PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Utility of the New Rheumatoid Arthritis 2010 ACR/EULAR Classification Criteria in Routine Clinical Care: A Cohort Study
AUTHORS	Yazici, Yusuf ; Kennish, Lauren; Labitigan, Monalyn; Budoff, Sam; Filopoulos, Maria; McCracken, W; Swearingen, Christopher

VERSION 1 - REVIEW

REVIEWER	Ismail Simsek, M.D Assoc. Prof. Gulhane School of Medicine Ankara, Turkey I have no competing interest regarding the study under review.
REVIEW RETURNED	27-Mar-2012

GENERAL COMMENTS	This paper analysis the use of new ACR/EULAR criteria (with particular focus on specificity) in rheumatology outpatients seen in routine care. This study adds to the recent literature on classification criteria for RA by showing that the new criteria have a relatively lower specificity compared to the 1987 criteria. While the validity of the new RA criteria has been tested in various cohorts, testing the criteria among consecutive patients seen in routine care is certainly a good idea as well as a necessary exercise. The paper is carefully and beautifully written. (The only, and really minor, suggestion I have is to place a dot between arthritis and Almost in page 11, line 22). Although it doesn't change the importance of the study, the statement " We believe this is the first study to examine the new 2010 ……" (page 11, line 6) seems to be improper considering the previous study by Kaneko et al. (as also cited by the authors in ref. 15) conducted among undiagnosed subjects who first visited the university hospital.

REVIEWER	David Walker Consultant Rheumatologist Freeman Hospital Newcastle on Tyne NE7 7DN I have no competing interests.
REVIEW RETURNED	24-Apr-2012

THE STUDY	With regard to how representative the patients are, this population is of new and return patients. It is acknowleged that the later criteria are aimed at earlier diagnosis so the populations should probably be sepatated so that we may assess how the criteria perform in the different populations,
GENERAL COMMENTS	This is an interesting investigation of the criteria described. It shows them to be more sensitive but less specific than the previous ones. As above I would like to see the data separated for new and review patients. It is acknowleged that this sensitivity may be appropriate for early referral from primary care. Do they have any suggestions from the data that would indicate which items are leading to the lack of specifity. They make the interesting point that "if you have eliminated all other possible diagnoses then you must have RA! It is interesting that the SLE and PSA criteria function better. Do they have an explanation for this? There is a typographical error in the intro. "of" should be "off"

REVIEWER	Yuko Kaneko Assisstant Professor Keio Univeristy School of Medicine, Department of Internal Medicine, Division of Rheumatology Japan Competimg interests: none
REVIEW RETURNED	01-May-2012

THE STUDY	Kennish et al. described the utility of the new criteria for rheumatoid arthritis in real world. This thesis is very important and interesting, but this current study has some limitations. First of all, the chronology of the time when the criteria were applied to subjects and the time of diagnosis and the time of analysis was unclear. If the criteria were applied at the patient's first visit to the hospital before the treatment was started, isn't this study retrospective? If this was prospective as described in the first page, the fact that the subjects included the patients who had been already treated with DMARDs, steroid and biologic agents had perhaps great impact on the condition of patients, including the number of joints, the value of CRP/ESR and even possibly titer of RF/anti-CCP. And the number of subjects was too small. Moreover more than 10% of patients were excluded from analysis due to insufficient data, but those might have different characteristics from those analyzed, which could influence the sensitivity and specificity.
RESULTS & CONCLUSIONS	The analysis of the data and interpretation of results were perhaps correct, but in the first place the subject group analyzed appears inappropriate.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1
Ismail Simsek, M.D
Assoc. Prof.
Gulhane School of Medicine
Ankara, Turkey

I have no competing interest regarding the study under review.

This paper analysis the use of new ACR/EULAR criteria (with particular focus on specificity) in rheumatology outpatients seen in routine care. This study adds to the recent literature on classification criteria for RA by showing that the new criteria have a relatively lower specificity compared to the 1987 criteria.

While the validity of the new RA criteria has been tested in various cohorts, testing the criteria among consecutive patients seen in routine care is certainly a good idea as well as a necessary exercise.

The paper is carefully and beautifully written. (The only, and really minor, suggestion I have is to place a dot between arthritis and Almost in page 11, line 22).

Although it doesn't change the importance of the study, the statement " We believe this is the first study to examine the new 2010 ……" (page 11, line 6) seems to be improper considering the previous study by Kaneko et al. (as also cited by the authors in ref. 15) conducted among undiagnosed subjects who first visited the university hospital.

Authors' response:
We thank the reviewer for his comments. We have modified the sentences as requested.

Reviewer: David Walker
Consultant Rheumatologist
Freeman Hospital
Newcastle on Tyne
NE7 7DN
I have no competing interests.

With regard to how representative the patients are, this population is of new and return patients. It is acknowleged that the later criteria are aimed at earlier diagnosis so the populations should probably be sepatated so that we may assess how the criteria perform in the different populations,

This is an interesting investigation of the criteria described. It shows them to be more sensitive but less specific than the previous ones. As above I would like to see the data separated for new and review patients. It is acknowleged that this sensitivity may be appropriate for early referral from primary care.
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It is interesting that the SLE and PSA criteria function better. Do they have an explanation for this?
There is a typographical error in the intro. "of" should be "off"
Authors' response:
We thank the reviewer for his comments. We have corrected the typo.
Most of the patients were not new patients (new=28) and two of those were RA patients hence we were not able to analyse the small numbers of patients separately. However as we discuss in our paper, we were trying to see how the new criteria would perform in an "all comers" setting to differentiate patients. As most classification criteria are also used as diagnostic criteria, we wanted to highlight the possible problems that may arise from the use of new RA criteria.

Even though we did not separately study which portions of the criteria are leading to low specificity , dependence on laboratory testing may likely be responsible as a lot of other inflammatory conditions have elevated antibody and inflammation markers, along with joint involvement.

Reviewer: Yuko Kaneko
Assisstant Professor
Keio Univeristy School of Medicine, Department of Internal Medicine, Division of Rheumatology
Japan
Competimg interests: none

Kennish et al. described the utility of the new criteria for rheumatoid arthritis in real world. This thesis is very important and interesting, but this current study has some limitations. First of all, the chronology of the time when the criteria were applied to subjects and the time of diagnosis and the time of analysis was unclear. If the criteria were applied at the patient's first visit to the hospital before the treatment was started, isn't this study retrospective? If this was prospective as described in the first page, the fact that the subjects included the patients who had been already treated with DMARDs, steroid and biologic agents had perhaps great impact on the condition of patients, including the number of joints, the value of CRP/ESR and even possibly titer of RF/anti-CCP. And the number of subjects was too small. Moreover more than 10% of patients were excluded from analysis due to insufficient data, but those might have different characteristics from those analyzed, which could influence the sensitivity and specificity.

The analysis of the data and interpretation of results were perhaps correct, but in the first place the subject group analyzed appears inappropriate.

Authors' response:
We thank the reviewer for his comments.
We have applied to criteria to prospectively collected data. The new criteria allows for historical data ascertainment and that is what we have done. We did the same when we were applying the other diagnostic criteria to the disease control groups. We agree having more patients would have been preferable but the numbers are similar to other validation studies and the differences were large enough that we feel the numbers of patient we studied were adequate for the points we wanted to highlight.

VERSION 2 – REVIEW

REVIEWER	Cynthia S Crowson, MS Assistant Professor of Biostatistics Mayo Clinic Rochester, MN USA
REVIEW RETURNED	01-Aug-2012

THE STUDY	This manuscript takes a different approach to assessing the 2010 ACR/EULAR classification criteria for RA. Rather than excluding patients with other diagnoses, as the criteria state, they decided to assess these patients. While they make a convincing case that this is what will happen in clinical practice, their argument falls short

	because the majority of patients in their cohort (>75%) are established patients. It is difficult to believe that the classification criteria will be useful in established patients in a clinical setting. However, this issue is clearly acknowledged as a limitation.
GENERAL COMMENTS	This manuscript takes a different approach to assessing the 2010 ACR/EULAR classification criteria for RA. Rather than excluding patients with other diagnoses, as the criteria state, they decided to assess these patients. While they make a convincing case that this is what will happen in clinical practice, their argument falls short because the majority of patients in their cohort (>75%) are established patients. It is difficult to believe that the classification criteria will be useful in established patients in a clinical setting. However, this issue is clearly acknowledged as a limitation. My only major concern is the statement made at the beginning of the discussion that the distinction between diagnostic and classification is arbitrary. This point is supported by a reference from the author of this paper. Are other references available? Typically classification criteria is designed to provide a homogenous group of patients for research studies. Classification criteria have a different purpose than diagnostic criteria. While it is true that classification criteria are often used as diagnostic tools in clinical settings, I believe the authors statement that their distinction is “arbitrary” is confusing and may be misleading. Please revise.

VERSION 2 – AUTHOR RESPONSE

Reviewer: Cynthia S Crowson, MS
Assistant Professor of Biostatistics
Mayo Clinic
Rochester, MN USA

This manuscript takes a different approach to assessing the 2010 ACR/EULAR classification criteria for RA. Rather than excluding patients with other diagnoses, as the criteria state, they decided to assess these patients. While they make a convincing case that this is what will happen in clinical practice, their argument falls short because the majority of patients in their cohort (>75%) are established patients. It is difficult to believe that the classification criteria will be useful in established patients in a clinical setting. However, this issue is clearly acknowledged as a limitation.

My only major concern is the statement made at the beginning of the discussion that the distinction between diagnostic and classification is arbitrary. This point is supported by a reference from the author of this paper. Are other references available? Typically classification criteria is designed to provide a homogenous group of patients for research studies. Classification criteria have a different purpose than diagnostic criteria. While it is true that classification criteria are often used as diagnostic tools in clinical settings, I believe the authors statement that their distinction is “arbitrary” is confusing and may be misleading. Please revise.

Response: We thank the reviewer for her comments. We would like to point out that the author of reference mentioned, where "arbitrary" was discussed, is in fact another Dr. Yazici, not the author of this manuscript but his father. We have now added a second reference that also states that there is really no difference between "diagnostic" and “classification" criteria. We believe this is a very important point to start discussing and hope our paper will be able to help.

VERSION 3 – REVIEW

REVIEWER	Cynthia S. Crowson, MS Assistant Professor of Biostatistics Mayo Clinic Rochester, MN USA Competing interests: none
REVIEW RETURNED	30-Aug-2012

- The reviewer completed the checklist but made no further comments.