



Original Article

Health Related Quality of Life and Psychopathological Symptoms in People with Hemophilia, Bloodborne Co-Infections and Comorbidities: An Italian Multicenter Observational Study

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Abstract. Background: The health-related quality of life (HRQoL) of people with hemophilia (PWH) is an important issue, especially considering people suffering from chronic diseases beyond hemophilia. The principal aim of this study was to investigate the presence and relevance of psychological symptoms, both internalizing and externalizing, lifestyle, and HRQoL in a group of Italian PWH with chronic bloodborne co-infections and comorbidities. Furthermore, the research describes the association between psychological aspects and the impact of disease-related characteristics (type of hemophilia, presence of co-infections, and comorbidities) on them.

Methods: Seventy patients (mean age 46.77 ± 11.3), 64 with severe hemophilia A (Factor VIII: C < 1 IU/dL) and 6 with severe hemophilia B (Factor IX < 1 IU/dL), were consecutively recruited from seven Hemophilia Centers in Italy of Italian Association of Hemophilia Centers (AICE). In order to assess psychological symptoms, HRQoL, and lifestyle, three psychological questionnaires were administered (the SCL-90-R, SF-36, and PSQ, respectively).

Results: A general decline in the quality of life and an increase in the tendency to adopt a lifestyle characterized by hyperactivity emerged. Inverse correlations were found between HRQoL and psychological distress. Although the SCL-90-R did not reveal symptoms above the clinical cut-off, co-infections significantly increased anxiety, depression, somatizations, paranoia, and social withdrawal. Lastly, HRQoL is impaired by co-infections as well as comorbidities.

Conclusion: Our preliminary results must be confirmed to deepen the findings between mental health and hemophilia.

Keywords: hemophilia; co-infection; comorbidity; distress; health-related quality of life.

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Introduction. Hemophilia is an inherited hemorrhagic disorder that, in the most severe forms, causes deep physical and psychological discomfort, mainly due to often life-threatening bleeding. In the last 20 years, great progress in the multidisciplinary management of PWH has been achieved. The availability of increasingly innovative replacement and non-substitutive treatments given on prophylaxis has radically changed the expectancy and the HRQoL, particularly in the younger generations with severe hemophilia A and B.¹

Several previous studies investigated the presence of psychological symptoms and the HRQoL in PWH. Most research agrees with the idea that specific factors in the medical history can determine a decline in specific components of HRQoL, such as physical activity, physical health, and social and interpersonal functioning.²⁻⁵ Other studies underlined the role of factors such as work status and perceived physical pain.^{6,7} Nevertheless, many problems are still associated with older adults affected by age-related comorbidities (diabetes, cardiovascular and respiratory diseases, renal insufficiency, cancer, etc.) that require specialized medical and psychological interventions. It is well known that the most serious comorbidities are chronic liver diseases closely related to hepatitis B (HBV) and hepatitis C (HCV) infections, as well as the sequelae caused by the human immunodeficiency virus (HIV)^{8,9} occurred in the 70-80s by the use of not virus-inactivated plasma-derived concentrates. However, even though vaccination against hepatitis B definitively defeated the virus in new generations, specific therapies against hepatitis C were applied,¹⁰ and combined therapy with highly active anti-retroviral drugs slowed the progression of HIV,¹¹ these infections keep on influence the concept of the disease and still have an impact on the mental health of people affected.¹²

The psychological dynamics in HIV-positive PWH were analyzed over the years by considering various parameters. Increased stress and anxiety in a population of HIV-positive hemophiliacs were observed. In addition, psychosocial problems related to the level of school education, familiarity with psychiatric illnesses, or a couple of problems were also described. More specifically, HIV-positives showed a greater negative impact on their sexual behaviors with a significantly higher prevalence of sexual dysfunctions than HIV-

negatives.¹³ However, completely different results were found by Italian authors that demonstrated that HIV-negative hemophiliacs have worse anxiety and depression scores, reporting more confusion and fear, than HIV-positives.¹⁴

At the same time, many research projects help to understand how to address these issues and manage physical and psychological symptoms associated with HIV infection.¹⁵ Similarly, changes in psychological dynamics are also observed in hemophiliacs with age-related comorbidities.¹⁶

The current literature still highlights the need to investigate these aspects further and broaden the clinical interest in psychological symptoms not yet evaluated. For instance, relevant emotional reactions towards the disease were neglected, such as the presence of externalizing symptoms (anger/hostility, paranoid ideation, etc.) typical in the literature discussing other severe chronic diseases (obstructive pulmonary disease, multiple sclerosis, alexithymia).¹⁷⁻²⁰

Aims of the study. The main purpose of our research was to describe specific psychological aspects: psychopathological symptoms, both internalizing (anxiety, somatic complaints, obsessions and compulsions, depression) and externalizing (hostility, paranoia, psychoticism, etc.), lifestyle, and HRQoL in a hemophiliac sample. A further objective was to highlight the possible association between the psychological aspects mentioned above. Lastly, the impact of specific factors related to hemophilia (type A or B, co-infections, and comorbidities) on the psychological dimensions was investigated.

Materials and Methods

Participants and Study design. In this multicenter observational study, 70 PWH (64 with severe hemophilia A: Factor VIII: C < 1 IU/dL and 6 with severe hemophilia B: Factor IX < 1 IU/dL) were consecutively recruited from seven Italian Hemophilia Centers (Bari, Catanzaro, Macerata, Padova, Roma, Palermo, and Scorrano) belonging to AICE. Criteria for inclusion in the study were age > 18 years old; medical diagnosis of hemophilia; absence of sensory disturbances of sight and/or hearing that limit the administration of the tests (i.e., previous head trauma, neurological condition,

alcoholism, or substance abuse, or neoplasms).

Ethical considerations. Informed consent was required from all persons, as well as the approval of the Ethics Committees of the respective Hemophilia Centers. This study complies with the Declaration of Helsinki and Italian privacy law (Legislative decree No. 196/2003). No treatments or false feedback were given, and no potentially harmful evaluation methods were used. Participation was voluntary, and participants could drop out at any time without any negative consequences. All data were stored only by using an anonymous ID for each participant. Subjects' anonymity was preserved, and the data obtained were used solely for scientific purposes.

Measures. After an accurate clinical interview, PWH underwent a psychopathological assessment procedure by administering three psychometric tests.

The Symptom Checklist-90-Revised was used to investigate internalizing and externalizing symptoms such as Somatization (SOM), Obsessive-compulsive (O-C), Interpersonal Hypersensitivity (I-S), Depression (DEP), Anxiety (ANX), Hostility (HOS), Phobic Anxiety (PHOB), Paranoid Ideation (PAR), and Psychoticism (PSY) (cut-off=1.00).²¹ The SCL-90-R provides three global indices: the Global Severity Index (GSI) represents the intensity of the level/depth of the distress; the Positive Symptom Total (PST) corresponds to the total number of symptoms, and the Positive Symptom Distress Index (PSDI) is used as an index of the subject's response style to the suffering.^{22,23}

The Short Form Health Survey (SF-36) was administered to evaluate the HRQoL. It is composed of eight scales: Physical Functioning (PF), Role (limitations) Physical (RP), General Health (GH), Bodily Pain (BP), Vitality (VT), Role (limitations), Emotional (RE), Mental Health (MH), and Social Functioning (SF). Questions and sub-scales of the SF-36 are organized so that a higher score represents better health of the subject.²⁴

The P Stress Questionnaire (PSQ) was performed to detect whether there is a present risk for stress-related physical disorders attributable to some characteristics of the personality configuration known as "Type A behavior".²⁵ The PSQ tool made up of 32 items, grouped into six scales: Sense of Responsibility (SR), Vigor (V), Stress Disorders (SD), Precision and Punctuality (PP), Spare Time (ST), and Hyperactivity (H). The standardization provides conversion into Stanine scores that are proper for scores that do not fall below 10 standard deviations. The Stanine (STANDARD NINE) is a method of scaling test scores that have a distribution between 1 and 9 with mean=5 and standard deviation=1.96.

Statistical analysis. Statistical analysis was performed

using Microsoft Excel and IBM SPSS Statistics software (Version 28.0.1.0). Considering the small sample size and the presence of unbalanced groups when divided by type of hemophilia, co-infections, and comorbidities, non-parametric statistical analyses were computed. First, descriptive analyses on the total sample were conducted: average values (mean and standard deviation) of the scores obtained from the total sample in the SCL-90-R, SF-36, and PSQ scales were calculated. In order to highlight possible associations between the psychological dimensions assessed, a Spearman Correlation was then performed considering the sub-scales of the SCL-90-R and the total scores of the SF-36 and the PSQ. In order to investigate the impact of specific factors related to hemophilia (type of disease, presence of co-infections, and comorbidities) on the psychological aspects assessed, the following analyses were made: a Mann-Whitney U tests for independent samples were used to calculate possible significant differences between type A group vs. Type B group considering symptoms (SCL-90-R), lifestyle (PSQ), and HRQoL (SF-36); a Mann-Whitney U tests for independent samples were made to detect possible significant differences between a co-infections group compared with a group without co-infections considering symptoms (SCL-90-R), lifestyle (PSQ), and HRQoL (SF-36); finally a Mann-Whitney U tests for independent samples was performed in order to assess possible significant differences between groups with comorbidities compared with a group without comorbidities taking into account symptoms (SCL-90-R), lifestyle (PSQ), and HRQoL (SF-36).

Results

Description of the Sample. Demographic and disease-related characteristics of the total sample are shown in **Table 1**.

Descriptive analysis of the total sample. Firstly, the SCL-90-R did not show scores indicative of psychopathological symptoms of relevance (above the clinical cut-off of 1.00) while, considering the global score of the SF-36, a tendency to perceive an impoverishment in one's health in the last year emerged. Lastly, the descriptive analysis conducted on the total score of the PSQ highlights the tendency to adopt behaviors and lifestyles characterized by a high sense of responsibility, vigor, precision and punctuality, hyperactivity, and somatic complaints (**Table 2**).

About the three measures, the possible linear relation between them was investigated through Spearman's Rho coefficient. In addition to the significant associations that emerged between all the clinical and global scales of the SCL-90-R, significant correlations can be observed between the global score of the SF-36 and those of the SCL-90-R. More specifically, it appears that

Table 1. Demographic and disease-related characteristics of the sample (N=70).

Age (years), <i>M (SD)</i>		46.77 (11.3)
Marital status, <i>N (%)</i>		
	Unmarried	23 (32.9%)
	Married/cohabitant	40 (57.1%)
	Separated/divorced	7 (10%)
Education Level, <i>N (%)</i>		
	Primary school graduation	2 (2.9%)
	Middle school graduation	15 (21.4%)
	High school graduation	44 (62.9%)
	University degree	9 (12.9%)
Current Occupation, <i>N (%)</i>		
	Employed	49 (70%)
	Retired/Not employed	19 (27.1%)
	Student	2 (2.9%)
Type of Hemophilia, <i>N (%)</i>		
	A (Factor VIII: C <1 IU/dL)	64 (91.4%)
	B (Factor IX <1 IU/dL)	6 (8.6%)
Co-Infections, <i>N (%)</i>		
	No	18 (25.7%)
	Yes	
	Total	52 (74.3%)
	HCV	35 (50%)
	HIV	1 (1.4%)
	HBV/HCV	5 (7.1%)
	HCV/HIV	1 (1.4%)

Table 2. Average values of the clinical and global scales of the psychometric tests.

	Mean	SD
Symptom-Check-List-90-Revised (SCL-90-R)		
Somatizations (SOM)	0.60	0.44
Obsessive-Compulsive (O-C)	0.53	0.53
Interpersonal Sensitivity (I-S)	0.41	0.46
Depression (DEP)	0.44	0.50
Anxiety (ANX)	0.45	0.50
Hostility (HOS)	0.31	0.35
Phobic Anxiety (PHOB)	0.20	0.36
Paranoid Ideation (PAR)	0.55	0.51
Psychoticism (PSY)	0.31	0.43
Short Form Health Survey (SF-36)		
Global score	8.99	0.12
P Stress Questionnaire (PSQ)		
Global score	63.4	21.5

psychological symptoms increase as the quality-of-life decreases. However, an opposite trend can be hypothesized: as the state of physical and mental health decreases, symptoms related to anxiety, phobic anxiety, depression, obsession and compulsion, somatic

complaints, interpersonal hypersensitivity, paranoid ideation, and psychoticism increase. Furthermore, the global score of the SF-36 shows a moderate inverse correlation with the global score of the PSQ (**Table 3**).

Comparison between sub-groups. In order to identify any significant differences in the manifestation of psychological distress attributable to disease-related characteristics (type A or B, presence or not of co-infections and comorbidities), the differences between these groups were assessed. The comparison of the scores of the SCL-90-R, SF-36, and PSQ according to the type of hemophilia (A or B) did not show noteworthy aspects. For none of these scales, there were no significant differences. On the contrary, the Mann-Whitney's U test that compared the scores of the psychological measures considering the presence of co-infections vs. the absence of co-infections highlighted noteworthy aspects. More specifically, significant differences between groups emerge both for SCL-90-R and for SF-36. It seems that co-infections presence favors an increase in psychological symptoms, internalizing, such as somatic complaints, interpersonal hypersensitivity, depression, anxiety, and externalizing, such as paranoid ideation and psychoticism. The scores of two global indices, the GSI and PST, are also

Table 3. Relationships between variables in the whole sample.

	1	2	3	4	5	6	7	8	9	10	11	12	13
1 SCL-90-R SOM	1												
2 SCL-90-R O-C	.59**	1											
3 SCL-90-R I-S	.64**	.92**	1										
4 SCL-90-R DEP	.71**	.80**	.76**	1									
5 SCL-90-R ANX	.78**	.72**	.75**	.79**	1								
6 SCL-90-R HOS	.49**	.60**	.66**	.58**	.70**	1							
7 SCL-90-R PHOB	.52**	.65**	.60**	.66**	.63**	.59**	1						
8 SCL-90-R PAR	.55**	.79**	.81**	.68**	.60**	.49**	.51**	1					
9 SCL-90-R PSY	.60**	.83**	.77**	.79**	.72**	.61**	.62**	.64**	1				
10 SCL-90-R GSI	.82**	.90**	.88**	.91**	.88**	.68**	.69**	.80**	.85**	1			
11 SCL-90-R PST	.76**	.89**	.86**	.89**	.83**	.66**	.71**	.81**	.82**	.96**	1		
12 SCL-90-R PSDI	.60**	.40**	.38**	.42**	.56**	.43**	.34**	.27*	.47**	.53**	.36**	1	
13 SF-36 Global score	-.54**	-.34**	-.34**	-.47**	-.37**	n.s.	-.34**	-.31**	-.33**	-.48**	-.44**	-.30*	1
14 PSQ Global Score	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	-.374**

Note: SCL-90-R = Symptom Check-List-90-Revised; SOM = Somatizations; O-C = Obsession-Compulsion; I-S = Interpersonal Sensitivity; DEP = Depression; ANX = Anxiety; HOS = Hostility; PHOB = Phobic Anxiety; PAR = Paranoid Ideation; PSY = Psychoticism; GSI = Global Severity Index; PST = Positive Symptom Total; PSDI = Positive Symptoms Distress Index; SF-36 = Short Form Health Survey; PSQ = P Stress Questionnaire.

Table 4. Average values (mean and standard deviation calculated on T scores) and comparison of the Symptom Check-List-90-Revised (SCL-90-R) between the group without co-infections and the group with co-infections.

	Absence of co-infections (n=18)		Presence of co-infections (n=52)		U	p
	M	SD	M	SD		
Somatizations (SOM)	49.48	6.7	57.66	10.8	690.5	.003
Obsession-Compulsion (O-C)	49.61	10.2	54.21	12.2	585.5	.112
Interpersonal Sensitivity (I-S)	47	6.4	55.16	12.7	676.5	.005
Depression (DEP)	48.42	10.9	52.9	11.3	640.0	.02
Anxiety (ANX)	49.7	12.9	55.67	13.5	675.0	.005
Hostility (HOS)	48.61	8.3	50.99	8.9	556.5	.218
Phobic Anxiety (PHOB)	49.65	8.9	52.9	11.6	522.5	.402
Paranoid Ideation (PAR)	49.85	8.6	56.91	12.2	632.5	.026
Psychoticism (PSY)	52.18	17.6	58.41	16.7	635.0	.021
Global Severity Index (GSI)	48.92	11.5	56.28	13.5	680.5	.004
Positive Symptom Total (PST)	48.25	11	55.61	12.2	662.0	.009
Positive Symptom Distress Index (PSDI)	52.98	20.7	55.46	10	535.0	.364

significantly higher in the group with co-infections (**Table 4**).

Furthermore, the co-infections presence determines a statistically significant worsening of the quality of life (U=270.5; p=.008).

The Mann Whitney's U test was also performed to investigate possible differences in the scores of SCL-90-R, SF-36, and PSQ between a group of PWH with comorbidities and a group of PWH without comorbidities. No significant differences emerge between these two groups, neither in the symptoms assessed with the SCL-90-R scale nor in the behavioral

and lifestyle aspects investigated through the PSQ. Conversely, the presence of other medical diseases in the anamnesis favors a reduction in the level of HRQoL (U=251.0; p=.01).

Discussion. On a descriptive level, the most interesting result is the significantly high average score on the PSQ. These data indicate the frequent tendency to adopt a lifestyle at risk of stress-related physical disorders and behavior characterized by a high sense of responsibility, vigor, hyperactivity, precision and punctuality, and reduced ability to take free time from working activities.

In this sample, one could assume that there is a tendency to adopt a lifestyle that does not favor the achievement of psychophysical balance but instead the tendency to implement potentially risky health behaviors. Clinical hypotheses are connected to the possible presence of an underestimation of risk in terms of denial of illness and non-acceptance of the role of the patient. For this reason, in a future perspective of evaluation, it would be interesting to investigate the subjective perception of disease connected to the adaptation to it (i.e., by Illness Behavior Questionnaire).²⁶ Consistent with what has already been widely described in the literature, the diagnosis of hemophilia is envisaged as an obstacle in the life of these people who perceive a limitation of their activities in favor of the protection of their body.^{5,6,27-29} For instance, some authors argue that participation in activities, such as sports or crowded social events, is influenced by the fear of incurring injuries and bleeding.³⁰ Moreover, it has highlighted the role of behavioral precautions, the uncertainty of actions, and the fear of unexpected bleeding on depression, frustration, isolation, and embarrassment.³¹ Other studies confirmed some aspects related to comorbidities (arthropathy, HCV/HBV/HIV co-infections, liver cirrhosis due to HBV/HCV infections, and coexisting heart and kidney diseases, for example) are ongoing challenges that block the accepting health status in these persons.^{32,33} As experienced in our sample, the correlation between the perceived quality of life and the adopted lifestyle further corroborates this point. It is possible to sustain that a lifestyle characterized by high activity levels is associated with a decrease in the state of health perceived by the subject. Hence, the need to pay attention to the lifestyle of these persons, stress management, positive thinking, and eating habits emerges.³⁴

Focusing on the psychopathological symptoms, our group recorded no scores above the clinical cut-off. However, noteworthy aspects emerged by investigating the correlation between the scores of the other psychometric tests administered. Confirming what already emerged in previous studies, the state of health appears to have an inverse correlation with two global indices of the SCL-90-R.^{4,5,28-30} This information describes the tendency to suffer psychologically more, as the decline in quality of life, in terms of limitations deriving from the physical disease, increases. Furthermore, confirming previous studies, the HRQoL appears to have an inverse correlation with most psychological symptoms, such as anxiety, phobic anxiety, depression, obsessions and compulsions, interpersonal hypersensitivity, and somatic complaints.^{3-5,28-30,35} Moreover, even the scores of paranoid ideation and psychoticism appear to have an inverse relationship with the HRQoL, highlighting the additional load of hostility, suspiciousness, withdrawal,

and social isolation on the state of health. However, due to our study's small sample size, it is impossible to define the causal role of the symptoms on the deterioration of the HRQoL. The opposite could also be true: a reduction in psychophysical well-being could lead to mental suffering.

One of the aims of this research was to investigate some disease-related characteristics' effects on the observed psychological aspects. Interesting data were highlighted by comparing the psychological distress between the group of patients with co-infections with those of the group without co-infections. Co-infections appear to have an important role in increasing psychological distress in terms of internalizing (anxiety, depression, somatic complaints) and externalizing (paranoia and psychoticism) symptoms. If the last aspect is considered, the expression of mental suffering on an interpersonal level has been described for the first time. To our knowledge, inadequacy, a sense of inferiority, self-depreciation, and suspiciousness resulting in social withdrawal and isolation were never detected. Our results effectively deepen previous studies supporting the data that infections compromise the patient's well-being causing medical complications and social impairment. Jones and colleagues focus on HIV infection and argue that there is a possible risk factor for the appearance of psychological symptoms, even before noticeable physical signs.³⁶⁻⁴⁰ The psychological dynamics in HIV-positive PWH were analyzed over the years by considering only parameters such as stress and the relationship between infections. Specifically considering HIV and mental suffering, the association is still confused even now that vaccinations and anti-retroviral therapies slow the progression of the disease.¹²

Also, considering the HRQoL, our findings agree with previous studies that focused on co-infections impact on this aspect. For instance, Cuesta-Barriuso et al. found significant differences between a group of PWH with HIV/HCV and the group without co-infections in HRQoL perceptions, concluding that the emotional representation of the disease plays an influential role.²⁸ Consistent with this assumption, other authors explained this association with the assumption that the HRQoL would be influenced by the level of acceptance of the infection and the ability to adapt to illness.^{38,41,42,43}

Our study underlines another aspect referred to as the HRQoL. It has been observed that comorbidities affect the global perception of health but not mental health. The various diseases the person suffers from determine the perception of one's functional limitations.

In summary, some important considerations emerge and suggest the need for further studies. For instance, future research could investigate the close relationship between the lifestyle characterized by hyperactivity and the deterioration in terms of quality of life and the association between the perception of limitations to the

activities of daily living and the increase in psychological distress. Furthermore, it would be useful to constitute a sample in which the group of co-infected and that of non-co-infected are balanced. This aspect would confirm the higher levels of externalizing symptoms, including paranoia, in the first group. In addition, various sub-groups of co-infected PWH could highlight interesting differences.

Finally, we emphasize the need always to consider the HRQoL, which in our study appears to be compromised by comorbidities. Considering that quality of life is one of the best indices for the clinician to estimate the patient's level of well-being, it is important to investigate the psychological aspects and the medical variables that can impact it.

Conclusions. The results of our preliminary research focus on the well-being of PWH and their emotional experience. Our results agree with literature reports and confirm that co-infections influence the manifestation of distress (in terms of anxiety and depression, while PWH experiences comorbidities are a consistent limitation of their lives. In addition, the study underlines for the first time that these patients also experience externalizing symptoms, including interpersonal sensitivity, embarrassment, and paranoia. Nevertheless, it has also emerged that the psychological variables investigated are associated. More specifically, a general decline in well-being is associated with more intense mental distress, even at a sub-clinical level. First, our results must be confirmed to deepen the findings between mental health

and hemophilia.

The poor clarity in the factors that favor the impairment in the perceived HRQoL and mental health remains an important clinical issue, and future studies must be carried out.

Unfortunately, more in-depth statistical analyses could not be performed because of the small sample size and its large heterogeneity. Nevertheless, further research may investigate a cause-effect relationship between the adopted lifestyle and the decrease in perceived HRQoL. In addition, it could be useful to verify if a greater perception of the limitations of the disease corresponds to effective psychological suffering and investigate how personality and psychological symptoms interact with each other and affect psychophysical well-being.

This preliminary research underlines the importance of multidisciplinary and multidimensional management where a psychological investigation supplements the clinical-medical evaluation. Psychological stress is frequently mentioned among the predisposing,⁴⁴ precipitating, or perpetuating factors⁴⁵ of physical pathologies in most medical fields, including cardiovascular events, malignancies, and neurodegenerative disorders.⁴⁶⁻⁴⁸ Despite these reports, the medicine units that benefit from the presence of clinical psychologists with specific curricula are still few. Nevertheless, psychological support is useful for understanding the clinical picture better and providing tailored interdisciplinary treatment.

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