Quality of life and mental health of patients with vascular malformations in a single specialist center in the United Kingdom

Short title: Quality of life in patients with vascular malformations

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ARTICLE HIGHLIGHTS

Type of Research: Single center observational study

Key Findings: Validated health-related quality of life questionnaires: RAND Health Care 36-Item Short Form Survey, hospital anxiety and depression scale, and visual analogue score for pain was analyzed in 253 patients with vascular malformations. Patients with vascular malformations reported significantly poorer quality of life compared with the UK general population. However, there were little variations between patients with low-flow vascular malformations and arteriovenous malformations.

Take home Message: Patients with vascular malformations have poorer quality of life than the UK general population. Therefore, the assessment and management of quality of life and mental health should be incorporated into the overall treatment strategies.

Table of Contents Summary

Patients with vascular malformations reported poorer quality of life compared to the UK general population in this prospective study of 253 patients. Assessment and management of quality of life and mental health should be incorporated into the overall treatment strategies.

ABSTRACT

Objective

Patients with vascular malformations suffer from chronic debilitating symptoms that have been shown to contribute negatively to their quality of life (QoL) and mental health. Despite this, the current literature evaluating the QoL and mental health of patients with vascular malformations remains scarce. The aim was to evaluate the QoL and mental health of patients with vascular malformations.

Methods

We prospectively analyzed the validated health-related QoL (HRQoL) questionnaires; RAND Health Care 36-Item Short Form Survey (SF-36), hospital anxiety and depression scale (HADS), and visual analogue score for pain (VAS-P) reported by 253 patients with vascular malformations in a specialist center of vascular anomalies in the UK over two years.

Results

Patients with vascular malformations reported significantly poorer SF-36 scores in all domains compared to the UK general population. Patients with low-flow vascular malformations, and arteriovenous malformations reported little variations in SF-36, HADS and VAS-P scores. No significant association was found between age, and any of the HRQoL scores other than the physical functioning in SF-36. Female patients reported significantly lower physical and social functioning of SF-36, and worse HADS-Depression than their male counterparts. Patients with syndromic vascular malformations reported significantly lower SF-36 scores in role–physical, role–emotional and bodily pain than non-syndromic vascular malformations.

Conclusions

This study concluded that patients with vascular malformations reported worse QoL than the UK general population. Therefore, the assessment and management of QoL and mental health should be incorporated into the overall treatment strategies of patients with vascular malformations.

Keywords

Quality of life, Mental health, Patient outcome assessment, Vascular malformations, Arteriovenous malformations

Conflicts of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Vascular malformations are lesions derived from aberrant embryonic development of vascular channels and feature dysplastic abnormally formed vessels, which may not be apparent at birth.[1,2] Patients with vascular malformations have been shown to be affected psychosocially, with significant poorer quality of life (QoL) reported when compared with the general population.[3] The poor QoL and mental health among vascular malformation patients is not only attributable to the physical symptoms but may be contributed by the challenges in the diagnosis hence leading to delays and uncertainties, and treatments with limited efficacy and prognosis.[3]

Early studies on QoL in patients with vascular malformations have been conducted using non-validated assessment tools.[4-6] More recent studies have used validated assessment tools, which offer further insightful understanding of the QoL of patients with vascular malformations, although the overall literature remains scarce and limited to relatively small studies.[3,7-15] Increased understanding and awareness of the importance of the QoL and mental health of these patients will help clinicians to provide and improve on a more holistic management[16] by taking into account mental and social factors when treating patients, rather than just focusing on the symptoms of the disease. Furthermore, QoL formed one of the core outcome domains for clinical research on peripheral vascular malformations in the recent consensus reached by the Outcome Measures for Vascular Malformations (OVAMA).[17] Therefore, the aim of this study was to evaluate the QoL, pain, anxiety and depression scores using validated questionnaires that were not disease specific for patients with vascular malformations, and to identify potential patient factors including age, gender, and anatomical location and subtypes of the vascular malformations that might be associated with poor scores in a single specialist center for vascular anomalies in United Kingdom (UK). These

questionnaires were administered during patient's ongoing evaluation and treatment therefore providing an overall snapshot of the QoL in patients with vascular malformations. To the best of our knowledge, this is the first QoL study for patients with vascular malformations in the UK. This is important in understanding how vascular malformation affects QoL of patients of different population or countries.

Methods

Study participants and design

This was a prospective two-year observational study of patients with vascular malformations cared for by a multi-disciplinary specialist center for vascular anomalies. All the patients who attend our out-patient clinics are routinely assessed for health-related QoL (HRQoL), pain, and anxiety and depression scores with validated questionnaires that are filled in by paper. At the time of filling out the questionnaires some patients maybe taking concomitant medication such as analgesia or anxiolytics which we did not alter for the study, and it was unknown whether these medications are for other co-morbidities or related to the vascular malformation. This study was approved by the local clinical audit and governance committee and informed consent was gained.

All patients who attended the out-patient clinics between February 1st 2018 and January 31st 2020 were recruited provided they fulfilled the following inclusion and exclusion criteria.

Inclusion criteria:

- Male and female of age 16 years old and above.
- Patients with a clinical and/or radiological (duplex ultrasonography and MRI and/or CT) diagnosis of vascular malformation.

Exclusion criteria:

- Patients under the age of 16. This age cut-off was chosen because RAND Health Care designed the Short Form 36 health survey questionnaire to include people aged 16 and over. In addition, patients younger than 16 years may be unable to fully understand and answer the questions listed in the questionnaires.[18]
- Any patients whose vascular malformation involved the central nervous system.
- Patients who declined to answer or were unable to fill in the study questionnaires; e.g. patients with limited understanding of English, learning disability and blindness.

Data collection and analysis

Patient demography, clinical data including the anatomical locations and types of vascular malformation, pain score, and HRQoL, anxiety and depression scores were analyzed. For subgroup analysis, the anatomical locations were divided into "head and neck (H&N)", "torso" which included thorax, abdomen and pelvis, "upper limbs", and "lower limbs", while the types were classified as "arteriovenous malformations (AVM)" and "low-flow vascular malformations" (LFVM). LFVM was defined as lesions that consist of either veins, capillaries, lymphatics or a combination, without any arterial component. The vascular malformations were also further subdivided into "non-syndromic" (isolated) and "syndromic".

HRQoL assessments

RAND Health Care 36-Item Short Form Survey (SF-36)

The SF-36 measures eight scales: physical functioning, role–physical, bodily pain, general health, vitality, social functioning, role–emotional, and mental health. Scoring was calculated using the recommended guidelines from the RAND Health Care.[18,19] Briefly, all 36 items

were scored on a 0 to 100 range. Then items in the same scale were averaged together to create the eight scale scores. The SF-36 scores of the patients with vascular malformation were then compared with the UK general population norms (n=2056) which were obtained from the UK Office of National Statistics Omnibus Survey, archived by the University of Essex.[20,21] This reference population represented a random sample of the population in Great Britain aged 16 and over who were interviewed at home.[20, 21]

Visual analogue score for pain (VAS-P)

Pain was assessed using the VAS-P. The score was determined by measuring on the 100 mm line between 'no pain' and the patient's mark, providing a range of scores from 0 - 100. A higher score indicated greater pain intensity. Jensen *et al* showed that the VAS-P scores could be correlated to and categorized according to pain intensity in post-surgical patients, where 0 - 4 mm correlated to no pain, 5 - 44 mm was mild pain, 45 - 74 mm was moderate pain and 75 - 100 mm was severe pain.[22]

Hospital Anxiety and Depression Scale (HADS)

Anxiety and depression were assessed using the HADS. The questionnaire was comprised of seven questions for anxiety (HADS-Anxiety) and seven questions for depression (HADS-Depression), which were rated on a four-point (0 - 3) Likert scale. A total of 21 points for each section with cut-off scores available for quantification i.e. ≥8 points was defined as clinically relevant for both anxiety and depression. The HADS questionnaire had been validated in many countries and settings.[23-25] It was one of the National Institute for Health and Care Excellence (NICE) recommended tools for diagnosis of anxiety and depression.[26]

Handling of missing items in SF-36 and HADS

Not all patients filled the SF-36 and HADS questionnaires completely leading to missing items. Our handling of missing items within the SF-36 questionnaire in this study followed the SF-36 manual. The manual suggested that missing items could be estimated by item mean imputation if respondent answered at least half of the items in a multi-item scale. If more than half of the items were missing, then the scale could not be calculated and would be regarded as missing.[27, 28] A total of 52 (20.6%) questionnaires were incompletely filled but the missing responses were random. Meanwhile, our handling missing items in the HADS were accounted for by applying the 'half rule' using individual subscale means.[29]

Statistical analysis

All statistical analysis was performed using StataCorp2017 (*Stata Statistical Software: Release 15*. College Station, TX: StataCorp LLC). The main outcome measures were variables of SF-36, HADS and VAS-P scores; all of which were measured on a continuous scale. The outcome measures were analyzed and compared between different groups of subjects; firstly, between all the study patients with vascular malformations and UK reference population norms, and then within their subgroups including age, sex, anatomical locations, and types. Our initial analyses compared the demographic characteristics of the two groups. The one continuous demographic variable i.e. age was found to have a skewed distribution; therefore, was compared between groups using the Mann-Whitney test. Categorical variables were compared between groups using the Chi-square test or Fisher's exact test when there were small numbers. Subsequently, the QoL outcomes were compared between subgroups. For each analysis, two sets of comparisons were made; namely 1) unadjusted comparison, and 2) adjusted for demographic characteristics i.e. age and sex. QoL outcomes were analyzed using quantile regression; also referred as least–absolute-value models – LAV.

Specifically, the median QoL was modelled, and compared between the groups of subjects. The exception to this method of analysis was for outcomes (role–physical and role–emotional) with a large proportion of outcome values with the same value. For these outcomes, the Mann-Whitney test was used for a simple unadjusted analysis, with no adjusted analysis performed for these outcomes. $P<0.05$ were considered significant.

Results

Patient demography and types of vascular malformation

Table 1 summarizes the demographic characteristics of the patients with vascular malformations recruited, in comparison with the UK general population, and within different subgroups of the study population. In total, 253 patients with vascular malformations were recruited, which were significantly younger, and with higher percentage of females. Significant difference in the anatomical location was also demonstrated between the non-syndromic and syndromic vascular malformation patient subgroup because the majority of the patients in the latter subgroup had Klippel-Trenaunay Syndrome, a condition that affected the lower limb. No other significant differences were noted. Figure 1. summarizes the breakdowns of the types of vascular malformations in the patient population in this study.

Only two patients did not complete the SF-36, twenty patients did not complete the HADS and eleven patients did not complete the VAS-P. The remaining questionnaires were either all completed or completed to an extent that allowed for handling of missing items as described above.

Patients with vascular malformations versus UK general population

Table 2. compares the SF-36 scores between the patients with vascular malformations and the UK general population.[20, 21] Patients with vascular malformations reported significantly poorer SF-36 scores in all domains, even after adjusting for the age and sex. The difference was largest for the pain outcome, with the median scores over 20 units lower in patients with vascular malformations.

The median (range) scores for HADS-Anxiety and HADS-Depression were 6 (range 0-21) and 3 (range 0-18), respectively; both did not amount to a clinical diagnosis of anxiety or depression. Meanwhile, the patients with vascular malformation reported the median (range) VAS-P score of 17 (range 0-100) which correlated with mild pain in post-surgical patients.

a. LFVM *versus* AVM

Table 3 compares the SF-36, HADS and VAS-P scores between patients with LFVM and AVM. Patients with LFVM, and those with AVM did not differ significantly in terms of SF-36, HADS and VAS-P scores; other than general health in SF-36 which became statistically not significant after adjusting for the demographics of the two groups. This is not surprising considering this was a snapshot study of the QoL, and would be expected to differ if this was a longitudinal study. For both LFVM and AVM patient groups, the median HADS score did not suggest any clinical diagnosis of either anxiety or depression, while the median VAS-P score corresponded to mild pain in post-surgical patients.

b. Sex

Table 4 summarizes the SF-36, HADS and VAS-P scores of male and female patients with vascular malformations. Female patients reported significantly lower physical and social functioning scores when compared with their male counterparts. Conversely, the HADS-

Depression scores were significantly higher in female than male patients. There were no other significant differences found in the rest of the SF-36 domains, HADS-Anxiety and VAS-P between female than male patients.

c. Age

Table 5 summarizes the effect of age on the SF-36, HADS and VAS-P scores of patients with vascular malformations. No significant association was found between age, and any of the SF-36, HADS and VAS-P scores other than the physical functioning in SF-36 which was significantly associated with patient age. Older patients with vascular malformations had lower scores. A 10-year increase in age was associated with a 4-point reduction in physical functioning scores. One possible explanation to this is older patients had less ability to compensate their physical symptoms, hence functioning when compared to younger individuals.

d. Non-syndromic *versus* syndromic vascular malformation

Table 6 compares the SF-36, HADS and VAS-P scores between the patients with non-syndromic and syndromic vascular malformation. After adjusting for the demographic differences, patients with syndromic vascular malformation reported significantly poorer SF-36 scores in role–physical, role–emotional and bodily pain domains when compared with those with non-syndromic vascular malformation. No significant differences in HADS and VAS-P scores were found between the two groups after adjusting for the patient demographic variations.

Discussion

This study provided a snapshot of the QoL and mental health, measured with SF-36, VAS-P and HADS of patients with vascular malformations. We did not collect any longitudinal or pre- or post-treatment data as this study was only to establish a baseline QoL. However, in our future studies we aim to collect longitudinal data to allow the assessment for the effects of the natural history or progression of the condition and the potential modifying factors including various treatment modalities, trauma and hormonal changes in relation to the QoL and mental health. Overall, patients with vascular malformations reported significantly lower QoL, hence poorer median SF-36 scores in all domains than the UK general population even after adjusted for age and sex. The median score of the HADS did not amount to a clinical diagnosis of either anxiety or depression. However, the median score was the same for both anxiety and depression when compared with the reference population. Meanwhile, the median VAS-P score of patients with vascular malformations was 17 which corresponded with "mild pain in post-surgical patients", and it ranged from no pain (0) to the maximum pain (100) the scale could measure. Unfortunately, we were not able to compare the HADS and VAS-P scores of the study patient population with the UK general population norms since the raw data from recent HADS study that was required for statistical analysis was not readily available to us.[30] A relatively old study reported the median score for HADS-Anxiety and HADS-Depression of the general adult population in the UK was 6 and 3, respectively.[30] However, it was likely that the patients with vascular malformations reported poorer mental health status as supported by their lower scores in the mental health and related domains in SF-36 when compared with the UK general population in this study.

Our results were consistent with the current literature that revealed an overall lower QoL in patients with vascular malformations when compared with their respective general

population.[20,21] Berger *et al.* [31] assessed the QoL of 111 patients with vascular malformations outside the central nervous system in comparison with the Norwegian population. The study reported lower mean SF-36 scores in all domains in the patient cohort, but no difference between the low-flow and high-flow vascular malformation, and among anatomical locations. This could be attributed to the small number of patients with high-flow lesions (n=9) compared to low-flow lesions (n=102). The comparison between head & neck and trunk/extremities vascular malformations did not show any difference in QoL could be because of the evaluation of one anatomical location with the rest of the body and that factors specific to the head & neck such as sleeping disturbance was not assessed. Durr *et al* found lower QoL and higher incidence of sleeping disorders in patients with head & neck vascular malformations compared with vascular malformations in other locations. However, it should be noted that this study was conducted in a pediatric population.[8] In addition, the difference in underlying molecular pathogenesis and biological processes that causes different inflammatory processes for subtypes of vascular malformations could account for the indifference. For example, recurrent thrombosis in venous malformation; recurrent infection in lymphatic malformation, and ischemia from steal phenomenon in AVM. Finally, vascular malformations of different anatomical location might affect the QoL and mental health differently, for example, in different domains of the SF-36 but with a similar overall score. Meanwhile, Fahrni *et al.*[3] assessed the QoL of 71 patients with vascular malformations outside the central nervous system using the SF-36, HADS, patient health questionnaire-15, and the pain disability index. The study demonstrated lower physical and mental summary scores in the patient cohort than in the German reference population while no differences were observed between the subtypes of vascular malformations. The latter may be due to the small sample size for the subtypes of vascular malformations therefore not demonstrating any statistical significance. In addition, due to the heterogenicity of the disease the wide spectrum of severity in signs and symptoms

amongst the subtypes may not be accounted for. Nguyen *et al.*[16] conducted a meta-analysis that consisted of six studies with a total of 320 patients. The results demonstrated patients with vascular malformations had higher bodily pain and mental stress when compared with the United States population. A study by England *et al* noted that pain, pain interference, and physical function were amongst the most important patient outcomes to measure. However, questions related to functional limitations varied depending on location of lesion. Therefore, highlighting the importance of developing a venous malformation location-specific patient report outcome measure that can be used clinically and in research.[32]

This study showed that patients with LFVM suffered just as much as those with AVM in terms of QoL, mental health and pain. This is despite AVM is often considered to be pathologically and clinically more serious than LFVM. Therefore, the psychosocial aspect of patients with LFVM should not be underestimated, and should be considered just as important as those with AVM. Meanwhile, our study also revealed that patients with syndromic vascular malformation have lower SF-36 scores in some of the domains; namely role–physical, role–emotional and bodily pain, than the non-syndromic cohort. This is not surprising as syndromic vascular malformation are typically complex, extensive, and associated with overgrowth and other forms of pathological involvement.[33] Our results are consistent with the existing literature. Oduber *et al*[34] compared the QoL of 78 patients with KTS with the general Dutch population and a selected group of patients with other chronic medical conditions including vascular malformations of the lower extremity, capillary malformations, hereditary hemorrhagic telangiectasia, psoriasis, and neurofibromatosis type 1. The study showed that the patients with KTS scored significantly lower than the general Dutch population in all the SF-36 domains except for the mental health and role–emotional. In addition, the KTS group scored significantly lower than other chronic medical conditions for physical functioning and bodily pain. Harvey *et al*[35] reviewed 410

patients with KTS to identify the presence of pain, psychiatric comorbidities, and psychosocial stressors. The study concluded that pain and psychiatric conditions, particularly depression and anxiety, were common amongst KTS patients.

The SF-36, HADS and VAS-P are non-disease specific validated assessment tools used for measuring HRQoL. It should be noted that the QoL tools used in this study are non-specific, nor validated in patients with congenital vascular malformations. Rather the HRQoL measuring tools used in this were generic and developed for other patient populations. However, the SF-36 was considered a promising measure for the HRQoL of the adult patients as it is well investigated in diseases that are clinically similar to vascular malformations such as vascular or lymphatic diseases and benign tumours.[17] Unfortunately, so far there is still lack of validated disease-specific QoL evaluation tools for vascular malformations, most likely contributed by the heterogeneity of the disorder and poor understanding of their pathophysiology. A recent study conducted by Horbach *et al*.[17] analyzed the suitability of all outcome measurement instruments available for vascular malformations. It was concluded that lymphatic malformation function is the only available disease-specific instrument to assess signs and life impact in pediatric patients with cervicofacial lymphatic malformations. Other instruments used were either generic or developed for other conditions with clinical similarities to vascular malformations. This highlights the importance of developing validated disease-specific questionnaires and outcome measure evaluation tools for patients with vascular malformations. Such validated tools would allow researchers to elicit and compare objective clinical and research information from patients; such as efficacy of therapy which would enable the comparisons between various treatment groups. Therefore, the OVAMA group are currently working on identifying alternative patient reported outcome measurements to measure and ultimately improve QoL in patients with vascular malformations.[36] Future research should focus on improving our

understanding of the risk factors that negatively affect the QoL of patients with vascular malformations, and developing efficacious management strategies that would be incorporated into clinical guidelines.

There were several limitations in this study. Firstly, the relatively small patient sample size might not be sufficient to cover the huge heterogeneity of vascular malformations. For example, patients with different types of vascular malformations particularly those that are rare and associated with various syndromes might not have been captured adequately in this study. There were also relatively few lymphatic malformations, likely because these patients were managed in a nearby major specialist lymphovascular unit. Furthermore, other demographic and patient characteristics such as social class, behavioral lifestyle, marital and relationship status and educational level which were not collected or analyzed in this study might have an impact on the QoL. Moreover, this study did not include detailed genetic classification of the vascular malformations because not all patients in our center received genetic tests. Most vascular malformations are sporadic and usually present as a single lesion, those that are inherited are also observed and may manifest as multiple lesions.[38] Therefore, comparing genetic cases of vascular malformations would provide a more accurate underlying pathogenesis pathway of vascular malformations that may help better delineate the spectrum of signs and symptoms, as well as QoL and mental health. This potentially would allow the identification of environmental factors that contribute to the QoL and psychosocial aspects of the patients, hence improve management. The HRQoL questionnaire assessment was conducted in the out-patient clinic setting compared to a home setting with the reference population. This was a possible cofounding factor but we attempted to control this by providing a relaxed environment and sufficient time when completing the questionnaires. In addition, the QoL tools used in this study were non-specific for patients with congenital vascular malformations and therefore

lacked concept elicitation hence other domains of QoL that are affecting these patients may have been overlooked and not assessed in this study, The reference population used was from 1997 whereas our study was from 2018-2020. The differences in age/sex between groups were accounted for by including them in the regression analysis. However, we were unable to control for the demographic changes from the reference population. Fourthly, with this clinic being a tertiary referral center, the patient cohort may represent a 'worse' cohort and ultimately have a poorer QoL compared to the general population with vascular malformations. Our patient sample population largely represented lesions from early embryonic stage i.e. extratruncular lesions. Meanwhile, patients with truncular lesions, which occurred during later embryogenesis, represented a smaller sample size in this study. These lesions typically result in hypoplasia or dilatation of vascular trunks, and were associated with more serious hemodynamic consequences related to the type of vascular malformation e.g. marginal and embryonic veins in some patients with KTS as truncular vascular malformations[37]. Patients under the age of 16 years were also excluded from the study partly due to the SF-36 and the UK general population reference data used were not designed for and comparable to this age group, respectively. Furthermore, the majority of the patients treated in our service were adults while the children were managed in a similar center in an associated pediatric specialist hospital. However, this particular age group may represent patients who are at high risk of disease progression hence, future studies on QoL and mental health should include children with vascular malformations. Finally, patients with learning disability were excluded from this study but only those who were unable to provide informed consent and/or unable to fill in the questionnaire. This particular subgroup of patients might have provided more insight in determining if congenital malformations were responsible for the learning disability and the subsequent impact on QoL but were excluded for the reasons as discussed above.

Conclusion

This study concluded that patients with vascular malformations reported worse HRQoL when compared with their respective UK general population. Therefore, the assessment and management of QoL and mental health should be incorporated into the overall treatment strategies of patients with vascular malformation. Future research should focus on improving our understanding of the risk factors that negatively affect the QoL of patients with vascular malformations, and developing efficacious management strategies that accounts for these factors and improvement in QoL and incorporate this into clinical guidelines.

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