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RESEARCH ARTICLE

EVALUATION OF SOCIO-DEMOGRAPHIC FACTORS AND COMORBIDITIES IN ADULT HEMOPHILIA PATIENTS

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ABSTRACT

Purpose: The association between socio-demographic factors and hemophilia status with the prevalence of comorbidities was evaluated.
Material and Methods: Patients with hemophilia A (n=111) and B (n=24) who completed the questionnaire form about their socio-demographic factors were included in our study. Factor and inhibitor levels, comorbidities, factor replacement therapies, hemophilic arthropathy, viral status and annual bleeding episodes were recorded.
Results: The median age was 39 years among 135 hemophilia patients, and 63.1% of all patients had severe hemophilia, which was significantly higher among hemophilia A (p=0.002). Most patients (74.8%) were treated with prophylactic factor replacement therapy. The inhibitor status was positive in 8.9% of all patients. The unemployment rate was found to be 33.3%. Annual bleeding episodes were higher in workers. Most patients (60%) had graduated from at least high school. Patients with severe hemophilia were significantly less educated than those with moderate to mild hemophilia (p=0.045). The prevalence of cardiovascular disease, hypertension, diabetes mellitus, and obesity was 6.7%; 17.8%, 13.3%, and 11.9% respectively. Although there was no association between obesity and annual bleeding episodes, right ankle was the most affected joint in overweight/obese patients.
Conclusion: Age-related comorbidities and the relationship between hemophilia status and social life need further investigation.

Key words: Hemophilia, comorbidity, socio-demographic, adult

INTRODUCTION

Hemophilia A and B are characterized by deficiency or complete absence of factor VIII and IX, respectively. Spontaneous bleeding episodes and/or prolonged bleeding after trauma or surgery are the main clinical manifestations of these conditions (1). Acute and chronic joint pain due to regular bleeding in joints along with progressive musculoskeletal damage, contribute to hemophilic morbidity and impair daily activities. Insufficient management of bleeding episodes increases the risk of hemophilia-

related morbidities and decreases the quality of life in patients with hemophilia (PWH) (2). Besides the negative effects on daily functioning, clinical signs and symptoms may also impact mental and social health (3). The quality of life and life expectancy of PWH significantly improved with the development and availability of clotting factor concentrates after the 1970s (4). However, during the 1980s, PWH struggled with bloodborne infections such as human immunodeficiency virus (HIV) and the hepatitis B and C viruses (HBV, HCV)) due to contaminated plasma-derived concentrates., The introduction of home treatment and prophylaxis in the 1990s allowed the long-term survival with minimal bleeding episodes (5). PWH are now living longer due to favorable factor replacement therapies, antiviral treatments, and comprehensive hemophilia care centers (6,7). Aging with hemophilia presents additional challenges beyond bleeding, such as hemophilia-related conditions (e.g., chronic arthropathy and viral infections) and aging-related comorbidities (e.g., cardiovascular diseases, cancer, osteoporosis, renal diseases, and dementia) (5,7,8).

Despite the availability of comprehensive care, the decrease in quality of life due to hemophilia and age-related comorbidities affects socio-demographic factors such as education, social, and working life in PWH. The disparity in socio-economic engagement between individuals with hemophilia and the general population has not been extensively investigated. In this study, we aim to evaluate the association between socio-demographic factors and hemophilia status. There is limited data on comorbidities of PWH due to the restricted availability of high-quality national registries worldwide. Therefore, we aim to define the prevalence of comorbidities in the associated study group.

MATERIAL AND METHODS

Study Design

135 cases (111 with hemophilia A and 24 with hemophilia B), all aged over 18, who were admitted to Ege University Adults Hemophilia and Thrombosis Center, a European Hemophilia Comprehensive Care Centre (EHCCC) certified facility, between 10 August 2016 and 30 December 2016, were included in the study. Data were collected retrospectively through an initial patient interview and a 1-year follow-up. Only patients who completed the questionnaire during the initial interview were included in the study. This questionnaire gathered data on patients' socio-demographic characteristics, including age, race, marital status (single, married, divorced/separated), education level (none, ≤ 5 years (primary school), ≤ 8 years (middle school), ≤ 12 years (high school), >12 years (university)), income, employment status divided into; full-time, part time, unemployed, student)), and insurance status (any public, private or none). Additionally, the questionnaire inquired about patients' comorbidities and joint health status over the past year. Comorbid conditions assessed included the cardiovascular disease, hypertension, diabetes mellitus, kidney disease, cancer, neurologic disorders, liver disease/hepatitis B and C, arthritis, and human immunodeficiency virus infection/acquired immunodeficiency syndrome (HIV/AIDS). Clinical chart reviews provided data on hemophilia type, severity (classified as severe (<0.01 IU/ml FVIII or FIX), moderate (0.01–0.05 IU/ml FVIII or FIX) or mild (0.05–0.40 IU/ml FVIII or FIX) hemophilia), treatment strategy (prophylaxis or on demand), inhibitor status, history of immune tolerance, hepatitis A, B, and C antibody status. Additionally, height and weight measurements were taken to calculate body mass index (BMI).

Statistical Analysis

Statistical data analysis was conducted using SPSS version 16.0 (2007, SPSS for Windows, SPSS Inc., Chicago, IL, USA). An exploratory analysis was performed to describe the study population. Categorical variables were summarized using frequency tables, while continuous variables were expressed using measures of central tendency and dispersion, such as mean ± standard deviation (SD) and median (range). Qualitative or categorical variables were described as and proportions. The chi-square test and Fisher's exact test were used to determine association between categorical variables. For quantitative data, the independent samples t-test and Mann–Whitney U test were used to analyze data with normal and skewed distributions, respectively. A p-value of < 0.05 was considered statistically significant.

Ethical Considerations

During the planning of the study, necessary permissions were obtained from Ege University Department of Hematology, where the study was conducted. The study was approved by the Ege University Clinical Research Ethics Committee (Date: 09.08.2016, Decision No: 16-7/1). Written and verbal

consent was obtained from all individuals included in the study.

RESULTS

Patients' clinical characteristics

A total of 135 patients who completed the questionnaire were included in the study. The median age was 39 years (range, 19-68). Among these, 111 patients (82.2%) had hemophilia A, and 24 patients (17.8%) had hemophilia B. The clinical and socio-demographic characteristics of patients are summarized in Table 1. A majority of the patients (n= 85, 63.1%) had severe hemophilia (plasma factor levels <1%), while those with moderate and mild hemophilia accounted for 17.7% (n=24) and 19.2 % (n=26), respectively. Among patients with hemophilia A, 71% (78/111) had severe hemophilia, compared to 29% (7/24) of patients with hemophilia B who had severe disease. Patients with mild disease were significantly more prevalent in hemophilia B than in hemophilia A (58% vs 9%, respectively; p=0.0001). Additionally, all but two of the patients with severe hemophilia (n=85) had at least one affected joint and 31.8% of them had three and more affected joints. In our cohort, 84.4% of patients had at least one joint with hemophilic arthropathy.

Prophylaxis treatment was reported by 101 (74.8%) patients and it was more commonly preferred in patients with hemophilia A than B, and in those with severe hemophilia compared to those with moderate or mild forms hemophilia patients (p=0,002 and p=0,0001, respectively). Ninety-six percent of patients on prophylaxis had at least one joint deterioration, while 52.9% of patients on on-demand treatment had at least one joint deterioration (p=0,001). The occurrence of spontaneous bleeding

Table 1. Characteristics of Patients

Variables, *N* (%)	**Total** N=135	**Hemophilia A** N= 111 (82.2)	**Hemophilia B** N= 24 (17.8)
Age in years, median (range)	39 (18-68)	40 (19-68)	38 (18-61)
Disease severity			
Severe	85 (63.1)	78 (71)	7 (24)
Moderate	24 (17.7)	23 (20)	3 (18)
Mild	26 (19.2)	10 (9)	14 (58)
Factor VIII treatment, n (%)			
Prophylactic treatment	101 (74.8)	89 (80.2)	12 (50)
On-demand treatment	34 (25.2)	22 (19.8)	12 (50)
Presence of inhibitor, n (%)			
Yes	12 (8.9)	10 (9)	2 (8.3)
No	118 (87.4)	96 (86.5)	22 (91.7)
Marital status, n (%)			
Single	43 (31.9)	32 (28.8)	11 (45.8)
Married	87 (64.4)	74 (66.7)	13 (54.2)
Divorced/separated	5 (3.7)	5 (4.5)	None
Current Occupation			
Full-time	43 (31.9)	37 (33.3)	6 (25)
Part-time	39 (28.9)	32 (28.8)	7 (29.2)
Unemployed	45 (33.3)	36 (32.4)	9 (37.5)
Student	8 (5.9)	6 (5.4)	2 (8.3)
Insurance type, n			
Any public	135	111	24
Private	3 (2.2)	2 (1.8)	1 (4.1)
No insurance	None	None	None
Education level			
No education	2 (1.5)	1 (0.9)	1 (4.2)
≤ 5 years (primary school)	39 (21.5)	27 (24.3)	2 (8.3)
≤ 8 years (middle school)	23 (17)	19 (16.7)	4 (16.7)
≤ 12 years (high school)	39 (28.9)	29 (26.1)	10 (41.7)
>12 years (university)	42 (31.1)	35 (31.5)	7 (29.2)

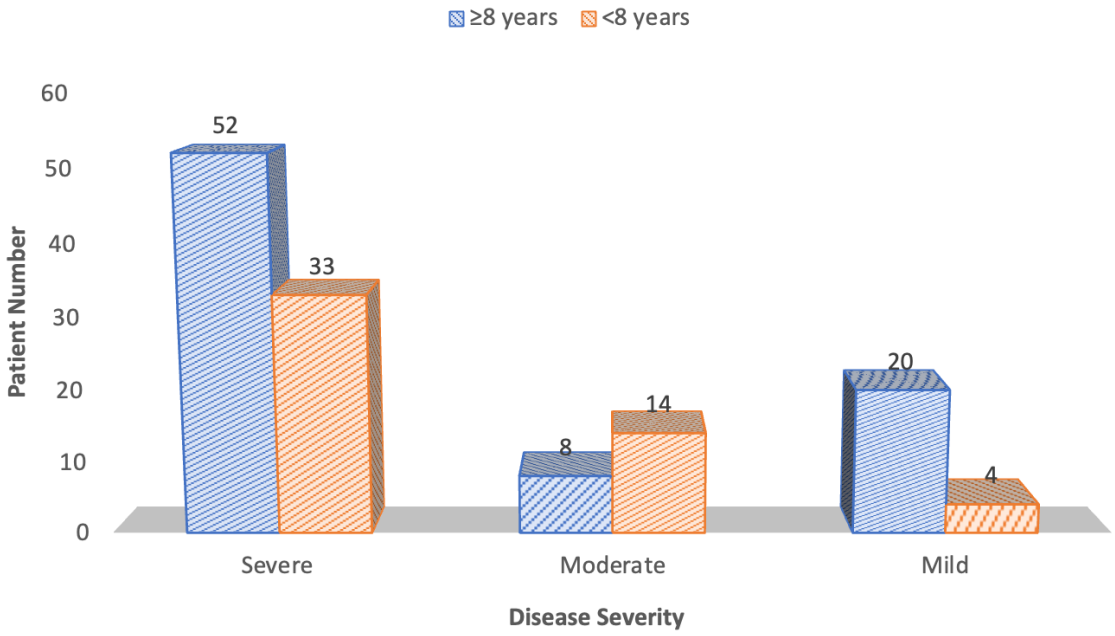

Figure 1. Association of Education Status and Hemophilia Disease Severity. Severe hemophilia patients were significantly less educated than moderate and mild hemophilia patients (p=0.045).

episodes in the previous year did not differ between patients treated with prophylaxis and those on on-demand therapy. However, bleeding episodes after trauma were significantly higher in patients on prophylaxis therapy (p=0,008). Inhibitor positivity was detected in 12 (8,9%) patients, 10 of whom had hemophilia A. Although 9 of the 12 inhibitor-positive patients had severe hemophilia, there was no association between inhibitor status and the type or severity of hemophilia.

Socio-demographic Characteristics

The marital status distribution among the patients was as follows: 64.4% (87) were married, 30.4% (41) were single, and 5.1% (7) were divorced (Table 1). There was no correlation between marital status and disease severity, hemophilia type, treatment modality, or annual bleeding episodes. All patients had public insurance. Of the participants, 5.9% (8) were students, and 60.2% (82) had a full-time or part-time job; however, 33.3% (45) were unemployed. Patients who were employed in any capacity experienced higher numbers of annual bleeding episodes and more affected joints compared to those who were unemployed (p=0.04). While only two patients were illiterate, 60% of the patients had graduated from high school and university (28.9% and 31.1%, respectively). There was no association between educational status and disease morbidity or bleeding episodes, but education status was correlated with hemophilia severity (p=0.045, data shown in Figure 1).

Comorbidities

The frequencies of comorbidities among all patients are summarized in Table 2. The mean BMI was 25,74 ±4,2 kg/m2. Among the patients, 5 had a BMI below 18.5; of these, 2 (40%) had severe disease, while the remaining 3 had mild to moderate disease. The distribution of patients within the BMI ranges of 18.5-24.9, 25-29.9, and ≥ 30 were 57, 57, and 16, respectively. There was no significant correlation between disease severity and BMI, with more than half of the patients in each BMI group having severe disease: 59% (34/57) in the 18.5-24.9 range, 66% (38/57) in the 25-29.9 range, and 68% (11/16) in the ≥30 range. Furthermore, no significant relationship was found between BMI and the number of affected joints or annual bleeding episodes. However, the frequency of affected joints varied with BMI; the right ankle was more commonly affected in patients with a BMI ≥ 25 compared to those with a BMI < 25 (p = 0.015). Hypertension was present in 17.8% (24) of the patients, all of whom were on medication, with prevalence of 17.1% (19/111) in hemophilia A and 20% (5/24) in hemophilia B. No significant correlations were found between hypertension and clinical characteristics such as disease type, severity,

Table 2. Comorbidities of Patients

	n (%)
HBV	3 (2.2)
HCV	13 (9.6)
HIV/AIDS	0
Liver Disease	2 (1.4)
Hypertension	24 (17.8)
Diabetes mellitus	18 (13.3)
Obesity [a]	16 (11.9)
Hypercholesterolemia/hyperlipidemia	8 (5.9)
Cardiovascular disease	9 (6.7)
Neurological Disease (stroke, epilepsy)	3 (2.2)
Cancer	4 (2.9)
Rheumatologic Disease	2 (1.4)
Endocrinological disease	4 (2.9)
Kidney disease	4 (2.9)

[a] Obese were calculated based on initial clinician form of height and weight; overweight is defined as BMI (=weight (kg)/height^2 (m)) ≥25 and <30; obese is defined as BMI ≥30.

inhibitor status, or bleeding episodes. Diabetes mellitus (DM) was diagnosed in 13.3% (18) of the patients, with higher annual bleeding episodes observed in patients with DM compared to those without (p=0.024). Of the patients, 61.5% (83) were smokers. Cardiovascular disease was reported in 6.7% (9) of patients; two had a history of myocardial infarction and one had undergone bypass surgery. There was no correlation between cardiovascular disease and disease type, severity, or annual bleeding episodes. Cancer history was noted in four patients, including diagnoses of acute leukemia, bone tumor, gastric cancer, and hepatocellular carcinoma. Kidney disease was observed in four patients over 40 years old, including one with membranous glomerulonephritis and three with kidney stones.

Hepatitis B and C were reported in 3 and 13 patients, respectively, with six still undergoing anti-HCV treatment. Cirrhosis due to HCV was observed in two patients, one of whom also had hepatocellular carcinoma. Among those infected with HCV, 15% of patients with severe hemophilia exhibited inhibitor positivity. Notably, none of our patients had an HIV infection.

DISCUSSION

Socio-demographic and epidemiological characteristics of adult PWH in our country are still overlooked and poorly defined. In our study group, a high proportion of patients (63.1%) had severe disease, and most were treated with prophylactic factor replacement therapy. The inhibitor positivity was reported at 8.9% among our participants. Kavaklı et al. reported inhibitor prevalence at 11.2% for hemophilia A patients and 15.8% for severe hemophilia A patients in Turkey (9). However, the prevalence of inhibitors in hemophilia patients varies widely in different studies, ranging from 6% to 27% (10-13).

PWH have a higher unemployment rate compared to the general population, largely due to joint deformities causing physical handicaps, and the inability to continue working because of bleeding episodes. The unemployment rate among all patients in our study was 33.3% while it ranges from 13% to 20% in industrialized countries and about 54% in underdeveloped countries (14,15). Our significantly higher unemployment rate is likely influenced by the overall high unemployment rate and the limited job opportunities in our country. There was a strong correlation between the patients' occupation and annual bleeding episodes; unemployed patients experienced fewer joint bleedings overall. This could be due to reduced physical activity among those not working. However, since the nature of the employed patients' jobs (whether desk-based or physically demanding) was not specifically assessed, it would be premature to attribute this trend solely to physical activity levels.

In various studies, 65% of hemophilia patients were found to have completed at least 12 years of education, equivalent to high school graduation (14). In our study, this ratio slightly lower at 60%. According to 2016 statistics, 35% of adults over 35 in Turkey had a university degree or higher, which is close to the 33.3% found in our survey. It is important to note that if this study were conducted in the eastern cities of Turkey, the proportion of university graduates among the patients might have been lower.

Previous studies have shown mixed results regarding the risk and prevalence of comorbidities in PWH compared to the general population. Few studies

have evaluated these comorbidities in PWH against an age-matched control group without hemophilia (13,16,17). Chronic viral infections and hypertension were found to be more prevalent in PWH, while cardiovascular disease (17), overweight, and hypercholesterolemia were reported less frequently (16). The incidence rates for DM and cancer were similar between cases and controls (13). Kulkarni et al. identified common risk factors for PWH, such as age, hypertension, smoking, obesity and DM, indicating that the prevalence of cardiovascular disease in PWH over 45 was comparable to that in the non-hemophilic population. However, other studies have reported lower mortality rates from cardiovascular disease in PWH. In our cohort, the prevalence of cardiovascular disease was 6.7%, slightly higher than the 6.1% reported for males over thirty in Turkey by the Turkish Statistical Committee but similar to previous retrospective studies. This underlines the importance of screening and primary prevention given the longer life expectancies of hemophilia patients. The prevalence of hypertension and DM in our study was 17.8% and 13.3%, respectively, which are lower than previously reported data (16). Interestingly, we observed that the annual bleeding rate was significantly lower in patients with DM. When reevaluating the data, we found that patients with DM were typically older and unemployed, leading to the hypothesis that reduced physical activity contributed to fewer bleeding episodes A study from Taiwan reported the prevalence of overweight and obesity was 61.8% in PWH aged 30 to 39 years, 60.6% in PWH aged 40 to 49 years, and 48% in PWH aged ≥50 years and showed that BMI and obesity also had positive correlation with annual joint bleeding rate (18). However, in our study, no correlation was found between BMI and annual bleeding episodes or disease severity. We did observe that the right ankle was the most commonly affected joint in patients with higher degrees of obesity.

HCV was the most common blood-borne virus in our study population, with an overall incidence of 11.8%. Prior to 1990, PWH were particularly susceptible to HCV and HBV infections. However, the risk significantly decreased after the implementation of mandatory serological and molecular testing; during blood donations. Currently, the expected seroprevalence of HCV infection in PWH is 3.6% (19). Hepatocellular carcinoma due to HCV infection was reported in one (1/13) patient in our cohort.

There are some limitations in our study. Firstly, it was retrospective, based on patients' recorded files, which may limit the accuracy and depth of data collected. Secondly, the correlation between socio-demographic factors and clinical features is suboptimal, as we were unable to evaluate aspects such as quality of life, physical activity, and physical and social functioning. Thirdly, while we reported the prevalence of comorbidities in our study group, these findings would be more robust if compared with an age-matched general population. Despite these limitations, to our knowledge, this is the first study in Turkey to describe the epidemiology and comorbidities of adult hemophilia patients, involving a larger number of patients than previously reported studies from other countries. Additionally, our findings indicate that the rate of university graduation and the unemployment ratio in our study group are comparable to those of the general population in our country.

CONCLUSION

Over the past seven decades, the availability of replacement factor products and new treatment strategies has significantly increased the life expectancy of the patients with hemophilia. However, treating older hemophilia patients and managing their emerging age-related diseases are still challenges for hematologists, due to relatively limited experience. Currently, there is no consensus or established guidelines for managing age-related diseases in PWH. Hemophilia caregivers and comprehensive care centers should be proactive in monitoring and managing the comorbidities in adults with hemophilia, ensuring patient well-being, and coordinating the optimal care. Moreover, further researches are essential to develop appropriate guidelines for managing older PWH.

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