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Original article

A cross-sectional study of the Birmingham Vasculitis Activity Score version 3 in systemic vasculitis

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Abstract

Objective. Assessment of disease activity in vasculitis can be achieved using the BVAS, a clinical checklist of relevant symptoms, signs and features of active disease. The aim of this study was to revalidate the BVAS version 3 (BVAS v. 3) in a cohort of patients with systemic vasculitis.

Methods. A total of 238 patients with vasculitis from seven countries in Europe were evaluated at a single time point. Spearman's correlation coefficients were calculated between BVAS v. 3 scores, vasculitis activity index (VAI), physician's global assessment (PGA), the physician's treatment decision, CRP and the vasculitis damage index (VDI) to demonstrate that the BVAS v. 3 measures disease activity.

Results. WG (63%), Churg–Strauss syndrome (9%) and microscopic polyangiitis (9%) were the most common diagnoses. The BVAS v. 3 showed convergent validity with the VAI [$\rho = 0.82$ (95% CI 0.77, 0.85)], PGA [$\rho = 0.85$ (95% CI 0.81, 0.88)] and the physician's treatment decision [$\rho = 0.54$ (95% CI 0.44, 0.62)]. There was little or no correlation between BVAS v. 3 and the CRP level [$\rho = 0.18$ (95% CI 0.05, 0.30)] or with the VDI [$\rho = -0.10$ (95% CI 0.22, 0.03)]. The inter-observer reliability was very high with an intra-class correlation coefficient (ICC) of 0.996 (95% CI 0.990, 0.998) for the total BVAS v. 3 score.

Conclusion. The BVAS v. 3 has been evaluated in a large cohort of patients with vasculitis and the important properties of the tool revalidated. This study increases the utility of the BVAS v. 3 in different populations of patients with systemic vasculitis.

Key words: Disease activity, Outcomes research, Systemic vasculitis, Vasculitis, Wegener's granulomatosis.

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Introduction

The vasculitides are a group of complex heterogeneous disorders where multiple organ systems can be involved. The common feature between these diseases is inflammation of blood vessels; usually categorized by the predominant calibre of the vessels involved. Most of the vasculitides can be fatal or organ threatening and require therapy with CSs alone or in combination with more potent immunosuppression.

Disease activity is a well-recognized concept for inflammatory diseases where high disease activity suggests the need to escalate treatment and low disease states indicate that the disease is under control with current therapy. This differs from the concept of damage in vasculitis,

which represents chronic scarring that is not responsive to further therapy [1]. Unfortunately, in systemic vasculitis there is no single biomarker that can reliably inform us about disease activity. Inflammatory markers such as CRP are non-specific and may be raised for multiple other reasons or may be low due to recent steroid treatment. Other assessments such as rising ANCA titres [2], PET scanning [3–5] and MRI have all been proposed as methods of measuring activity but none have yet proved to satisfactorily perform this function [6, 7]. Instead, the current best method of determining disease activity is to use a comprehensive clinical tool that can capture the multi-organ nature of vasculitis [8].

The importance of accurately quantifying disease activity is to allow physicians to make informed decisions about how to manage potentially toxic therapies. The current most widely used generic tool to quantify disease activity in systemic vasculitis is the BVAS [8–10]. The original version was developed by consensus expert opinion in 1994 and consisted of 59 items grouped into nine organ systems [8]. The BVAS was subsequently modified for use in the European Vasculitis Study Group (EUVAS) trials [version (v.) 2] [9] and more recently to the current version: BVAS v. 3 [10]. The main difference between BVAS v. 3 and v. 2 is that the persistent boxes for each variable were replaced by a single box for the whole form, which is only ticked if all the items are due to persistent disease. There was a reduction in the number of items from 64 to 56 by merging or omission, but the overall maximum score was maintained. The weighting of items that was decided by expert consensus in the original version has remained relatively unchanged between the three versions.

The BVAS v. 3 has undergone initial validation in a cohort of 313 patients with mixed primary and secondary vasculitis from the UK [10]. The objective of this study was to revalidate the BVAS v. 3 in a different cohort of patients from Europe.

Patients and methods

Two hundred and thirty-eight consecutive patients (both inpatients and outpatients) with new or existing diagnoses of vasculitis were recruited from 11 centres in 7 European countries: UK (55), Netherlands (51), Denmark (49), Germany (47), Italy (25), Czech Republic (6) and Sweden (5). Local medical ethics requirements were met by each participating site. Only UK sites required formal ethics approval. Continental European sites did not require formal ethical approval as this was an observational study and did not involve any specific intervention. Participants gave their written informed consent before participating in the study. Basic demographics, type of vasculitis and duration of disease were recorded (Table 1). All patients were assessed for disease activity and disease damage.

Disease activity was measured using the BVAS v. 3, vasculitis activity index (VAI) [11], physician global assessment on a 100-mm visual analogue scale (PGA), treatment decision (description given in Table 2) and CRP. The VAI is an alternative validated measure of disease activity, which incorporates a subjective score for nine organ systems based on perceived severity of involvement (each organ scored 0–4), and then the overall score divided by the number of organ systems scored [11]. The BVAS v. 3 was tested against alternative measures of disease activity to assess convergent validity. Convergent validity tests the extent to which assessments that should theoretically be related to each other are in fact related. To demonstrate that BVAS v. 3 does not measure damage, we tested it against the vasculitis damage index (VDI), which is a validated measure of damage in systemic vasculitis. Inter-observer reliability (reproducibility) of BVAS v. 3 was examined in patients independently assessed by two observers on the same day ($n = 20$).

Table 1 Baseline demographics of the revalidation cohort

Diagnosis	*n* (%)	F	M	Median age (range), years	Median disease duration (range), months
WG (renal)	98 (41.2)	39 (40)	59 (60)	56 (17–85)	38 (1–362)
WG (non-renal)[a]	51 (21.4)	26 (51)	24 (47)	53 (19–75)	68 (1–269)
Churg–Strauss syndrome[a]	23 (9.7)	12 (52)	10 (43)	68 (45–82)	20 (2–252)
Microscopic polyangiitis	22 (9.2)	10 (45)	12 (55)	56 (17–81)	38 (2–219)
Other[b]	13 (5.5)	10 (77)	3 (23)	62 (29–84)	34 (0–228)
Mixed essential cryoglobulinaemia[a]	9 (3.8)	7 (78)	1 (11)	56 (27–77)	49 (8–420)
HscP	7 (2.9)	4 (57)	3 (43)	23 (19–78)	18 (2–336)
Takayasu arteritis	6 (2.5)	6 (100)	0 (0)	32 (21–62)	98.5 (36–145)
Behçet's disease	5 (2.1)	3 (60)	2 (40)	39 (21–66)	120 (24–480)
Leucocytoclastic skin vasculitis	2 (0.8)	1 (50)	1 (50)	55 (25–84)	41.5 (5–78)
Polyarteritis nodosa (Hep B negative)	2 (0.8)	1 (50)	1 (50)	57 (37–78)	160 (114–206)

[a]Gender was missing for one patient. [b]Other vasculitis comprised: ANCA-positive vasculitis not fitting any specific diagnosis; CNS vasculitis; drug-induced vasculitis; Goodpasture's disease; systemic rheumatoid vasculitis; not further specified; SLE vasculitis; GCA; hypocomplementaemic urticarial vasculitis.

TABLE 2 Comparison of the range of diagnosis and BVAS (v. 3) scores between the current study and the original validation cohort

Diagnosis	Current study, patients from Europe ($n = 238$)		Original validation cohort, patients from the UK ($n = 313$), Mukhtyar *et al.* [10]	
	n (%)	BVAS v. 3 median score (range)	*n* (%)	BVAS v. 3 median score (range)
WG (general)	98 (41.18)	1 (0–36)	101 (32.27)	1 (0–37)
WG (non-renal)	51 (21.43)	0 (0–39)	54 (17.25)	0.5 (0–25)
Churg–Strauss syndrome	23 (9.66)	0 (0–14)	28 (8.95)	0 (0–24)
Microscopic polyangiitis	22 (9.24)	2 (0–22)	15 (4.79)	2 (0–25)
Other[a]	13 (5.46)	0 (0–15)	46 (14.70)	4 (0–34)
Mixed essential cryoglobulinaemia	9 (3.78)	5 (0–26)	6 (1.92)	6.5 (0–24)
HScP	7 (2.94)	1 (0–13)	10 (3.19)	3.5 (0–21)
Takayasu arteritis	6 (2.52)	0 (0–4)	9 (2.88)	0 (0–2)
Behçet's disease	5 (2.10)	6 (0–18)	25 (7.99)	2 (0–19)
Leucocytoclastic skin vasculitis	2 (0.84)	2.5 (2–3)	9 (2.88)	2 (0–6)
Polyarteritis nodosa (Hep B negative)	2 (0.84)	0.5 (0–1)	10 (3.19)	0 (0–6)

[a]Other vasculitis comprised: ANCA-positive vasculitis not fitting any specific diagnosis; CNS vasculitis; drug-induced vasculitis; Goodpasture's syndrome; systemic rheumatoid vasculitis; not further specified; SLE vasculitis; GCA; hypocomplementaemic urticarial vasculitis; granulomatous nephritis; PM; SS-related vasculitis.

Statistical analysis

R version 2.9.1 (26 June 2009), USA was used for the statistical analysis. The distributions of the BVAS v. 3 scores were not normally distributed, so we used a non-parametric approach based on ranks to measure its correlation with the VAI, treatment decision, CRP and PGA. In instances where more than one observation was available in a single patient, measurements from the patient's first visit were used for correlation.

Spearman's rank correlation coefficient (ρ) was calculated by independently ranking the two scores, then calculating the Pearson correlation between the ranks rather than the original measurements. The CIs for ρ were calculated using Fisher's transformation.

We used the intra-class correlation coefficient (ICC) to calculate inter-observer reliability for the overall BVAS v. 3 score. This method estimates the average correlation between all possible orderings of pairs, and was calculated using a one-way analysis of variance (ANOVA). To assess reliability between observers for each of the categories in the BVAS v. 3 score, a linear-weighted κ-statistic was calculated, in which observed and expected proportions of agreement are modified to include partial agreements by assigning a weight of between 0 (complete disagreement) and 1 (complete agreement) to each category.

Results

The demographics of the cohort are shown in Table 1. WG (63%), Churg–Strauss syndrome (9%) and microscopic polyangiitis (9%) were the most common diagnoses. The remaining patients suffered from a mixture of other primary and secondary vasculitides. The BVAS v. 3 score ranged from 0 to 39 (maximum possible score 63) with the largest range seen in patients with WG. There were 115 patients who were in remission (BVAS v. 3 score of 0) and 123 patients with active disease (BVAS v. 3 score $\geqslant 1$). Table 2 compares the range scores for each diagnosis between this cohort and the original validation cohort.

Convergent validity

Of 238 patients, 234 (98%) had a treatment decision recorded. There was moderate correlation between BVAS v. 3 and treatment decision [$\rho = 0.54$ (95% CI 0.44, 0.62)] (Fig. 1). The correlation remained the same when patients in remission (BVAS v. 3 = 0) were excluded from the analysis [$\rho = 0.54$, (95% CI 0.40, 0.65)]. Definitions for the treatment decisions are given in Table 3. Subgroup analysis of the 147 patients with WG revealed a similar correlation [$\rho = 0.58$ (95% CI 0.46, 0.68)]. Of the 238 patients, 217 (91%) had CRP levels recorded on the same day the BVAS v. 3 score was measured. There was a low correlation between BVAS v. 3 and CRP levels [$\rho = 0.18$ (95% CI 0.05, 0.30)] (Fig. 1). BVAS v. 3 correlated strongly with the PGA [$\rho = 0.85$ (95% CI 0.81, 0.88)] and the VAI ($\rho = 0.82$, 95% CI 0.77, 0.85); $n = 188$ for both (Fig. 1). The correlation remained strong when patients in remission (BVAS v. 3 = 0) were excluded from the analysis; BVAS v. 3 with PGA [$\rho = 0.79$ (95% CI 0.71, 0.85)] and the BVAS v. 3 with VAI ($\rho = 0.75$, 95% CI 0.66, 0.82).

Divergent validity

There was no correlation between BVAS v. 3 and a concurrent measure of disease damage (the VDI) [$\rho = -0.10$ (95% CI −0.22, 0.03)] (Fig. 2).

FIG. 1 Comparison between potential measures of disease activity and the BVAS v. 3; (**A**) treatment decision, (**B**) CRP, (**C**) PGA and (**D**) VAI.

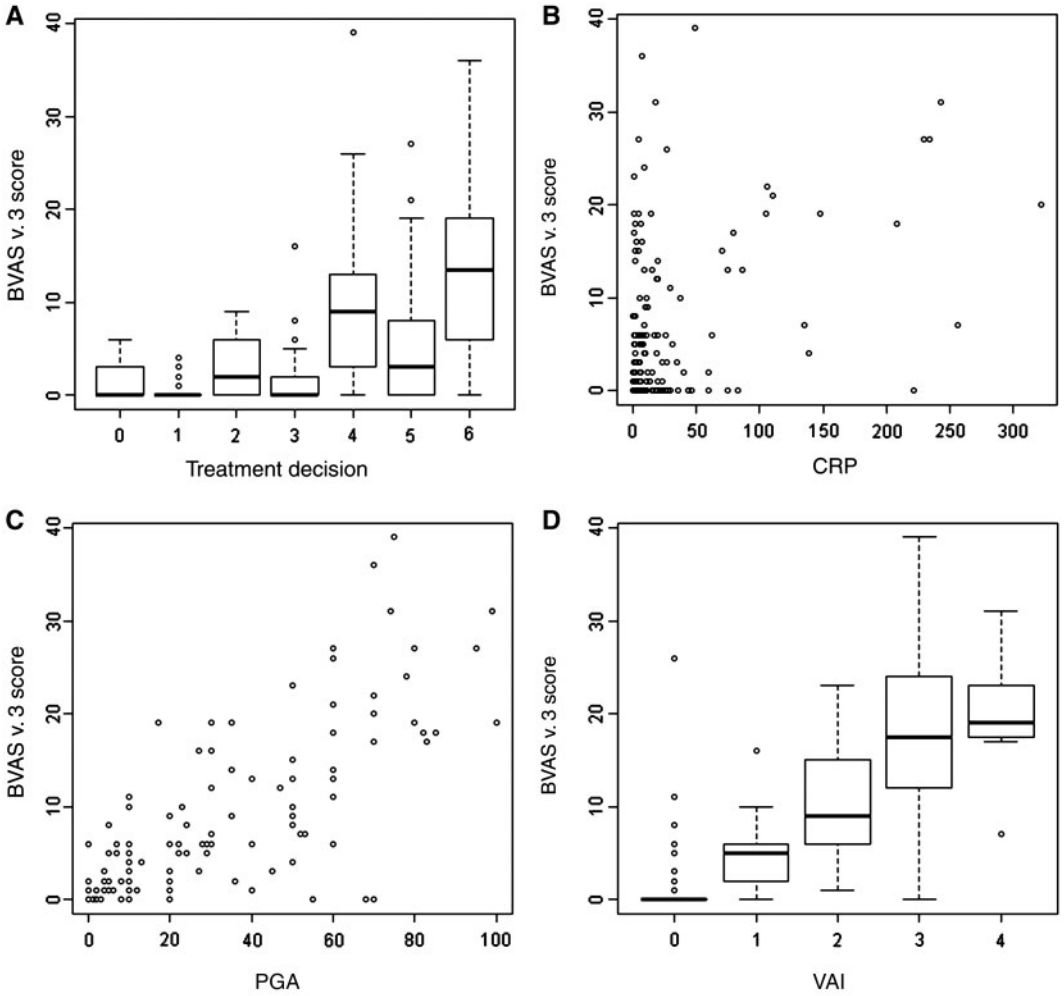
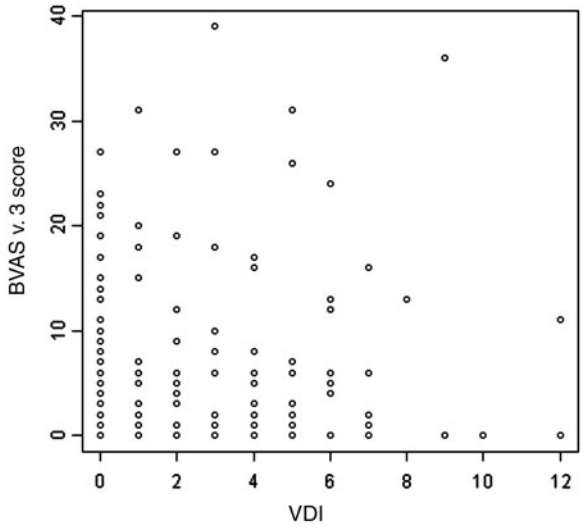


TABLE 3 Treatment decision categories and definitions

Category	Treatment decision	Definition
6	Major escalation	Commencing any immunosuppressive agent, glucocorticoid or plasmapheresis, without stopping or reducing the dose of any other treatment OR Increasing the dose of glucocorticoid and immunosuppressive agent
5	Continue at major level	No change to a therapeutic regimen that includes CYC or biologic therapy
4	Minor escalation	Increasing the dose of immunosuppressive agent or glucocorticoid
3	Continue at minor level	No change to a therapeutic regimen that excludes CYC and biologic therapy
2	Reduction at major level start at minor level	Reduction or stopping of one or more drugs that includes CYC or biologic therapy AND Commencing another drug
1	Reduction of therapy	Reduction or stopping of one or more drugs without increasing or commencing any other drug
0	No therapy	No therapy

Fig. 2 Comparison of disease activity (BVAS v. 3) with disease damage (VDI), $n = 238$.



Reliability

The inter-observer reliability ($n = 20$) was very high with an ICC of 0.996 (95% CI 0.990, 0.998), for the total BVAS v. 3 score. The κ-statistics for the individual organ systems of BVAS v. 3 for inter-observer reliability demonstrated perfect agreement [κ= 1.0 (95% CI 1.0, 1.0)] for cutaneous, mucous, ENT, chest, cardio, abdominal, renal and nervous systems. There was good agreement for general [κ = 0.71 (95% CI 0.29, 0.94)] and mucous membranes [κ = 0.88 (95% CI 0.00, 1.0)], although CIs were wide due to the small numbers. The κ-statistics for the cardiovascular and abdominal systems were not defined because all items were recorded as absent by both observers in all 20 patients.

Discussion

Quantifying vasculitis disease activity and extent of organ involvement assists clinical decision making. In the absence of a suitable biomarker that can quantify disease activity, a structured clinical tool like the BVAS v. 3 is necessary. The BVAS provides a standardized measure of disease activity in clinical trials, and provides a structured approach for these heterogeneous, multisystem disorders on which treatment decisions in clinical practice can be based.

This study reinforces the validity of the BVAS v. 3 and increases the generalizability of the tool. The original validation study included patients from the UK only [10], whereas this study includes patients from six other countries across Europe. The BVAS is a generic tool intended for all types of vasculitis, but has been used primarily in assessment of disease activity in ANCA-associated vasculitis in clinical trial settings [12].

There is no gold standard for measuring disease activity in vasculitis, and hence our decision to compare multiple alternative methods. The BVAS v. 3 correlated well with the VAI and an informed PGA (PGA performed after completing the BVAS v. 3 form), which both measured disease activity at the same time point. In addition, there was only a moderate correlation between BVAS v. 3 and treatment decision, which was expected. Treatment decision is dependent on what has happened to a patient's disease activity recently (i.e. serial BVAS scores) rather than at a single time point. For example, at disease onset, if a patient has haemoptysis and renal failure their disease would be considered to be very active and the BVAS score would be high. The treatment decision would be to start immunotherapy. If we then determined the patient's disease activity 4 weeks later, the haemoptysis and renal failure may have resolved, and therefore the BVAS score would be low. The treatment decision at that point would likely be to continue therapy at a major level because of the recent high disease activity and the knowledge that if treatment is reduced too soon the disease may flare. However, if the BVAS was repeated 6 months later and the score was still 0, the treatment decision would be likely to reduce therapy. Due to the cross-sectional nature of this study, we are unable to directly infer from our results that the BVAS v. 3 influences treatment decisions.

The feasibility of the tool has already been confirmed by earlier versions of the BVAS by their use in clinical trials involving over a thousand patients (the BVAS v. 3 is a condensed version of the previous versions) [10, 13–18]. All versions of the BVAS have high investigator acceptance. The BVAS v. 3 form takes <3 min to complete and requires minimal training, although training is important to achieve optimum reliability and reproducibility. A training manual, complete with practice cases and an on-line calculator are available on the European Vasculitis Study Group (EUVAS) web site: http://www.vasculitis.org/.

Achieving remission (the total absence of disease), maintaining remission and reducing the frequency of flares have been the primary outcome measures in most therapeutic trials in vasculitis in the past decade [10, 13–18]. These endpoints have almost always been defined in terms of the BVAS score, where remission is a BVAS score of 0 and a flare is a rise in the BVAS score from 0. Experts in vasculitis, trial investigators and regulatory agencies have accepted the BVAS as the best available measure of disease activity, which reinforces the content and construct validity of the tool [19]. In addition, the BVAS score at baseline has been shown to predict disease damage that occurs within the first 6 months [20], which in turn predicts mortality [20, 21].

This study has limitations. It is a cross-sectional study with few longitudinal data. The study design was not conducive to adequately assessing sensitivity to change. In the original validation study [10], this exercise was carried out in 39 patients for whom data were available at 0 and 3 months after introduction of treatment classified as major escalation. The treatment was expected to reduce

disease activity in the majority of patients. The BVAS v. 3 met that expectation in a clinically meaningful and a statistically significant way. This aspect of the BVAS v. 3 can be reassessed in future controlled clinical trials [18]. A further limitation of the study is the small number of patients with large-vessel vasculitis and non-ANCA-associated medium and small-vessel vasculitides that were evaluated. We think that it is important to continue to evaluate patients with these other forms of vasculitis to add to the utility of the tool for those conditions and allow for cross-comparison between diseases. There is potential circularity in using the PGA as one of the reference standards to evaluate the BVAS v. 3. Investigators in this study both had expertise in vasculitis care and are involved with research in this area. As a consequence, it is probable that the PGA was influenced by completion of the BVAS v. 3 form. We included the PGA in this study because it is a well-recognized comparator when developing or validating disease activity scores in other rheumatological diseases [22–24]. In order to reduce this potential bias when validating the BVAS v. 3, we used several alternative methods of assessing disease activity such as the VAI, CRP and treatment decision.

In summary, this study adds support to the validity of the BVAS v. 3 and provides data that can be combined with other studies to continue to refine the tool. The current weighting of BVAS items is based on expert opinion [8, 10]. The next evolution of the BVAS is likely to be in the form of improving the weighting of individual items based on available data sets (e.g. cross-sectional studies such as this and the previous validation study [10], as well as data from the long-term follow-up of the EUVAS trials [14–17], and the Wegener's Granulomatosis Etanercept Trial (WGET) [13]). Mahr *et al*. [25] have attempted to improve the scoring of an alternative version of the BVAS designed specifically for WG (BVAS/WG) using the PGA as the reference standard. This method does not improve on expert opinion because it uses a subjective physician score as the reference to reweight items. We would advocate that objective endpoints are used as the external anchors to determine new weighting. For example, variables known to influence rates of remission and relapse, renal survival, cardiovascular survival and mortality, or these events themselves could be used. We have previously published a systematic review exploring these factors [26].

Rheumatology key messages

- Quantifying disease activity in vasculitis is important for clinical decision making and research.
- The BVAS v. 3 is a validated practical tool to quantify disease activity in systemic vasculitis.

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