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Health status and clinical characteristics of patients with haemophilia in the Kyrgyz Republic

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Abstract. Haemophilia is an X-linked inherited bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) in haemophilia A or factor IX (FIX) in haemophilia B. This study aimed to examine the demographic profile, health status and clinical characteristics of patients with haemophilia A and B in the Kyrgyz Republic. A total of 81 patients with haemophilia were enrolled, including 70 with haemophilia A and 11 with haemophilia B. Data collected comprised age, educational level, FVIII/FIX activity levels, the presence of anti-FVIII/FIX inhibitors, treatment regimen, viral infections and annual bleeding rate. In addition, the translated and validated version of the Haemophilia Quality of Life Questionnaire for Adults (Haem-QoL-A) and the Haemophilia Joint Health Score (HJHS) were used. Factor VIII inhibitors were identified in four patients, while one patient had factor IX inhibitors. No patient in the study cohort received prophylactic therapy; however, inadequate on-demand treatment was reported. With regard to viral infections, nine patients (11.1%) were found to have transfusion-transmitted

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viruses. The median annual bleeding rate was 23 bleeding episodes per year (range 2-49). The mean Haem-QoL-A score was 54.26 ± 18.73. The average total haemophilia joint health score for adult patients with haemophilia A/haemophilia B was 39.2 ± 18.7 ($p < 0.05$). There are significant problems for adult patients with haemophilia in the Kyrgyz Republic, such as insufficient treatment and the lack of prophylaxis. To solve these problems, it is necessary to develop a strategy for improving the health care system, training health care professionals and providing sustainable funding

Keywords: haemophilia; coagulation factors VIII and IX; health status; clinical characteristics

Introduction

Haemophilia is an X-linked inherited bleeding disorder caused by a deficiency of coagulation factor VIII (FVIII) in haemophilia A or factor IX (FIX) in haemophilia B. This deficiency results from mutations in the corresponding genes encoding these coagulation factors [1]. This disorder is inherited in an X-linked recessive manner, meaning that it almost exclusively affects males, who possess only one X chromosome (inherited from their mother). If the mother is an asymptomatic carrier, there is a 50% chance that she will pass on the affected gene to her son. Females need to inherit two defective alleles (one from each parent) to develop the disease because the disorder is an X-linked recessive pattern of inheritance. Thus, clinical symptoms predominantly occur in males, while females who are carriers of the mutated gene are generally asymptomatic. However, it is worth noting that about 80% of affected females have de novo mutations, and in about 30% of cases with haemophilia, there is no family history [1,2].

Typical sites of severe bleeding in haemophilia patients include joints (haemarthrosis) and muscles, especially deep muscle groups like the iliopsoas muscle, calf and forearm. Recurrent joint haemorrhages can cause chronic arthropathy and, in the advanced stage, loss of joint mobility [2]. Replacement therapy involves the intravenous infusion of coagulation factor concentrates (CFCs) VIII and IX, either on demand to treat acute bleeding episodes or according to prophylactic regimens to prevent bleeding [3]. A worldwide survey of factor VIII use showed that replacement therapy has significantly reduced morbidity and mortality in individuals with haemophilia A in high-income countries [4,5]. The use of factor replacement therapy is also increasing in developing countries. However, in the Kyrgyz Republic, due to the low awareness of haemophilia and the high cost of the treatment, affected individuals do not receive adequate care. Insufficient treatment leads to severe complications such as chronic pain, joint deformity, arthropathy, disability, and even death in childhood or early adulthood [6].

Patients' income level within a country also influences the availability of treatment and the outcome. In some low- and lower-middle-income countries with inadequate health care resources, some patients with haemophilia die from bleeding without receiving any replacement therapy, and the majority of survivors have joint deformity and other sequelae [7]. Therefore, the evaluation of clinical data is important for the recognition of problems and the initiation of early intervention. This approach may decrease the occurrence of haemophilic arthropathy, enhance the quality of life of patients and create a basis for further targeted intervention. This study aimed to investigate the demographic characteristics, health status, and clinical data of patients with haemophilia A and B in the Kyrgyz Republic.

Materials and Methods

This descriptive study was conducted among 81 patients with haemophilia registered in the National Centre for Oncology and Haematology of the Ministry of Health of the Kyrgyz Republic. The severity of haemophilia according to international classification was based on activity levels of coagulation factors: mild (0.05-0.40 IU/dL), moderate (0.01-0.05 IU/dL) or severe (<0.01 IU/dL) [8]. Patients' characteristics including sex, age, education level (in the Kyrgyz national education system, there are three main levels: primary, secondary, and higher education) and marital status, clinical manifestations, family history, type of haemophilia, severity of the disease, presence of haemophilic arthropathy (chronic pain, reduction of joint mobility, muscle weakness, and loss of function), viral infections, and presence of factor VIII/factor IX inhibitors were documented. In addition, information was gathered on bleeding episodes and replacement therapy, including on-demand treatment, inadequate treatment (defined as the use of coagulation factor replacement only in cases of severe bleeding, such as intracranial or gastrointestinal haemorrhage, or when bleeding causes intolerable pain), and low-dose prophylaxis (10-15 IU/kg, once or twice weekly).

Laboratory diagnostics and analyses. Factor VIII:C and IX:C levels were measured using one-stage clotting assays (Coagpia® APTT-N; Sysmex Co.). Anti-factor VIII/IX inhibitors were detected and quantified using the Bethesda assay. A positive inhibitor titre was defined as >0.6 Bethesda units (BU)/mL, and titres ≥5 BU were considered high. Detection of blood-borne viruses. Testing for hepatitis B surface antigen (HBsAg), antibodies to hepatitis C virus (anti-HCV) and HIV antigen/antibodies was performed using ELISA. In cases of a positive anti-HIV screening result, confirmation was undertaken by referral of blood samples to the Republican AIDS Centre of the Ministry of Health of

the Kyrgyz Republic for Western blot analysis; however, no confirmed positive results were recorded among the patients.

The annual bleeding rate (ABR) was calculated retrospectively from the medical records of each patient. The outcome measure was the validated translation of the Haemophilia Quality of Life Questionnaire for Adults (Haem-QoL-A) [9]. This consists of 41 items divided into 4 domains: physical health, emotions and feelings, work and studies, and treatment. Missing values were coded as 0 and not used in the calculation of the scores. In the total and domain scores, raw scores were converted into a 0 to 100 scale, with 0 representing the best and 100 the worst quality of life. Joint health status was measured using version 2.1 of the Haemophilia Joint Health Score (HJHS), a standardised tool developed by the World Federation of Haemophilia (WFH) to evaluate joint damage and functional impairment in patients with haemophilia, including chronic arthropathy. This instrument assesses pain, swelling, range of motion and muscle strength, as well as radiographic changes, and thus allows the monitoring of disease progression and effectiveness of treatment. The scale includes 6 joint-specific domains (0 to 20 each) and a global gait score (0 to 4), with a total possible score ranging from 0 to 124. The higher the HJHS score, the poorer the joint status.

Data analysis was carried out by using SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA). Results were expressed as frequencies and percentages for categorical variables. Continuous variables are expressed as medians (25^{th} to 75^{th} percentiles) or means ± standard deviation (SD), depending on the situation. Factor consumption was compared using a paired t-test, assuming a normal distribution of the data. The level of significance was set at $p < 0.05$. The strength of association between HJHS and Haem-QoL-A scores was assessed using Pearson's correlation coefficient. Ethical approval was obtained from the Bioethics Committee of I.K. Akhunbaev Kyrgyz State Medical Academy (Protocol No. 31, 10 September 2024).

Results

A total of 81 patients participated in this study: 70 with haemophilia A (Group 1) and 11 with haemophilia B (Group 2). The socio-demographic characteristics, health status, and clinical data of the study population are shown in Table 1. Stratified analysis according to disease severity showed that 41 (58.6%) patients in Group 1 and 6 (54.5%) patients in Group 2 had severe haemophilia. Twenty (28.6%) and 4 (36.4%) patients had moderate disease severity, whereas 9 (12.8%) and 1 (10%) patients in groups 1 and 2 had mild haemophilia, respectively.

Table 1. Clinical characteristics of patients with haemophilia

Variables	Haemophilia A, n (%) 70 (86.4%)	Haemophilia B, n (%) 11 (13.6%)	P
Severity ■ severe (<1%) ■ moderate (1-5%) ■ mild (>5%)	 41 (58.6%) 20 (28.6%) 9 (12.8%)	 6 (54.5%) 4 (36.4%) 1 (10.0%)	 =0.325 <0.004 <0.004
Viral infection	7 (10.0%)	2 (18.2%)	<0.002
Joint arthropathy	53 (75.7%)	9 (81.8%)	=0.273
Family history ■ present ■ absent ■ unknown	 42 (60.0%) 25 (35.7%) 3 (4.3%)	 7 (63.6%) 4 (36.4%) 0	 =0.174 =0.318 <0.001
Inhibitor ■ low titre ■ high titre	4 (5.7%) 3 (4.3%) 1 (1.4%)	1 (9.1%) 0 1 (9.1%)	<0.002 <0.002 <0.001
Education ■ primary ■ secondary ■ higher	 33 (47.1%) 27 (38.6%) 10 (14.3%)	 2 (18.2%) 6 (54.5%) 3 (27.3%)	 <0.002 <0.002 <0.004
Married	46 (65.7%)	8 (72.7%)	=0.295
Unmarried	24 (34.3%)	3 (27.3%)	<0.004

Note: * – $p < 0.05$ indicates a statistically significant difference between groups
Source: compiled by the authors

Infection by virus was detected in 7 (10%) and 2 (18.2%; $p < 0.05$) patients in Group 1 and Group 2, respectively. Joint arthropathy was more frequent in patients with haemophilia B, although not significant. No difference was found between the groups regarding family history and marriage status. Inhibitor form of haemophilia was detected in four patients in Group 1 (5.7%; $p < 0.05$), which was significantly higher than

in Group 2, with an inhibitor detected in one patient (9.1%). As for the educational level, in Group 1, 33 (47.1%) patients had primary education, 27 (38.6%) had secondary education, and 10 (14.3%) had higher education. In Group 2, two (18.2%) patients had primary education, six (54.6%) had secondary education, and three (27.3%) had higher education. Thus, Group 2 had significantly fewer patients with primary education and more with secondary and higher education ($p < 0.05$).

Of the total cohort, 24 patients with haemophilia A and all 11 patients with haemophilia B were tested for HBsAg, anti-HCV and anti-HIV antibodies. In Group 1, positive results for HBsAg were detected in 4.7% (n = 1), anti-HCV antibodies in 37.5% (n = 9), and no patients tested positive for anti-HIV antibodies. In Group 2 (haemophilia B), HBsAg was detected in one patient (9.1%), antiHCV antibodies in 18.2% (n = 2), and anti-HIV antibodies were not found in any of the patients in this group (Table 2).

Table 2. Comparison of viral detection results across age groups

Type of haemophilia/ infection	HBsAg (+) n (%)	Anti-HCV (+) n (%)	HIVAg/Ab (+) n (%)	Total
Haemophilia A, n = 24	1 (4.7%)	9 (37.5%)	0	10 (41.7%)
Haemophilia B, n = 11	1 (9.1%)	2 (18.2%)	0	3 (27.3%)
p value	<0.002	<0.002		<0.002

Note: * – $p < 0.05$ indicates a statistically significant difference between groups
Source: compiled by the authors

Bleeding and quality of life. In the study cohort, joint arthropathy was detected in 77.8% of haemophilia A and B (63 of 81) according to the joint examination. Among patients with haemophilia A, joint arthropathy was detected in 82.9% (61 of 70), and among patients with haemophilia B, in 72.7% (8 of 11). Before the introduction of specific measures, all patients with haemophilia were treated on demand, and only in cases of severe bleeding were intravenous plasma products administered. The median number of annual bleeding episodes was 23 (range 2-49). In total, 67 adult patients filled in the Haem-QoL-A questionnaire, 13 of whom were excluded from the analysis because of incomplete answers. The joints of 43 patients were scored, whereas 24 patients could not be scored because of severe arthropathy. The mean HJHS scores in the different age groups of adults (18-24, 25-34, and ≥35 years) were 33.27 ± 17.39, 47.62 ± 18.15, and 54.26 ± 18.73, respectively. The mean HJHS score was significantly lower in the youngest group. In 40 patients, the Pearson's correlation coefficient between the HJHS score (mean 39.24 ± 19.31) and the Haem-QoL-A score (mean 54.26 ± 18.73) was calculated and found a weak positive correlation ($r = 0.262$, $p = 0.006$, <0.05).

Discussion

It is estimated that there are more than 400 children and adults with haemophilia in Kyrgyzstan, but many of them remain unregistered and undiagnosed because of the low level of awareness about the disease and financial problems. Despite some progress in the treatment of haemophilia, the majority of patients with haemophilia still have problems with diagnosis and treatment throughout the world. Thus, the current study aimed to attract more attention from government agencies, insurance funds and social services to improve care for patients with haemophilia and their families.

In this study, severe haemophilia was found in 58% of patients, and the moderate form of the disease was found in 29.6% of patients. Unlike the study results by V. Payal *et al.* [10] and E. Berntorp *et al.* [11], a smaller proportion of patients with severe haemophilia was found. This may be due to the fact that bleeding episodes in patients with moderate and severe haemophilia occur more often and are more easily identified. The most frequent haemorrhagic manifestations in them were recurrent haemarthroses, especially in the elbows, knees, and ankles, which led to progressive joint destruction, irreversible disabling arthropathy and chronic pain [12,13].

A positive family history of haemophilia was found in 60.5% of the patients, in line with other reports that about 30% of newly diagnosed cases of haemophilia have no family history because they are the result of de novo mutations [10,11]. In terms of education, most of the patients had only a primary education (43.2%), while 40.7% had an incomplete secondary education. The educational status of patients with haemophilia was found to be similar in Bangladesh, where educational attainment is also limited by poverty and illness [14]. Therefore, in this study, only 16% of the patients were able to complete higher education. A national registry of haemophilia has been maintained in the United Kingdom since 1968, with approximately 5,000 people registered with haemophilia A. The prevalence of haemophilia B is thought to be about one-fifth that of haemophilia A [11]. In the current study, 86.4% of the patients had haemophilia A and 13.3% had haemophilia B. This is comparable to the general distribution of coagulation disorders, of which haemophilia A is the most frequent (72.3%), followed by haemophilia B (11.5%) [14]. Therefore, it is likely that haemophilia B occurs less frequently and consequently fewer patients with this condition require hospital-based treatment.

In the Kyrgyz Republic, recombinant or highly purified plasma-derived coagulation factor concentrates are not available for prophylaxis for many patients with haemophilia because they are too expensive. The mainstay of treatment for these patients in the past, and at present, is the transfusion of fresh frozen plasma (FFP) and cryoprecipitate. Both methods carry a high risk of transfusion-transmitted infections. Positive HBsAg was found in 4.7% of the patients. The low prevalence of hepatitis B among these patients could be explained by mandatory HBsAg screening of blood donors and the introduction of a national hepatitis B vaccination programme. Hepatitis C virus (HCV) infection is another major cause of mortality in patients with haemophilia [15,16]. The most important route of transmission is through the administration of pooled coagulation factor concentrates, cryoprecipitate or fresh frozen plasma [17]. In the presented study, the prevalence of HCV positivity was relatively high at 37.5%. Importantly, all the patients with viral infections were more than 18 years old, because the screening of blood from healthy donors for antibodies to the HCV virus has been part of routine screening since 1993, and so, most of the patients with a positive HCV antibody were excluded. Concerning HIV, no cases were positive in both groups; this can be explained mainly by the history of blood transfusions. It is, therefore, important to consider the prevention of viral infection and improvement in blood quality as these are directly related to the prognosis and quality of life in patients with haemophilia.

Inhibitors are a major complication of replacement therapy in haemophilia A and B. The major complication is the development of alloantibodies (inhibitors) that inactivate FVIII activity in about 30% of the patients. The management of inhibitors may involve the use of very expensive bypassing agents or immune tolerance induction that may seriously affect the quality of life of the patients and complicate the treatment [18]. In this study, not all patients with a positive inhibitor test received immunotherapy, and some of the patients may have had transient inhibitors. However, the statistical analysis showed that the percentage of inhibitors in the 70 patients with haemophilia A was only 2.9%, which is much lower than the frequency reported in literature for haemophilia A (2%-30%) [19]. Several reasons could be responsible for the low frequency of inhibitors; these include the infrequent infusion of coagulation factor, late detection of inhibitors and/or late start of factor therapy. In this study, the frequency of inhibitors in patients with haemophilia B was 9.1%. According to P. Giangrande *et al.* [20], the frequency of inhibitor development in haemophilia B is much lower than that in haemophilia A and ranges between 1% and 6%. The results in this study generally agree with this observation, and this could be due to the small number of patients with haemophilia B in the study.

The 2020 World Federation of Hemophilia (WFH) Guidelines for the Management of Hemophilia (3rd edition) definitely say that prophylaxis decreases the risk of breakthrough bleeding and, hence, stress that access to additional doses for early treatment is necessary [8]. Only 10% of the world's population with haemophilia, mainly in upper-middle income countries, have some, although still not enough, access to care [21], and the remaining 15% living in high-income countries have access to state-of-the-art treatments and treatment protocols [22]. However, it is known that an estimated 75% of people with haemophilia worldwide, mostly in low- and lower-middle-income countries, have little or no access to therapy [23]. The current situation is still typical for patients with haemophilia in the Kyrgyz Republic. The development of joint arthropathy in these patients is associated mainly with on-demand treatment or the absence of prophylaxis due to financial difficulties or lack of medications. As a result, patients develop arthropathy of varying degrees, which sometimes leads to disability. Among all registered patients with haemophilia in Kyrgyzstan, it is estimated that only 15% of patients under 18 years of age and older receive prophylaxis. Prophylactic treatment in children has significantly improved. Therefore, the promotion of prophylactic therapy is important for improving joint protection and the overall quality of life in these patients.

In the current study, the mean total HJHS score was 40.1 ± 20.0 ($p < 0.05$). In the study of 29 adult patients with moderate haemophilia in 11 centres in England, Scotland and Wales, the mean total HJHS score was 10.8 ± 5.2 [24]. Their results were better than in the presented study. Also, a positive correlation was found between HJHS and Haem-QoL-A scores ($r = 0.273$, $p = 0.008 < 0.05$), which indicates that the higher the HJHS score, the lower the quality of life. Although in recent years, significant successes have been achieved, and the outcomes of treatment have improved, patients with haemophilia still suffer from joint dysfunction, acute and chronic pain, and mental health problems, which adversely affect health-related quality of life [25]. Consequently, the role of prophylactic therapy in the preservation of joints in patients with haemophilia is undeniable.

In the Kyrgyz Republic, for haemophilia patients, FVIII/FIX are procured at the rate of 13 million IU per year within the framework of the republican budget. In addition, the World Federation of Hemophilia (WFH) provides humanitarian aid at a rate of 6 million IU per year. Thus, the total amount of FVIII/FIX is 19 million IU, which is 2.8 IU per capita and is only enough for treatment for 8 to 10 months of the year without prophylaxis. For adults with haemophilia, there is no prophylaxis, since the National List of Reimbursed Medicines does not finance prophylaxis for adults; for children with haemophilia, prophylaxis has recently been introduced and may be discontinued when they reach the age of majority. In connection with the shortage of

coagulation factors in recent years, 18 (14.2%) patients underwent joint surgery and were enrolled in a multicentre, prospective, open-label clinical study of the first modern plasma-derived FVIII of Russian production, Etoplasm. Etoplasm was effective both for prophylaxis and treatment of bleeding episodes, as well as for surgical interventions, including major ones. A good safety profile of the drug was noted; no development of inhibitors, allergic reactions, thrombotic events, or thromboembolic complications was registered [26].

Conclusions

Adult haemophilia patients in the Kyrgyz Republic have significant problems (inadequate treatment and absence of prophylaxis). These patients do not receive proper care because of insufficient awareness of the disease and inadequate health insurance programmes. This study demonstrates the significant unmet needs and challenges of patients with haemophilia. To overcome these problems, a wide range of activities is needed, from improving the material and technical base of healthcare institutions to increasing the number of medical workers and organising systematic public funding. The increase in accessibility of affordable prophylactic products through public funding is of particular importance.

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Conflict of Interest

The authors declare no conflicts of interest.

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