Development and validation of an electronic medical record-based disease activity index for Behçet's disease

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ABSTRACT

Objective. *The disease activity of Behçet's disease is inadequately defined, and there is no consensus on how it should be measured. The aim of this study was to verify the usefulness of a simplified electronic medical record (EMR)-based activity index (EMRAI) for Behçet's disease.*

Methods. *A total of 73 Korean patients with Behçet's disease participated in this study. Two dermatologists interviewed each participant independently using two activity scoring systems: the EMRAI and the Behçet's Disease Current Activity Form (BDCAF). Overall agreement between raters, correlation between activity scoring indices, and total interview run-time were evaluated.*

Results. *The EMRAI significantly correlated with the BDCAF (Spearman's correlation coefficient, r=0.835), physician-assessed overall activity score (r=0.782), erythrocyte sedimentation rate (r=0.520) and C-reactive protein level (r=0.422). The weighted kappa score for inter-rater agreement of EMRAI showed very good reliability compared with that of BDCAF (0.894 and 0.693, respectively). The mean total run-time for the EMRAI was shorter than that required to administer the BDCAF (95 s and 115 s, respectively).*

Conclusion. *The EMRAI, an EMR-based simplified activity index of Behçet's disease, facilitates rapid and simple gathering of disease activity data and clinical information.*

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Introduction

Behçet's disease (BD) is a multisystemic inflammatory disease characterised by recurrent oral aphthous and genital ulcers; ocular and cutaneous lesions; and occasionally articular, vascular, gastrointestinal, and neurologic involvements (1, 2). Physicians who treat BD patients are required to understand various clinical manifestations and manage complex symptoms using a multidisciplinary approach. To achieve this goal, experts in many clinical fields should share and standardise clinical information, especially clinical activity scoring. The judgment of disease activity is a central question in patient management. However, because there are no reliable laboratory markers that correlate with the clinical activity of BD, various disease activity scoring indices have been designed for patients with BD (2-13). Among these scoring systems, the most commonly used index is the Behçet's Disease Current Activity Form (BDCAF), which emphasises overall assessment of disease activity and was cross culturally validated by performing a Rasch analysis of data from five countries (China, Korea, Iraq, Turkey, and UK) (7). The original BDCAF was revised in 2006 (http://www.behcet.ws/pdf/BehçetsDiseaseActivityForm.pdf), and the scoring of each item was dichotomised (0, no symptoms; 1, presence of symptoms) (14). In this scoring system, patients are asked to recall episodes of BD-related symptoms that occurred in the previous 4 weeks, and clinicians determine whether the reported symptoms were due to BD or not. Certain items have a high rate of variability among observers because of their relatively short and intermittent nature or vaguely defined symptoms, *e.g.* headache (15). Moreover, some scoring systems might be too complicated for disease activity assessment in clinical practice (6). In this context, a more simplified, practical activity index with reliable inter- and intra-rater concordance would be the most useful to clinicians.

Electronic medical records (EMRs) are increasingly being employed in clinical settings. This technology is able to capture clinical information about individuals each time they make contact with the health care system and to make this information available across the care continuum. A very advantageous feature of EMRs is their ability to supply

data for clinical researches (16). In this study, we have developed a simple and reliable EMR-based scoring system to evaluate BD activity and have attempted to validate its reliability by comparing it with that of the BDCFA.

Materials and methods

Study design and case selection

A prospective study protocol was designed and approved by our institutional review board committee of Severance Hospital, Seoul, Korea. Written informed consent was obtained from all participants prior to their enrolment. A total of 73 Korean patients (20 males and 53 females (M:F = 1:2.65); median age, 47.8 years; age range, 23–70 years) who visited the BD Specialty Clinic of Severance Hospital, Seoul, Korea, between October 2012 and April 2013 and fulfilled the diagnostic criteria of the International Study Group for BD were enrolled in this study (17).

Two dermatologists (D.Y.K. and M.J.C.) interviewed each participant independently. The raters practiced using both activity forms for the newly developed index and the BDCFA for randomly selected patients and discussed reasons for disagreements. The practice was repeated until 80% agreement was reached using both activity forms. After they were familiarised with both indices, the raters began interviewing the enrolled participants.

Each dermatologist completed both activity forms for each patient. The record for the new activity scoring system, the electronic medical records-based activity index (EMRAI) was electronically entered into the EMR system (Supplementary Fig. 1), and the BDCAF was completed in a pencil-and-paper manner. The total run-time for each interview was measured. Because the first interview can affect the run-time of following interview, the order of activity forms was randomised using computer-generated random numbers. Only the run-time of the first activity form was measured.

Development of the new disease activity index and scoring of both activity forms

The EMRAI contains nine symptom-related dichotomised scoring items and two laboratory results, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The selection of each item was based on previous activity scoring systems, including the BDCAF. Scoring criteria were modified in pilot studies until clinicians identified an index that was repeatable and correlated well among all investigators.

The BDCAF item scores are 0 or 1 depending on the presence of each clinical features, such as headache, oral and genital ulcers, arthralgia, arthritis, skin lesions, and gastrointestinal (GI) symptoms, which were present during the 4 weeks prior to the day of assessment (7). The involvement of the eye, nervous system, and major vessels were assessed for the presence or absence of relevant symptoms over the previous 4 weeks and scored if the symptoms were new. The disease activity index score of BDCAF was calculated by summing up the score of each index to yield a score between 0 and 12. The physicians also rated their assessments of overall disease activity within the preceding 4 weeks by indicating it on a scale comprised of seven faces with different expressions on the BDCAF. The physician-assessed objective overall disease activity (PGA) was transformed as a 7-point scale that ranged from 0 to 6.

Statistical methods

Agreement between two dermatologists was assessed with the Cohen's kappa statistic, which is commonly used to evaluate the degree of agreement (18). The strength of agreement was evaluated as follows: poor, <0.20; fair, 0.21–0.40; moderate, 0.41–0.60; good, 0.61–0.80; and very good, 0.81–1.00. Kappa values were computed for each of the 73 comparisons between each pair of dermatologists for both the EMRAI and BDCAF indices. Overall agreement between dermatologists was evaluated by a weighted average of the individual kappa values.

The differences in mean score of activity scoring systems and total run-time were analysed using Mann-Whitney U-tests. Inter-scale correlation coefficients were obtained using the Spearman rank correlation technique, and inter-rater differences were calculated by the Wilcoxon signed rank test.

For all statistical analyses, a *p*-value less than 0.05 was considered statistically significant. All of the statistical analyses were performed using SAS statistical package (version 9.2; SAS Institute Inc., Cary, NC, USA).

Results

EMRAI item selection and definition

After reviewing previous diagnostic criteria and activity scoring systems of BD, including BDCAF, nine symptom items were selected based on agreement among the all authors. The EMRAI items include oral and genital ulcers, ocular symptoms, skin lesions, epididymitis, and symptoms related to the involvement of joints, the GI tract, the vascular system, and the central nervous system (CNS). The presence of each item increases the score by 1. Both ESR and CRP were also dichotomised as 0 or 1 if the laboratory measurement was greater than the upper limit of the normal range (reference ranges of ESR and CRP in this study were 0-20 mm/hour and 0-8 mg/dL, respectively). These scores were then summed to yield a total EMRAI score.

Table I. Clinical characteristics of the study population of 73 patients with BD.

Clinical variables	Number of BD patients
Age*	47.84±10.62
Sex	
Male	20 (27.4%)
Female	53 (72.6%)
Oral ulcers	73 (100%)
Genital ulcers	65 (89.0%)
Eye lesions	20 (27.4%)
Skin lesions	69 (94.5%)
Arthritis	34 (46.6%)
GI involvement	9 (12.3%)
Vascular involvement	5 (6.8%)
CNS involvement	2 (2.7%)
Epididymitis	0 (0%)
Positive HLA-B51†	23 (42.6%)
ESR (mm/hour)**	32 (2-120)
CRP (mg/dL)**	2.58 (0.3-70.98)

BD: Behçet's disease; CNS: central nervous system; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GI: gastrointestinal; HLA-B51: human leukocyte antigen-B51.
Data are presented as *mean±standard deviation and **median range.
†HLA-B51 was assessed in 54 patients.

Characteristics of patient profiles and validation of the EMRAI in enrolled patients

The clinical characteristics of the 73 enrolled participants are shown in Table I. All participants had recurrent oral aphthosis. The prevalence of the cardinal symptoms were as follows: skin lesions (94.5%), recurrent genital ulcer (89.0%), joint involvement (46.6%), eye lesions (27.4%), gastrointestinal involvement (12.3%), vascular involvement (6.8%), and CNS involvement (2.7%). Positive human leukocyte antigen (HLA)-B51 genotype was reported in 42.6% of the 54 patients who underwent this test. The median ESR and CRP values were 32 mm/hour and 2.58 mg/dL, respectively, at the time of study.

The mean total scores of the EMRAI and BDCAF were 3.76±1.72 and 2.84±1.47, respectively. The maximum theoretical EMRAI score is 11, and the highest score in this study was 8. EMRAI and BDCAF scores were significantly correlated (r=0.835, Table II). Correlation coefficients between total EMRAI and BDCAF scores between two raters were not statistically different (Table II). Both scores were significantly correlated with PGA (Table II), ESR, and CRP (Table III).

EMRAI reliability

Inter-rater reliability assessed by the weighted kappa scores for total EMRAI and BDCAF scores were 0.894 (95% CI, 0.844-0.944) and 0.693 (95% CI, 0.601-0.785), respectively (Table IV). The kappa statistic for each EMRAI item varied from 0.797 to 1.000, whereas those of BDCAF varied from 0.637 to 1.000. As patients with nausea/vomiting and epididymitis were not enrolled in this study, the kappa coefficients for these items could not be calculated. In EMRAI, only the kappa score of joint symptom item did not reach the level of 'very good agreement' (kappa=0.797, Table IV). For the BDCAF, the kappa scores of oral ulcer, pustule, joint pain, arthritis, and headache were less than 0.8. Among the items, both arthritis and headache in the BDCAF showed the lowest strength of agreement (kappa=0.639 and 0.637, respectively).

Table II. The mean of the EMRAI and BDCAF scores and the correlation between them.

	Overall	Rater 1	Rater 2	*p*-value*
Mean±SD				
EMRAI	3.76 ± 1.72	3.82 ± 1.76	3.92 ± 1.69	0.749
BDCAF	2.84 ± 1.47	2.86 ± 1.54	2.99 ± 1.42	0.507
PGA	2.98 ± 1.46	3.20 ± 1.48	2.94 ± 1.45	0.325
Correlation**				
EMRAI *vs*. BDCAF	0.835	0.855	0.812	0.402
EMRAI *vs*. PGA	0.834	0.825	0.844	0.609
BDCAF *vs*. PGA	0.782	0.735	0.826	0.108

BDCAF: Behçet's Disease Current Activity Form; EMRAI: electronic medical record-based activity index; PGA: physician-assessed objective overall disease activity; SD: standard deviation.
*p-values are the inter-rater differences by Mann-Whitney U-test or Wilcoxon signed rank test.
**Spearman's rank correlation coefficient.

Table III. Correlation between two scoring systems and ESR and CRP.

	EMRAI		BDCAF	
	r*	*p* value	r*	*p*-value
ESR	0.520	<0.001	0.395	<0.001
CRP	0.422	<0.001	0.237	0.004

BDCAF: Behçet's Disease Current Activity Form; CRP: C-reactive protein; EMRAI: electronic medical record-based activity index; ESR: erythrocyte sedimentation rate.
*Spearman's rank correlation coefficient.

Table IV. Inter-rater agreement measurement.

EMRAI	kappa (95% CI)	BDCAF	kappa (95% CI)
Total score*	0.894 (0.844-0.944)	Total score*	0.693 (0.601-0.785)
Oral ulcer	0.833 (0.676-0.990)	Oral ulcer	0.766 (0.554-0.878)
Genital ulcer	0.901 (0.793-1.000)	Genital ulcer	0.862 (0.731-0.993)
Ocular symptoms	0.871 (0.729-1.000)	Ocular symptoms	0.833 (0.650-1.000)
Skin lesions	0.824 (0.689-0.959)	Erythema	0.807 (0.671-0.943)
		Pustule	0.712 (0.537-0.886)
Joint symptoms	0.797 (0.655-0.938)	Joint pain	0.773 (0.626-0.919)
		Arthritis	0.639 (0.393-0.884)
GI involvement	1.000 (1.000-1.000)	Nausea/vomiting	-
		Diarrhoea	1.000 (1.000-1.000)
CNS involvement	1.000 (1.000-1.000)	CNS involvement	1.000 (1.000-1.000)
		Headache	0.637 (0.308-0.966)
Vascular involvement	1.000 (1.000-1.000)	Vascular involvement	0.842 (0.628-1.000)
Epididymitis	-	Epididymitis	-

BDCAF: Behçet's Disease Current Activity Form; CI: confidential intervals; CNS: central nervous system; EMRAI: electronic medical record-based activity index; GI: gastrointestinal.
*weighted kappa score.

Table V. Comparison of total run-time between the BDCAF and EMRAI systems.

	BDCAF (mean, range; seconds)	EMRAI (mean, range; seconds)	*p*-value
Overall	115.0 (75.0-270.0)	95.0 (48.0-225.0)	<0.001
Rater 1	120.0 (75.0-270.0)	95.0 (60.0-225.0)	0.009
Rater 2	112.5 (75.0-225.0)	97.0 (48.0-180.0)	0.008

BDCAF: Behçet's Disease Current Activity Form; EMRAI: electronic medical record-based activity index.

The same items in both activity indices were matched to calculate inter-scale agreement. Seven items including oral and genital ulcers; ocular symptoms; epididymitis; and gastrointestinal, CNS, and vascular involvement were identical between the two activity scoring indices. Two items in the EM-

RAI can be paired with corresponding symptoms in the BDCAF (erythema/pustules and joint pain/arthritis). However, because no EMRAI item could be matched with headache in the BDCAF, this item was excluded for the inter-scale reliability assessment. The inter-scale agreements as analysed by Cohen's kappa were also assessed. The results showed good inter-scale agreement (from 0.782 up to 1.000) by each observer except for CNS involvement conducted by rater 2 (kappa=0.486).

In addition, subgroup analysis stratified by severity was conducted on the patient group who had ocular involvement (n=20). The results from the subgroup analysis were consistent with the results from the total patient group (Supplementary Tables I-III).

Comparison of run-times for both disease activity scoring systems

The total run-times required to complete the activity indices were compared. The order of index administration was determined in randomised manner using random computer-generated numbers. The mean total run-times were 95.0 s (range, 48-225 s) for the EMRAI and 115 s (range, 75-270 s) for the BDCAF, and this difference was statistically significant (Table V).

Discussion

In this investigation, we attempted to develop and validate a new practice-friendly and simplified activity scoring system for BD, which we termed the EMRAI. The results suggest that the EMRAI is a valid inventory as evidenced by good correlation with the BDCAF, PGA, and inflammatory laboratory markers. Moreover, it can be administered over a relatively short time.

The disease activity of BD is poorly or inadequately defined, and there is no consensus on how it should be measured (14). Moreover, the lack of a standardised, reliable measurement is an impediment to interpreting the existing literature and to conducting quantitative clinical trials of therapeutic agents. The new EMRAI score was developed to meet the clinical need for a reliable, easy-to-use scoring instrument for BD that was less complex than the BDCAF, which was originally developed on behalf of the International Scientific Committee on BD with the participation of researchers in five countries (7). The questions in the BDCAF are easy to ask and follow the format of a clinical interview. Each item in BDCAF asks for events only in previous 4 weeks, which most patients can recall. Based on these merits and representativeness, we adopted the BDCAF as a standard form for the development of the EMRAI. However, for some items in the BDCAF, such as 'headache', it is difficult to define whether headache is actually a BD-related symptom (15). As expected, the relatively low inter-rater agreement of the 'headache' item in our study might be due to the ambiguous characteristics of headache. In joint-related items, the kappa coefficient of arthritis was lower than that of joint pain in the BDCAF. This result raises concern about the difficulty of non-rheumatologists in defining arthritis by physical examination. In this context, we found that the simplified item 'joint symptoms' in the EMRAI demonstrated better inter-rater agreement. Similarly, in the BDCAF, skin lesions are divided into erythema and pustules. Because it is difficult for non-dermatologists to reliably make this visual distinction, this variable is a potential source of variability. Another difference between the two scales is whether a point is given when there is a symptom related to major organ involvement, including the ocular and nervous systems and major vessel involvement. In the latest version of the BDCAF, any newly developed symptoms of these three organs are only scored as 1 point. For example, recurring ocular pain on a previously affected eye does not receive a point in the BDCAF system, but the EMRAI does add a point to the total activity score.

The incorporation of laboratory markers into the disease activity score has rarely been attempted for BD. The reliability of ESR and CRP as activity markers have previously been investigated in BD with contradictory results (19-21). Although several new serologic markers have been suggested, most of them are only available for research-based measurement (19,22-25). For this reason, both ESR and CRP remain available alternatives that can be roughly correlated with BD activity in BD (20, 21).

As a consequence of the characteristics outlined above, the EMRAI score appeared to be easier to calculate than the BDCAF score in clinical practice. Indeed, it is necessary to judge whether reported symptoms are relevant for scoring or not when calculating the BDCAF. This process was simplified to determine the presence of nine symptom items and the elevation of two laboratory results in the EMRAI. Moreover, using the EMR recoding system facilitates more rapid charting of activity score compared to the pencil-and-paper BDCAF.

In the current study, inter-rater agreement between observers of the same interviewing procedures was better for the EMRAI than the BDCAF. This could be explained by the unification of similar symptoms and the elimination of ambiguous item. Moreover, agreement was extremely good for most of the selected items except joint symptoms (kappa=0.797), whereas the kappa score of 6 items among 11 tested variables in the BDCAF only exceeded a level of 0.80 (Table IV). However, because kappa is influenced by response prevalence, rarely reported symptoms including CNS and vascular involvement are needed to re-evaluate these results in a larger study population.

Medical information technology has recently advanced in many countries. Our institution adopted an electronic medical record system in 2005. Sophisticated information retrieval systems for medical records have enabled clinicians to improve clinical research efficiency (26). The EMR database is designed to facilitate the rapid collection of detailed clinical information about individual patients, which can then be employed in the EMRAI to improve observational research (26, 27).

Possible pitfalls of the EMRAI include ignoring different weighting depending on symptoms. In some previously reported activity scales, such as the Total Clinical Activity Index (13), Behçet's Syndrome Activity Scale (BSAS) (14),

and Iranian Behçet's Disease Dynamic Activity Measure (IBDDAM) (28), each symptom was given a weight according to symptom severity. However, the question of which symptoms should be regarded as more or less important in the judgment of disease activity is still under debate. In this sense, asking about the presence or absence of each cardinal symptom can be intuitive and follow the natural order of the clinic interview. In addition, it can take longer to verify laboratory results in institutions where the EMR system has not been established. The relative importance of these potential limitations will be clarified by broader experience with the application of the EMRAI in clinical practice.

In summary, the results of our study clearly demonstrate that the EMRAI, an EMR-based simplified activity index of BD, allows for rapid and clinical practice-friendly gathering of disease activity data and clinical information in a manner that is comparable with data obtained with the latest version of the BDCAF. It should be emphasised that the authors do not advocate that the EMRAI should replace other indices, but conversion to the electronic formats of these activity indices will make their administration less cumbersome and time-intensive and facilitate more efficient data retrieval. Furthermore, this conversion may increase the utility of activity measures in clinical practice.

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