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Letter to the Editor

Comparison of quality of life, emotional and functional profiles in older people with and without severe haemophilia

S. Riva, [1-2,] E. Marchesini[3], E. Oliovecchio[3], A. Coppola[4], E. Santagostino[1], P. Radossi[5], G. Castaman[6], L. Valdrè[7], C. Santoro[8], A. Tagliaferri[4] C. Ettorre[9], E. Zanon[10], G. Barillari[11], I. Cantori[12], T. M. Caimi[13], G. Sottilotta[14], A, Iorio[15] and P. M. Mannucci[1]

1 Angelo Bianchi Bonomi Haemophilia and Thrombosis Centre, Fondazione IRCCS Ca' Granda Maggiore Hospital Foundation,Milan, Italy
2 Department of Psychology and Padagogic Science, St Mary's University, Twickenham, London, UK
3 Hemophilia Centre-SC Vascular and Emergency Department, University of Perugia, Italy
4 Regional Reference Centre for Inherited Bleeding Disorders, University Hospital of Parma, Italy
5 Oncohematology Department Istituto Oncologico Veneto, Castelfranco Veneto Hospital, Italy
6 Center for Bleeding Disorders and Coagulation, Department of Oncology, Careggi University Hospital, Florence, Italy
7 Unit of Angiology and Coagulation Disorders, S. Orsola-Malpighi University Hospital, Bologna, Italy
8 Hematology Department of Cellular Biotechnologies and Hematology, Sapienza University of Rome, Italy
9 Hemophilia and Thrombosis Center, Policlinico Giovanni XXIII, Bari, Italy
10 Department of Cardiovascular Sciences, Vascular Medicine Unit, University of Padua, Italy
11 Center for Haemorrhagic and Thrombotic Disorders, General and University Hospital, Udine, Italy
12 Haemophilia Center, Regional Reference Center for Inherited Bleeding and Thrombophilic Disorders, Civil Hospital, Macerata, Italy
13 A De Gasperis Cardiovascular Department, Niguarda Ca' Granda Hospital, Milan, Italy
14 Hemostasis and Thrombosis Unit, "Bianchi-Melacrino-Morelli" Metropolitan Hospital, Reggio Calabria, Italy
15 Department of Clinical Epidemiology and Biostatistics, Department of Medicine, McMaster University, Hamilton, Canada

The management of patients with haemophilia (PWH) has dramatically changed, due to the availability of more and safer replacement products and specialized treatment centers attending them comprehensively. Accordingly, these patients have reached a life expectancy close to that of males in the general population [1,2] and many of them attain older ages. Thus, there is a cohort characterized not only by co-morbidities, such as arthropathy and chronic viral infections, related to their previously inadequate treatments but also to the multimorbidities inevitably associated with aging.

With this background, the association of Italian haemophilia treatment centres (AICE) chose to start in 2015 an observational cohort study (Sixty Plus Haemophilia Registered Assessment, S+PHERA) including the great majority of PWHs (n=102) aged 60 or more in the country attending 14 haemophilia treatment centers (HTCs) and a control group of age-matched men without haemophilia (n=204) chosen randomly from 6 general practices of the areas where PWH live. The broad purpose of this cohort study that received ethical approval was to compare PWHs with their unaffected age peers at enrollment and then at the end of a 5-year follow-up for their clinical status (3-5) but also for health-related quality of life (HrQoL), functional and social proficiency.

All PWHs have severe disease (FVIII or FIX <1%), 90 of them haemophilia A and 12 haemophilia B. Table 1 shows that at enrolment PWH and controls had the same median age (65 years) and provides details on replacement therapy regimens in PWH. As expected PWH had a higher rate of history of bloodborne viral infections. According to the Cumulative Illness Rating Scale as detailed elsewhere [4], the sensitivity index and the comorbidity index were more compromised by illness in PWH than for their peers, particularly pertaining to the comorbidity index (Table 1).

We report herewith the HrQoL, emotional profile and functional proficiency in daily activities as collected at enrollment using a set of tools administered by means of a direct patient

interview. For this analysis, data were obtained from only 88 of 102 PWH (86%) and 147 of 204 controls (72%) (Table 1), because not all the initially enrolled patients and controls were able to attend the HTCs when these tests were administered.

HrQoL evaluation: generic and haemophilia-specific tools were used:

⇒ The EQ-VAS is a vertical visual analogue scale that employs values between 100 (best imaginable health) and 0 (worst imaginable health) to provide a global assessment of patient health. [6].

⇒ The WHOQOL-Old is a generic tool developed from WHOQOL-100 that gives an overall description of health, emotional and social status. Responses were rated on a 5-point Likert scale (1 to 5), higher scores indicating a better quality of life. Sum scores were created for each of the six facets and for the total WHOQOL-OLD.

⇒ The Haem-A-QoL$_{\text{Elderly}}$, used to assess haemophilia-specific HrQoL and thus not done in controls, was adapted to older PWH from the validated Haem-A-QoL basic questionnaire [7], because in the latter not all domains and questions are applicable to older PWH.

Functional evaluation: To assess the level of functioning in the everyday life we used:

⇒ The Activities of Daily Living (ADL) scale includes six basic activities that people do every day without assistance. The total score ranges from 0 to 6: individuals get 1 when they perform normally, or 0 when they show no normal functioning [8].

⇒ The Instrumental Activities of Daily Living(IADL) scale includes more complex daily activities and is based on how an individual usually performs a task [9]. It contains 8 items rated with a summary score ranging from 0 (low functioning) to 8 (high functioning).

Emotional evaluation: The Geriatric Depression Scale (GDS) is a 30-item questionnaire with participants asked to answer yes or no in reference to how they felt during the past week. [10].

Scores ranging from 0 to 9 indicate no depression, between 10 and 19 mild depression, between 20 and 30 severe depression.

Data are expressed as percentages for categorical variables, means and SD for normally distributed continuous variables. Differences at enrollment between PWH and controls were tested using the two-sample t tests or the Mann-Whitney test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. A two-sided P value <.05 was considered statistically significant.

Results on health related quality of life. HrQoL was definitely worse in PWH than controls according to the generic EQ-VAS (Table 2). With the more specific WHOQOL-Old (Table 2), older PWH showed the highest impairments in the domain "death", while controls reported more impairments than PWH in "sensory" and "intimacy". This suggests that PWH are more concerned about death, controls about the loss with aging of sensory capacity and of having personal and intimate relationships.

Pertaining to the impact of their health status on HrQoL as assessed by the disease-specific Haem-A-QoL$_{Elderly}$ tool obviously not applied to controls without hemophilia (Table 3), older PWH showed the highest impairment in the dimensions 'physical activity & leisure', 'physical health', and 'relationships'. Concerning 'physical activity and leisure', 42.4% of PWH mentioned 'always' that they 'could not travel as they wanted', and 28.2% 'that they could not do the same things as others'. Concerning 'physical health', 52% of them reported "always/often" that "it was difficult for me to move my arms or legs" and 51% "reported "always/often" that "I could not walk as I wanted". Finally, pertaining to 'relationships', around three-quarters of older PWH reported that they failed to have "a normal relationship because of haemophilia'. When controlled for clinical variables (e.g. HIV, HCV, inhibitor status and disability index) and for social variables (e.g. education, marital status) no differences were found in PWH pertaining to the overall HrQoL measured with the Haem-A-Qol$_{elderly}$, but specific differences were found for

some questionnaire domains in relation to HCV and marital status. The domain "work" was more affected for PWH with HCV (mean difference=11; 95% CI: -5.9-27.9, t=1.23, P=.03) while the domains "physical" and "relationships" were most affected in PWH living alone (mean difference = -9.3, 95% CI: -16.1- -2.6, t=2.79, p=.03 and mean difference -7.9, 95% CI: -15.9 - 0.04, t=1.99, P=.02, respectively).

Results of the emotional evaluation. Table 2 shows that the degree of depression was higher in PWH than controls. Of 88 PWH 71 (80.6%) could be defined as having "mild depression" (scores between 10 and 19), 3 (3.4%) "severe depression" (between 20 and 30). Among controls, 29 (24%) had "no depression" and 111 (76%) "mild depression".

Results of the functional evaluation. Pertaining to their capability of functioning for simple activities of daily living as measured by ADL, older PWH showed slightly lower mean scores, but in more of them than controls ADL scores were less than 6 (25.3% vs 6.8%, P<.001), indicating a lower self-sufficiency in performing activities related to self care. On the other hand, there were no difference between PWH and controls for the more complex activities of daily living measured by IADL.

All in all, this report provides a snapshot of a cohort of older PWH with severe haemophilia A or B pertaining to their functional and emotional profiles in comparison with age-matched peers without bleeding disorders. It is well established that treatment developments and comprehensive management programs dramatically increased life expectancy in older PWH, at least in high income countries [2]. Hence older PWH currently experience age-related clinical problems observed in the general elderly population. Even though these two cohorts of PWH and non-affected age peers are broadly comparable from a clinical point of view, they did differ from a psychological and social point of view. The impact of a chronic genetic disorder is associated with detriments in HrQoL, particularly when associated with comorbid diseases [11,12]. The negative impact on HrQoL varies across symptoms and functional areas: the

magnitude of detriment in PWH appears to be worse than in their age peers because it is associated with symptoms causing debility (e.g. anxiety and depression) or with conditions determining disablement (as reported by the ADL) or isolation (e.g. living alone/not married). The strength of this study is the use an array of tools and an optimal control group for the comparison of the quality of life of older PWH and their functioning in the activities of daily life. Limitations are that it was carried out in a single, high-income country characterized by the presence of a collaborative network of specialized HTCs. These results are witnessing the pivotal role of HTCs in the development of programs specially tailored for older PWH [13-14], but it remains to be seen whether or not this basically encouraging scenario applies to other cohorts of older PWH.

In conclusion, the HrQoL, emotional and functional capacities of older PWH were generally lower than those of their age peers without hemophilia, perhaps due to the peculiar burden of having a chronic illness from birth which may affect the ability to cope with life events as well as social and relational positions. These results emphasize the key role of specialized and comprehensive HTCs (including a psycho-emotional assessment and care over time), as well as of specific programs meant to make aging successful in PWH [13-14], in order to reduce the gap with age-matched peers without haemophilia who receive standard care by their general practitioners.

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Conflicts of interest

- P.M. Mannucci is member of the scientific board for the Bayer Awards and has also received honoraria from Bayer, Kedrion and Novo Nordisk for lectures at educational symposia. A. Coppola acted as paid consultant for Bayer, Novo Nordisk and received speaker honoraria from Wefern Uniqure. G. Castaman received speaker honoraria from CSL Behring, acted as member of advisory boards for CSL Behring, Sobi, Novo Norkisk Kedrion, Sanofi, Wefern Uniqure, Takeda and Alexion, he also acted as paid consultant for Roche and his Institution received research funds from CSL Behring, Pifzer and Sobi. L. Valdrè acted as Advisory Board member to Bayer and Sobi and received speaker honoraria from Novo Nordisk, Roche and Baxalta. C. Santoro acted as paid consultant for Bayer, CSL Behring, Sobi, Roche, Novo Nordisk and Takeda. A. Tagliaferri acted as Advisory Board member for Bayer and Roche. G. Sottilotta acted as paid consultant to Shire, Novo Nordisk and CSL Behring.

- S. Riva, A. Iorio, E. Oliovecchio, E. Santagostino, P. Radossi, E. Zanon, I. Cantori and M.T. Caimi declare no conflict of interest.

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Table1. Baseline characteristics of the study populations of older persons with and without hemophilia (expressed in percentages, except for age and CIRS)

	Older persons with hemophilia **(*n=88*)**	**Older persons without hemophilia (*n=147*)**	***P* values (only those statistically significant)**
Demographic and clinical characteristics			
Age (years) and median range	65 (61-75)	65 (60-74)	
Partner status			<0.0001
Married	63	85	
Single	30	5	
Widowed	4	3	
Divorced	3	2	
Living			
In the family	77	75	
Alone	23	25	
School education			
Illiterate	3	5	
Elementary level	24	27	
Middle level	28	37	
High school	37	22	
University	8	9	
Occupation			<0.001
Unemployed	20	4	
Farmer	0	1	
Labourer	13	53	
Clerk/teacher	42	24	
Professional	25	18	
History of viral bloodborne infections			
HCV	91	5	
HBV	42	1	
HIV	11	0	
Cancer history	7	10	
Diabetes on treatment	16	22	
Cumulative Index Rating Scale (CIRS)			
Severity index (median)	1.6 (1.5-1.6)	1.4 (1.3-1.4)	< 0.001
Comorbidity index (median)	2	1	< 0.001
Factor replacement therapeutic regimen			
On demand	65	-	
Secondary prophylaxis	43	-	
On immunetolerance	2	-	

Table 2. Results of tools assessing quality of life and the emotional and functional status as obtained at baseline in older persons with and without haemophilia

	Older persons with haemophilia (n=88)	**Older persons without haemophilia (n= 147)**	**P value**
TOOL			
EQ-VAS	57.2±2	77.4±14.7	<.001
WHOQOL-Old			
Sensory	2.3±0.5	2.1±0.5	.006
Autonomy	3.5± 0.6	3.4± 0.6	n.s.
Past - present - future activities	3.4± 0.8	3.4± 0.6	n.s.
Social	3.4± 0.9	3.6± 0.7	n.s.
Death	2.6 ± 0.9	2.9 ± 0.9	.004
Intimacy	2.8± 0.6	2.5± 0.6	.024
Total	15.7 ±1.9	15.9 ±1.6	n.s.
Geriatric Depression Scale			
(total score)	12.5± 3.2	11.3± 2.7	.001
Activities of Daily Living (ADL)			
(total score)	5.5 ±1.1	5.9 ± 0.4	<.001
Instrumental Activities of Daily Living (IADL)			
(total score)	6.4± 1.8	6.5±1.4	n.s.

Results are expressed as mean scores ± SD, n.s. denotes not statistically significant

Table 3. Characteristics of older persons with haemophilia using the Haem-A-QoL$_{elderly}$ instrument

	N items	*Min*	*Max*	*Mean*	*SD*
Physical	7	21.4	100.0	55.0	18.1
Feeling	6	.00	100.0	38.5	24.6
View	9	30.5	88.8	47.6	17.2
Family	4	.00	87.5	28.0	23.1
Others	9	.00	80.5	37.0	21.1
Physical activity & leisure	4	18.7	100.0	62.9	18.1
Work	4	.00	100.0	36.0	31.6
Dealing	2	.00	87.5	14.8	20.1
Treatment	7	10.7	82.1	29.1	19.5
Future	9	.00	91.6	36.0	23.4
Relationships	2	12.5	100.0	54.1	19.1
TOTAL	63	15.8	79.7	40.5	15.2