/

[3] Alperstein W, Corrales F, Tamariz L, Palacio G and Davis J. Prevalence of Hypertension (HTN) and cardiovascular risk factors in a hospitalized paediatric Haemophilia population, J Pediatr Hematol. Oncol. 40 (2018) 196–199.

[4] Franchini M and Mannucci PM. Co-morbidities and quality of life in elderly persons with haemophilia. Br J Haematol 2010; 148: 522-33.

[5] Fransen van de Putte DE, Fischer K and Pulles AE. Non-fatal cardiovascular disease, malignancies, and other co-morbidity in adult haemophilia patients. Thromb Res 2012; 130: 157–62.

[6] Zeynep C, Pelin K, and Birsen U. Myocardial functions, blood pressure changes, and arterial stiffness in children with severe haemophilia A. Original article journal homepage: www.elsevier.com/locate/thromresl.

[7] Pocoski J., A. Ma, CM Kessler, S. Boklage and TJ Humphries. Cardiovascular comorbidities are increased in US patients with haemophilia A: a retrospective database analysis, Haemophilia 20 (2014) 472–478, https://doi.org/10.1111/hae.12339.

[8] Ragni MV and Moore CG. Atherosclerotic heart disease: prevalence and risk factors in hospitalized men with haemophilia A. Haemophilia 2011; 17: 867–71.

[9] Limjoco J, CD Thornburg, Risk factors for cardiovascular disease in children and young adults with haemophilia, Haemophilia 24 (2018) 747–754, https://doi.org/10.1111/hae.13585.

[10] Mannucci PM and Mauser-Bunschoten EP. Cardiovascular disease in haemophilia patients: a contemporary issue. Haemophilia 2010; 16 Suppl 3: 58–66.

[11] Maria R. Hemophilia in Morocco. Current status and prospects. Thesis for obtaining the doctorate in Medicine 2012; pg 2–44.

[12] Madouni S and Madani K. Management of hemophilia, Memory of the internship, faculty of Medicine, Abou Beckr University of Algeria, 2013; pg 8–12.

[13] World bleeding disorders registry 2019 data report: http://wbdr.wfh.org/ags/

[14] Schved JF. Hemophilia treatments. Medical and Surgical Encyclopedia. Ed. Elsevier Masson SAS, Paris 2008: Hematology, 13-021-B20: p 1–11.

[15] Chambost A and Meunier S. Challenges of early pediatric management of severe hemophilia. Archives of Pediatrics. 2006; 13: 1423-30.

[16] Sharathkumar A, Soucie J, Trawinski B, Greist A, Shapiro A et al. Prevalence and risk factors of cardiovascular disease (CVD) events among patients with haemophilia: experience of a single haemophilia treatment center in the United States (US). Haemophilia 2011; 17: 597–604.

[17] Rosendaal FR, Smit C, Varekamp I, Bröcker-Vriends AH, Van Dijck H, Suurmeijer TP, et al. Modern haemophilia treatment: medical improvements and quality of life. J Intern Med 1990; 228: 633-640.

[18] Kulkarni R, Soucie JM and Evatt BL, Hemophilia Surveillance System Project Investigators. Prevalence and risk factors for heart illness among males with haemophilia. Am J Hematol 2005; 79: 36–42.

[19] Wong M, Macgregor D, Stuckless S, Barrett B, Kawaja M and Scully MF. Health-related quality of life in a cohort of adult patients with mild hemophilia A. J Thromb Haemost 2008; 6: 755–761.

[20] Yidiz R, Miesbach W, Alesci S, Krekeler S, and Seifried E. Comorbidities and bleeding pattern in elderly haemophilia A patients. Haemophilia 2009; 15: 894–9.

[21] Staritz P, de Moerloose P, Schutgens R and Dolan G. Applicability of the European Society of Cardiology guidelines on management of acute coronary syndromes to people with haemophilia- an assessment by the ADVANCE Working Group. Haemophilia 2013; 833–40.