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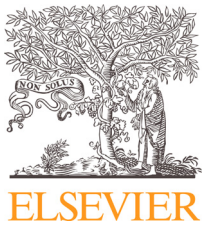

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Long-term changes of health-related quality of life in patients with peripheral vascular malformations – a prospective observational study

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Summary *Purpose:* The aim of this observational study was to assess health-related quality of life (HRQOL) changes in patients with vascular malformations, over a period of almost eight years, and to assess clinical and demographic characteristics possibly associated with HRQOL changes.
Methods: Eighty out of 111 patients who were included in a previously published comparative HRQOL study accepted inclusion in this follow-up study. HRQOL at baseline and follow-up was assessed with the Short-Form 36-item questionnaire (SF-36). Median observation time was 7.9 years. Linear mixed models and linear regression models were applied to assess HRQOL change and possible associations with demographic and clinical variables.
Results: The median age of the patient cohort at baseline evaluation (n = 111) was 27.0 years. Ninety-six out of 111 (86.5%) patients were diagnosed with venous malformations. Significantly higher SF-36 scores at follow-up were found for the physical domains *Role limitations due to* (RLDT) *physical problems* (difference=13.5; 95% CI [1.6, 25.3]) and *Bodily pain*

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(difference=11.3; 95% CI [3.8, 18.8]). No deterioration of HRQOL was found in any domain. In multivariate analyses, female gender, muscle/bone involvement, and higher age were associated with a positive relative change in SF-36 in the domains *Physical functioning, RLDT physical problems,* and *RLDT* emotional problems, respectively. Invasive treatment was not associated with long-term HRQOL change.

Conclusions: Over a period of almost eight years, significant improvement of SF-36 scores was observed in the physical domains RLDT physical problems and bodily pain. Female gender, muscle/bone involvement, and higher age were associated with HRQOL improvement in certain domains.

Introduction

Vascular malformations are benign congenital lesions with an estimated prevalence of 1.2%.[1] According to the currently accepted classification, there are four main categories of vascular malformations, depending on the vessel types involved; capillary (CM), venous (VM), lymphatic (LM), and arteriovenous malformations (AVM), or a combination of these.[2] About 2/3 of all vascular malformations are diagnosed as VM.[3]

Vascular malformations are by definition present at birth and grow proportionally with the child, without regression. Symptoms often occur in childhood, and frequently, the lesions progress during puberty, after trauma, or during pregnancy.[4-6] Vascular malformations may affect all tissue types in any anatomical region; hence, the clinical presentation may be highly variable. The most frequent symptoms include soft tissue swelling, pain, skin discoloration, and cosmetic disfigurement.[7] Vascular malformations are usually either treated conservatively with elastic stockings or invasively with surgery or endovascular techniques. In large or infiltrative venous and lymphatic malformations unresponsive to invasive treatment, medical treatment with Sirolimus has shown promising effect,[8,9] and more drugs are under evaluation. Curative treatment of these chronic lesions is rarely possible, and the main treatment goal is symptom control and pain relief.

In a recently published study, we assessed health-related quality of life (HRQOL) of 111 Norwegian patients with vascular malformations outside the central nervous system (CNS).[10] Both mental and physical aspects of HRQOL were affected in patients with vascular malformations, when compared to HRQOL of the background population. Higher patient age and malformations involving muscles or bone were associated with impairment of physical aspects of HRQOL. Our findings supported results from other studies assessing HRQOL in similar patient groups.[11-13] With this knowledge, treatment evaluation should focus on patient reported outcome measures (PROMs) like HRQOL. Unfortunately, there is yet no consensus regarding evaluation methods for outcome measures after treatment, and until now, the evidence level of such studies is generally poor.[14,15] Furthermore, in chronic conditions like vascular malformations, it is important to understand how the clinical course impacts on HRQOL in the long term. Data to enlighten this issue, however, are currently lacking. In the current study, we present our long-term HRQOL data on patients with vascular malformations.

The primary aim of this prospective observational study was to assess HRQOL changes in patients with vascular malformations over a period of almost eight years, and to assess selected clinical and demographic predictive factors possibly associated with these changes. The secondary aim was to compare baseline HRQOL of treated and nontreated patients.

Patients and methods

Study sample

The study was conducted at the national treatment center for vascular anomalies in Norway, which is organized as a multidisciplinary clinic. Between September 2011 and December 2012, 111 patients aged 14 years and above and referred for the first time to our center were consecutively included in the comparative HRQOL study described above, after diagnostic work-up had confirmed a diagnosis of vascular malformation. For all patients, baseline HRQOL assessment was performed prior to treatment decision making. All patients were invited by mail to participate in the present follow-up study. Inclusion started in December 2019, and reminders were sent out every 6 and 10 weeks. By December 2020, 80 out of 111 (72.1%) patients had responded and accepted inclusion. All patients received the SF-36 questionnaire, which was filled in and returned to our center by mail. Median time interval between baseline quality of life assessment (T0) and follow-up (T1) was 7.9 years (range 7.2-9.2).

The protocol of the study was approved by the regional ethics committee and the local data protection officer. Written consent was obtained from all patients.

Diagnostic work-up

The diagnostic work-up was based on clinical evaluation and imaging with ultrasound and MRI, which for all patients were performed prior to the baseline HRQOL assessment between September 2011 and December 2012. This provided information about the malformation type, anatomical location, and

tissue involvement. Treatment data were retrospectively collected from the electronic patient journal, providing information about whether or not the patients had received invasive treatment in the time interval between HRQOL assessments, as well as the treatment modality and time of treatment.

Quality of life assessment

HRQOL was assessed with the SF-36 questionnaire, which is a standardized, nondisease specific questionnaire frequently used in HRQOL evaluation. The questionnaire consists of 36 questions that can be transformed into eight domains covering both physical and mental aspects of HRQOL. The physical domains are *Physical functioning*, *Role limitation due to (RLDT) physical functioning*, *Bodily pain*, and *General health*. The mental domains are *Social functioning*, *RLDT emotional problems*, *Mental health*, and *Vitality*. SF-36 data were recoded to create raw-scale scores for each domain and then transformed into scores in a 0-100 scale, as described by Ware.[16] A higher score indicates better quality of life. SF-36 data collected in 2011-2012 (T0) were available for all patients and were compared with SF-36 data from the same patient group obtained in 2019-2020 (T1).

Possible predictive factors

The following categorical variables were analyzed to assess possible association with change in SF-36 score: *Treatment* - whether or not the patient received invasive treatment in the observation period (invasively treated vs. untreated or conservatively treated). *Tissue involvement* - which tissue types were affected by the malformation (muscle/bone vs. subcutis). *Anatomical location* - in which anatomical region the malformation was located (head and neck vs. trunk or extremities) and gender (male vs. female). Furthermore, *age* was included in the analyses as a continuous variable.

Statistical methods

Continuous data are described with median and range, while categorical data are described with counts and percentages. To compare groups, we used Fisher's exact test for categorical data and the Mann-Whitney U test for continuous data. To assess possible changes in SF-36 scores between T0 and T1, we fitted linear mixed models for repeated measures for each domain. To assess possible associations between selected variables (invasive treatment, tissue involvement, anatomical location, gender, and age) and change in SF-36 scores, we fitted multiple linear regression models including the variables listed above. Further, multiple linear regression models were fitted to assess differences in baseline SF-36 scores between treated and nontreated patients. The results of the linear regression analyses are expressed as regression coefficients (B) with 95% confidence intervals (CI). Confidence intervals were constructed using bootstrapping with 10000 repetitions. All analyses were considered exploratory, so no correction for multiple testing was done. *P*-values <0.05 were considered statistically significant. All analyses were conducted using SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

Results

Demographic and clinical characteristics of the patient cohort are presented in Table 1. In total, we analyzed 111 patients at T0, of which 47 patients (42.3%) were males. Median age at T0 was 27.0 years (range 14-63), and 96 (86.5%) patients were diagnosed with venous malformations. Our data did not reveal any statistically significant differences in clinical and demographic characteristics between patients who responded to follow-up at T1 ($n = 80$) and the patients who did not respond ($n = 31$) (see appendix).

Of the 80 patients who responded to follow-up, 58 patients (72.5%) received invasive treatment between T0 and T1. A total of 22 patients (27.5%) were either untreated or treated with conservative methods like compression garments and pain medication. No patients in either group received Sirolimus in the observation period.

HRQOL change between T0 and T1

In Table 2, we present the results from univariate analyses showing the estimated mean SF-36 scores of the patient cohort at T0 and T1. All analyses were run separately for each SF-36 domain. Significantly higher SF-36 scores at T1 compared to T0 were found for the physical domains *RLDT physical problems* (B = 13.5; 95% CI [1.6, 25.3]) and *Bodily pain* (B = 11.3; 95% CI [3.8, 18.8]). In these domains, stratified analyses of invasively treated and conservatively-/untreated patients showed significantly higher SF-36 scores at T1 compared to T0 only for the invasively treated group, though we observed a trend toward higher scores also in the conservatively-/untreated group.

In multivariate analyses, we assessed whether selected variables were associated with changes of SF-36 scores (see Table 3). For physical functioning, there was a significant difference between genders, with females scoring on average almost 13 points higher than males (B = 12.8; 95% CI [6.0, 19.8]) at T1 compared to T0. For RLDT physical problems, patients with muscle/bone involvement scored on average almost 20 points higher than patients with subcutaneous lesions (B = 19.8; 95% CI [1.4, 39.6]) at T1 compared to T0. Moreover, for RLDT emotional problems, higher patient age was significantly associated with higher scores at T1 compared to T0. No statistically significant differences were found between invasively treated patients and conservatively-/untreated patients.

Baseline differences between treated and nontreated patients

In a multivariate analysis assessing SF-36 scores at T0 and adjusted for age and gender, patients who were invasively treated in the observation period scored significantly lower than conservatively-/untreated patients in all domains (see Table 4). The most pronounced differences were observed in *RLDT physical problems* (B = -24.7; 95% CI [-40.7, -7.8]),

Table 1 Clinical and demographic characteristics of the patient cohort at baseline (T0) and follow-up (T1).

		Baseline (T0) ($n = 111$)	Follow-up (T1) ($n = 80$)
Median age (range)		27 years (14-63)	36.5 years (21-71)
Gender (%)	Males	47 (42.3)	14 (45.2)
	Females	64 (57.7)	17 (54.8)
Diagnosis (%)	Venous malformation	96 (86.5)	68 (85.0)
	Arteriovenous malformation	9 (8.1)	8 (10.0)
	Arteriolo/Capillary-Venous malformation	4 (3.6)	3 (3.8)
	Lymphatic-venous malformation	1 (0.9)	1 (1.3)
	Lymphatic malformation	1 (0.9)	0 (0)
Anatomical region (%)	Head and neck region	27 (24.3)	20 (25.0)
	Upper extremity	22 (19.8)	15 (18.8)
	Trunk	11 (9.9)	9 (11.3)
	Lower extremity	51 (45.9)	36 (45.0)
Tissue involvement (%)	Subcutis	37 (33.3)	24 (30.0)
	Muscle	30 (27.0)	21 (26.3)
	Bone	1 (0.9)	0 (0)
	Subcutis and muscle	35 (31.5)	31 (38.8)
	Subcutis, muscular and bone	7 (6.3)	4 (5.0)
	Subcutis, muscular and internal organs	1 (0.9)	0(0)
Treatment (%)	Sclerotherapy	63 (56.8)	41 (51.2)
	Embolization	5 (4.5)	4 (5.0)
	Sclerotherapy and embolization	2 (1.8)	2 (2.5)
	Surgery	7 (6.3)	5 (6.3)
	Sclerotherapy and surgery	6 (5.4)	6 (7.5)
	Conservatively-/untreated	28 (25.2)	22 (27.5)

RLDT emotional problems (B = -22.7; 95% CI [-33.3, -12.3]), and *Bodily pain* (B = -15.9; 95% CI [-26.0, -5.8]).

Discussion

In the present study, we assessed long-term HRQOL changes in a cohort of vascular malformation patients who were referred to a national treatment center at the age of 14 years and above at the time of diagnosis. Our main finding was that mean SF-36 scores were significantly higher at follow-up than at baseline for the physical domains *RLDT physical problems* (B = 13.5; 95% CI [1.6, 25.3]) and *Bodily pain* (B = 11.3; 95% CI [3.8, 18.8]) (Table 2), implying that certain physical aspects of HRQOL may improve over time in patients with these chronic conditions. This finding, together with the fact that no significant deterioration of HRQOL was found for any domains, is valuable knowledge concerning the long-term prognosis for patients with vascular malformations.

A stratified, univariate analysis of long-term change in SF-36 scores showed significant improvement over time in invasively treated patients in *RLDT physical problems* and *Bodily pain* (Table 2). However, in multivariate analyses (Table 3), no significant association between invasive treatment and HRQOL change could be confirmed. Hence, there may be several other factors affecting HRQOL change, and it should be emphasized that although our study provides follow-up data on invasively treated patients, it was not designed to assess treatment outcome; the time interval from treatment to follow-up assessment varied substantially, and the group of invasively treated patients was heterogenic, both regarding treatment methods and type of diagnosis. Moreover, baseline SF-36 scores of patients who received invasive treatment in the observation period were significantly lower than scores in conservatively-/untreated patients in all domains (Table 4). Therefore, it is likely that HRQOL impairment was emphasized in treatment decision making, and that such patients were selected for invasive treatment. In a long-term perspective, patients with low SF-36 scores at baseline may be likely to improve their scores relatively more than patients with higher baseline scores, which may have facilitated the significant improvement observed in invasively treated patients. Improved long-term HRQOL in patients with chronic conditions like vascular malformations may also reflect better disease acceptance and increased ability to handle pain and physical challenges over time. This may explain the trend toward higher follow-up scores also in conservatively/nontreated patients, and it should be emphasized that the lack of significant improvement in this group might have been due to few patients and limited statistical power.

Although the improvement of SF-36 scores was statistically significant in two of the physical domains, the clinical impact of this finding remains uncertain. In patients with vascular malformations, no consensus has been reached regarding “cut-off” values for differences in SF-36 scores that reflect a clinically relevant change. However, for other pa-

Table 2 Mixed model analysis shows marginal mean SF-36 scores (95% CI) at T0 and at T1, including stratified analysis of treated and untreated patients. Estimated differences between T0 and T1 (95% CI).

Domain	T0 ($n = 111$)	T1 ($n = 80$)	Difference (95% CI)
Physical functioning	79.8 (75.8, 83.9)	84.4 (79.8, 89.0)	4.6 (-1.5, 10.7)
Invasively treated	77.7 (72.6, 82.7)	82.0 (76.1, 87.9)	4.3 (-3.4, 12.0)
Conservatively-/untreated	86.3 (80.6, 91.9)	90.7 (84.4, 96.9)	4.4 (-3.8, 12.6)
Social functioning	79.3 (74.4, 84.1)	82.2 (76.7, 87.7)	3.1 (-4.7, 10.9)
Invasively treated	76.5 (70.5, 82.6)	77.2 (70.2, 84.2)	0.6 (-8.5, 9.8)
Conservatively-/untreated	87.5 (80.5, 94.5)	95.5 (91.1, 99.8)	8.0 (-0.1, 16.0)
RLDT physical problems	58.1 (50.0, 66.2)	71.6 (62.8, 80.4)	**13.5 (1.6, 25.3)***
Invasively treated	52.1 (42.5, 61.7)	67.7 (57.1, 78.3)	**15.6 (1.4, 29.7)***
Conservatively-/untreated	75.9 (62.1, 89.7)	81.8 (65.7, 97.9)	5.9 (-14.8, 26.6)
RLDT emotional problems	76.3 (69.0, 83.6)	75.4 (67.3, 83.6)	-0.9 (-11.7, 10.0)
Invasively treated	70.7 (61.4, 79.9)	67.8 (57.4, 78.2)	-2.9 (-16.7, 10.9)
Conservatively-/untreated	92.9 (86.4, 99.3)	95.5 (88.5, 102.3)	2.6 (-6.6, 11.8)
Mental health	75.2 (71.6, 78.7)	75.7 (72.7, 78.7)	0.5 (-4.1, 5.1)
Invasively treated	72.6 (68.3, 77.0)	74.5 (71.0, 78.1)	1.9 (-3.7, 7.5)
Conservatively-/untreated	82.7 (77.4, 88.0)	78.7 (73.0, 84.5)	-4.0 (-11.6, 3.6)
Vitality	52.4 (48.7, 56.1)	51.0 (46.4, 55.6)	1.4 (-7.2, 4.5)
Invasively treated	49.0 (44.9, 53.2)	47.6 (42.2, 53.1)	-1.4 (-8.2, 5.4)
Conservatively-/untreated	62.3 (55.0, 69.6)	59.8 (52.0, 67.6)	-2.5 (-13.0, 7.9)
Bodily Pain	56.4 (51.6, 61.2)	67.7 (62.0, 73.5)	**11.3 (3.8, 18.8)***
Invasively treated	52.4 (46.8, 58.1)	64.1 (57.1, 71.0)	**11.7 (2.8, 21.8)***
Conservatively-/untreated	68.2 (59.8, 76.6)	77.4 (67.5, 87.2)	9.2 (-3.5, 21.8)
General health	68.3 (63.7, 72.9)	68.7 (63.6, 73.9)	0.4 (-6.4, 7.3)
Invasively treated	65.3 (59.8, 70.8)	65.7 (59.6, 71.8)	0.4 (-7.7, 8.5)
Conservatively-/untreated	77.1 (69.5, 84.8)	76.6 (66.6, 86.6)	0.6 (-12.8, 11.7)

* significant difference between T0 and T1. RLDT= Role limitation due to.

Table 3 Multivariate linear regression analysis shows association between selected variables and change of SF-score between T0 and T1. Regression coefficient (B) with 95% confidence interval.

	Physical functioning	Social functioning	RLTD physical problems	RLTD emotional problems	Mental health	Vitality	Bodily Pain	General health
Age Years	-0.1 (-0.3, -0.2)	-0.1 (-0.5, 0.4)	0.0 (-0.7, 0.7)	**0.7* (0.0, 1.4)**	0.0 (-0.3, 0.3)	0.0 (-0.4, 0.4)	-0.1 (-0.6, 0.4)	0.2 (-0.2, 0.6)
Gender Female vs. Male	**12.8 (6.0, 19.8)***	8.7 (-2.5, 20.5)	6.6 (-14.6, 27.2)	12.7 (-4.2, 29.3)	1.1 (-7.7, 9.1)	-0.4 (-10.2, 10.6)	9.0 (-4.1, 21.7)	7.6 (-1.7, 17.1)
Treatment Invasively treated vs. Conservatively-/untreated	-2.4 (-10.6, 5.1)	-7.7 (-18.8, 4.0)	21.8 (-0.8, 45.9)	-5.3 (-20.1, 11.1)	4.5 (-3.6, 13.1)	1.3 (-8.9, 11.6)	7.2 (-7.3, 21.7)	-0.6 (-9.8, 8.6)
Tissue Muscle/bone vs. Subcutis	5.4 (-1.9, 12.4)	-2.3 (-13.3, 8.7)	**19.8 (1.4, 39.6)***	-5.9 (-21.7, 10.4)	3.1 (-12.6, 6.0)	-1.9 (-14.5, 10.2)	7.7 (-5.3, 20.9)	2.1 (-8.2, 12.2)
Anatomical location Trunk and extremities vs. head and neck	-2.6 (-11.2, 6.6)	0.1 (-14.1, 16.4)	11.9 (-14.2, 37.0)	5.1 (-15.7, 26.4)	-8.6 (-22.4, 4.2)	-3.1 (-20.0, 12.8)	6.9 (-10.7, 24.5)	3.5 (-10.8, 18.3)

* = significant difference between groups.

Table 4 Multivariate linear regression analysis, adjusted for age and gender, shows differences in SF-36 scores at T0 between invasively treated patients and conservatively-/untreated patients. Regression coefficients (B) with 95% confidence intervals.

Domain	Regression-coefficient B (95% CI)
Physical functioning	**-8.8 (-16.5, -1.1)***
Social functioning	**-11.4 (-20.5, -2.1)***
RLDT physical prob	**-24.7 (-40.7, -7.8)***
RLDT emotional prob	**-22.7 (-33.3, -12.3)***
Mental health	**-10.4 (-17.2, -3.5)***
Vitality	**-13.2 (-21.4, -4.8)***
Bodily Pain	**-15.9 (-26.0, -5.8)***
General health	**-12.0 (-20.2, -3.6)***

RLDT= Role limitation due to.
* Significant difference between groups.

tient groups, several studies have attempted to identify so-called minimally clinically important differences (MCIDs) for SF-36, which are interpreted as the smallest change of SF-36 score that may be perceived by the patients as meaningful. In a study by Ogura et al., they included 310 patients with orthopaedic oncologic conditions who were treated surgically.[17] They estimated that a difference of 5 points in the physical and mental component summary scores most likely would be perceived as meaningful by patients after the treatment. Ward et al. studied 243 patients with active rheumatoid arthritis who underwent treatment.[18] MCID was estimated to 7.1 for *Physical functioning* and 4.9 for *Bodily pain*. The other domains had low responsiveness. In a study by McElhone et al., they included 101 patients with systemic lupus erythematosus.[19] For improvement, they found a MCID of 3.8 for *Physical functioning*, 10.8 for *RLDT physical problems*, 10.9 for *Bodily pain*, and 2.8 for *General health*. The patients in these studies are not directly comparable to our patient population. However, it seems that a difference in SF-36 score greater than 10 points in the physical domains may indicate a clinically relevant change. Hence, we hypothesize that the significantly improved SF-36 scores in *RLDT physical problems* and *Bodily pain* in our material have clinical relevance.

According to our data, no significant deterioration of long-term HRQOL could be confirmed in any domains. It should be emphasized that the median age of the patient cohort was 27 years at the time of diagnosis and baseline HRQOL evaluation, and accordingly, our results are not applicable to patients who present with vascular malformations in childhood. In fact, there is evidence that both VMs and AVMs tend to progress symptomatically during childhood and adolescence; Liu et al.[20] evaluated 272 patients with AVMs and observed a high risk of progression both in childhood and adolescence. Hassanein et al.[4] reported on the risk of symptom progression during childhood and adolescence in patients with untreated VMs. In 475 patients, the risk of progression was 26.1% in childhood, 74.9% during childhood and adolescence and 93.2% through adulthood. The relative risk of progression in adolescence compared to childhood was 2.6, which may be explained by pubertal hormones affecting VM progression. Interestingly, pregnancy was not associated with increased risk of progression in any of the above-mentioned studies. Even though the authors did not report on HRQOL, the results imply that patients with AVMs and VMs presenting in childhood have unfavorable long-term prognosis.

To the best of our knowledge, there are no previously published observational studies evaluating long-term HRQOL in a cohort of both invasively treated and conservatively-/untreated patients with vascular malformations. In the recent years, however, an increasing number of studies have used HRQOL as an outcome measure, recognizing that patient perceived health change is essential when evaluating treatment outcome in benign conditions like vascular malformations. Horbach et al.[21] evaluated HRQOL in 77 adult patients after Bleomycin sclerotherapy with a median follow-up time of 22 months. They found significantly higher SF-scores after treatment in the physical domains *Physical functioning, RLDT physical problems, Bodily pain*, and in the mental domains *Social functioning* and *Mental health*. The study was limited by retrospective evaluation of pretreatment HRQOL, which provided unreliable baseline measures. In a prospective study by Ono et al.[22], HRQOL was assessed in 28 patients with VMs, before and up to 12 months after sclerotherapy. Mean age was 25.3 years. Deep tissues like muscles or bone were involved in 22/28 malformations. Significant improvement was found in *Bodily pain* at 12 months post treatment, and in *RLDT physical functioning* significantly improved 6 months post treatment. The higher follow-up SF-36 scores of treated patients in the physical domains are in line with the results of our study, though the follow-up time in these studies was considerably shorter. In a study by Linden et al.[23], clinical outcome after endovascular treatment was retrospectively assessed in 66 adult patients with vascular malformations. Clinical success, defined as a partial or complete relief of symptoms, was reported in 49% at 1 year follow-up, decreasing to 42% at 5-year follow-up period. Although no HRQOL data were available, the study implies that a considerable proportion of invasively treated patients has favorable long-term outcome for up to 5 five years. However, major limitations of Linden's study were the retrospective evaluation of pretreatment status, as well as nonstandardized evaluation methods. Although there is an increased focus on HRQOL, we have not been able to find studies evaluating long-term HRQOL of nontreated or conservatively treated patients. Furthermore, prospective long-term HRQOL follow-up stud-

ies after treatment seem to be lacking. Such studies are needed in the future to determine the impact of invasive treatment on HRQOL.

Strengths and limitations

Long-term HRQOL data on patients with vascular malformations are currently sparse. The present study, with an observation time of almost eight years in both invasively treated and conservatively-/untreated patients, and with a prospective design, adds new knowledge about how the clinical course impacts on HRQOL in the long term. However, there are several limitations to our study. Firstly, our statistical models yielded large CIs for most of the domains, which may be explained by the relatively small patient cohort, as well as a considerable variation in our data. A larger sample size would have been desirable to provide more precise statistical estimates. Secondly, to evaluate change in HRQOL in patients with vascular malformations, better instruments than the SF-36 questionnaire may exist. The *Outcome measures for Vascular malformation* (OVAMA) project aims to develop a standardized strategy for treatment evaluation[24] and has recently launched a condition specific questionnaire for patients with vascular malformation, the so-called OVAMA questionnaire.[25] The group has stated that SF-36 may be unresponsive to change in HRQOL in patients with vascular malformations. This was based on a systematic evaluation of the SF-36 questionnaire, and they propose that alternative PROMs are needed to measure HRQOL.[26] The patient-reported outcome measurement informative system (PROMIS) may be a better option, which should be taken into consideration in future studies regarding HRQOL in this patient group.

However, for the time being, SF-36 is one of the most widely used instruments and with the long observation time, we believe that SF-36 is adequate for the purpose of this study.

Conclusion

In this prospective observational study assessing HRQOL changes in patients with vascular malformations over a period of almost eight years, we found significantly higher SF-36 scores at follow-up for the physical domains *Role limitation due to (*RLDT) physical problems and Bodily pain, implying that certain physical aspects of HRQOL may improve over time. Significant improvement was observed in invasively treated patients who had lower baseline SF-36 scores than conservatively/-untreated patients. In multivariate analyses, however, only female gender, muscle/bone involvement, and age were associated with long-term SF-36 change in certain domains. The study was limited by a relatively small sample size, and there are reports indicating that SF-36 may be unresponsive to changes in HRQOL in this patient group. However, we think the results add knowledge regarding long-term prognosis in both invasively treated and conservatively-/untreated patients.

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There were no sponsors involved in this study.

Ethical approval

Ethical Approval was given by the Regional ethical committee in Norway, dated 06.11.2019. Reference number 33673.

Declaration of Competing Interest

None of the authors have conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.bjps.2022.10.024.

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