Il fenomeno della sottodiagnosi e del sottotratamento
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Il fenomeno della sottodiagnosi in AR

- Sottodiagnosi
- DIAGNOSI corretta
- Sovradiagnosi
2010 Rheumatoid Arthritis Classification Criteria

An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative


This criteria set has been approved by the American College of Rheumatology (ACR) Board of Directors and the European League Against Rheumatism (EULAR) Executive Committee. This signifies that the criteria set has been quantitatively validated using patient data, and it has undergone validation based on an external data set. All ACR/EULAR-approved criteria sets are expected to undergo intermittent updates.

The American College of Rheumatology is an independent, professional, medical and scientific society which does not guarantee, warrant, or endorse any commercial product or service.
Over the last decade, the optimal use of disease modifying antirheumatic drugs have dramatically enhanced the success of RA management.

Undoubtedly, treating patients at a stage at which evolution of joint destruction can still be prevented would be ideal.

However, at present, clinical trials of RA treatments are hampered by lack of criteria allowing for study enrollment of patients at early stages of disease. Thus, to date it has not been possible to effectively investigate the efficacy of early interventions in terms of their ability to prevent later-stage RA, since there are no validated or accepted uniform criteria to classify such individuals with early disease.

Aletaha et al, 2010 Rheumatoid Arthritis Classification Criteria. ARTHRITIS & RHEUMATISM Vol. 62, No. 9, September 2010, pp 2569–2581
Target population (Who should be tested?): Patients who
1) have at least 1 joint with definite clinical synovitis (swelling)*
2) with the synovitis not better explained by another disease†

Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡:

A. Joint involvement§
   1 large joint¶
   2–10 large joints
   1–3 small joints (with or without involvement of large joints)#
   4–10 small joints (with or without involvement of large joints)
   >10 joints (at least 1 small joint)**

B. Serology (at least 1 test result is needed for classification)††
   Negative RF and negative ACPA
   Low-positive RF or low-positive ACPA
   High-positive RF or high-positive ACPA

C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡
   Normal CRP and normal ESR
   Abnormal CRP or abnormal ESR

D. Duration of symptoms§§
   <6 weeks
   ≥6 weeks

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Joint involvement</td>
<td>0 1 2 3 5</td>
</tr>
<tr>
<td>B. Serology</td>
<td>0 2 3</td>
</tr>
<tr>
<td>C. Acute-phase reactants</td>
<td>0 1</td>
</tr>
<tr>
<td>D. Duration of symptoms</td>
<td>0 1</td>
</tr>
</tbody>
</table>
• Early rheumatoid arthritis (RA) and very early RA are major targets of research and clinical practice. Remission has become a realistic goal in the management of RA, particularly in early disease.
  – The 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA classification criteria,
  – the EULAR treatment recommendations for RA, and
  – the EULAR recommendations for the management of early arthritis focus on early disease and translate the knowledge related to early RA into classification and management.

Zeidler H. The need to better classify and diagnose early and very early rheumatoid arthritis. J Rheumatol. 2012 Feb;39(2):212-7
Nevertheless, there is a need for further improvement and progress. Results from 6 recent studies are summarized, evaluating the performance of the 2010 ACR/EULAR RA classification criteria.

The data show a significant risk of misclassification, and highlight that overdiagnosis and underdiagnosis may become important issues if the criteria recommend synthetic and biological disease-modifying antirheumatic drugs. The possible effect of misclassification on spontaneous and drug-induced remission of early and very early RA awaits further elucidation. Such research will eventually lead to more reliable diagnostic and classification criteria for new-onset RA.

Zeidler H. The need to better classify and diagnose early and very early rheumatoid arthritis. J Rheumatol. 2012 Feb;39(2):212-7
How are the new criteria performing in the clinic?

• The objective of the 2010 ACR/European League Against Rheumatism classification criteria for RA was to distinguish patients at high risk for developing persistent erosive and/or inflammatory disease from those with undifferentiated inflammatory arthritis.

• These criteria were developed for use in clinical trials; in order to implement these criteria most effectively, they need to be validated in real-world settings.

• The 1987 criteria may have led to underdiagnosis in the case of patients with positive anti-citrullinated peptide antibody values but no evidence of radiographic progression of joint erosion, or overdiagnosis in the case of some patients with FM; similarly, the possibility that the 2010 criteria may result in overdiagnosis cannot be excluded.

Bykerk VP, Massarotti EM. The new ACR/EULAR classification criteria for RA: how are the new criteria performing in the clinic? Rheumatology (Oxford) 2012 Dec;51 Suppl 6
How are the new criteria performing in the clinic?

- Prospective validation of the 2010 criteria has been carried out in several cohorts, with reported sensitivities ranging from 0.50 to 0.60 and specificities from 0.88 to 0.97. The sensitivity and specificity of the 2010 criteria were 0.74 and 0.66 when compared against the gold standard of needing MTX therapy in the opinion of experienced clinicians, and 0.69 and 0.72 against the standard of having persistent synovitis despite DMARDs after 1 year.

- Other comparisons have yielded similar sensitivities and specificities, ranging up to 0.85 for the gold standard of needing MTX therapy. Questions remain concerning the utility of the 2010 criteria for non-arthritis health care practitioners, who may be less than expert in identifying swollen joints and may underestimate the number of joints affected by synovitis.

Bykerk VP, Massarotti EM. The new ACR/EULAR classification criteria for RA: how are the new criteria performing in the clinic? Rheumatology (Oxford) 2012 Dec;51 Suppl 6
Cardiovascular Risk in Rheumatic Patients: The Link between Inflammation and Atherothrombosis

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Abstract

In addition to a high prevalence of the metabolic syndrome and a significant under-diagnosis of vascular risk factors (VRFs), the effect of chronic inflammation also represents the cornerstone of the raised cardiovascular (CV) risk in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Moreover, the finding that among current anti-inflammatory treatments, the use of tumor necrosis factor (TNF)-α blockers is associated with optimal rheumatologic and CV outcomes further supports the impact of inflammation on the CV risk. However, up-to-date treatment guidelines suggest that TNF-α blockers should be used only after the failure of traditional disease-modifying antirheumatic drugs (DMARDs). Early predictors of the therapeutic efficacy of traditional DMARDs are needed to identify candidates for TNF-α blocker treatment. Furthermore, whether the CV risk should be taken into account while choosing antirheumatic treatments is an emerging issue to be addressed. Common educational programs for specialists and general practitioners and appropriate CV prevention programs, taking into consideration traditional VFRs as well as the inflammatory status, should be planned to prevent ischemic events and to achieve optimal inflammation control in rheumatic patients.

Keywords
- cardiovascular risk
- rheumatoid arthritis
- psoriatic arthritis
- ankylosing spondylitis

Together with the progressive disability secondary to the joint impairment, cardiovascular (CV) risk is a major issue in patients with rheumatic diseases. In this clinical setting, a high prevalence of the metabolic syndrome (MetS) and of its major features (obesity, hypertension, impaired fasting glucose, hypercholesterolemia, hyperglycemia) have been described. However, such an association does not entirely explain the extent of premature atherosclerosis in rheumatic subjects and inflammation appears to act synergistically with traditional vascular risk factors (VRFs), thus contributing to the atherosclerotic process and to the increased CV risk. Monocytes, CD4+ T lymphocytes and most proinflammatory cytokines (tumor necrosis factor [TNF]-α, interleukin [IL]-1β, IL-6, and IL-18) play a central role in the pathophysiology of major atherogenesis, and are involved in the induction and in the maintenance of the atherosclerotic process.
Sottodiagnosi e sottotrattamento
Aggressive rheumatoid arthritis registry in Italy. Characteristics of the early rheumatoid arthritis subtype among patients classified according to the ACR criteria

Gruppo Italiano Artrite Reumatoide Aggressiva (GIARA)

• The major conclusion of this preliminary analysis is that an overall tendency to undertreatment is discernable.
The Italian registry of aggressive rheumatoid arthritis - the GIARA project

- In 1999, the Italian Society of Rheumatology started a project to determine the prevalence and clinical characteristics of aggressive rheumatoid arthritis (ARA).
- For 1 year, all patients with RA for > 5 years and referred to participating centers were entered in a registry and classified as having ARA if they fulfilled the following criteria:
  - 10 swollen joints for at least 6 weeks, positive rheumatoid factor (RF), and at least one bone erosion (if disease duration of 2 years); (a) RF-positive and having 10 swollen joints or at least one newly eroded joint, or (b) if RF-negative, having 10 swollen joints and at least one newly eroded joint (if disease duration > 2 to < 5 years).

Marchersoni A et al. The Italian registry of aggressive rheumatoid arthritis - the GIARA project. J Rheumatology 2007 Dec;34(12):2374-81
The frequency of ARA was 15% in the 2-year group and 63% in the > 2 to < 5-year group, but 35% of the patients in the 2-year group had erosions. Bone erosions were associated with disease duration, a Health Assessment Questionnaire value > 1.5, female sex, and RF positivity.

In an Italian RA population, the GIARA (Gruppo Italiano Artrite Reumatoide Aggressiva) criteria for ARA were met by 15% of the patients with disease duration of 2 years, but erosions were seen in 35%. Upon referral, most of the RA patients were inadequately treated and had other conditions.
Erosioni articolari

gravi erosioni
ipertrofia sinoviale
tumefazione dei tessuti molli
erosione del processo stiloideo ulnare
Tavolo 2 – Area clinica della Reumatologia

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• è un network mondiale di servizi professionali di consulenza direzionale, revisione contabile, fiscalità e transaction. EY conta 250.000 dipendenti in tutto il mondo. Il network è presente con più di 700 uffici in 150 Paesi.
Tavolo 2- Area Clinica della Reumatologia
Artrite Reumatoide - Background

Definizione
L'artrite reumatoide è una malattia infiammatoria cronica, sistemica ed invalidante che colpisce la membrana sinoviale delle articolazioni, che aumenta di volume e invade la cartilagine, provocandone l'erosione e la graduale distruzione. Questo processo proliferativo si estende all'osso e alle articolazioni fino a colpire l'intero organismo, in particolare occhi, polmoni, cuore e reni.

Prevalenza
In Italia ci sono circa 200.000 pazienti prevalenti con artrite reumatoide (circa lo 0,33% della popolazione).

Trattamento con biologici
Nell'artrite reumatoide i farmaci biologici sono utilizzati al verificarsi congiunto delle seguenti condizioni: in seconda linea dopo il fallimento dei o intolleranza ai cDMARD e tsDMARD e con malattia in fase attiva o con danno strutturale progressivo.
Artrite Reumatoide - Trattamento

200.000 prevalenti

In Italia circa 58.000 pazienti con artrite reumatoide sono eleggibili al trattamento con biologico. Secondo un confronto con KOL tale dato si abbasserebbe a circa 43.000 pazienti.

Tuttavia si stima che solo 38.000 pazienti siano effettivamente trattati.

Come conseguenza, in Italia si stimano circa 20.000 pazienti affetti da artrite reumatoide in sottotrattamento. Considerando l’esperienza dei KOL, tale dato si potrebbe abbassare a 5.000 pazienti.

Costo dei biologici?  
Accentrimento dei centri specialistici?  
Ritardo di ingresso al percorso di cura presso il reumatologo?  
Impossibilità di prescrizione per le farmacie territoriali?

4) Canevà-ANAMAR-SIR (2008), «Primo rapporto sociale sull’artrite reumatoide»
5) ABC spilt idei (C/VI/A)
OUTPUT 1 - Percezione del fenomeno del sottotrattamento

Qual è la percezione del Tavolo circa il fenomeno del sottotrattamento dei farmaci biologici, da ben distinguere rispetto ai fenomeni di sottodiagnosi e ritardo di primo accesso alla cura, rispetto alle stime fornite nello studio E&Y?

Percezione di sottostima
dati non precisi
Fonti discutibili

Un percorso ad ostacoli
PRIMO RAPPORTO SOCIALE SULL'ARTRITE REUMATOIDE
2008
L’incidenza e la prevalenza di queste malattie non sono particolarmente elevate, con l’eccezione della Ps, ma nel loro insieme rappresentano nel panorama italiano una frazione non secondaria della popolazione. Prevalenze più elevate si riscontrano, per alcune di esse, nei Paesi del Nord Europa. *

Applicando dati di prevalenza alle popolazioni di Regno Unito, Germania, Italia, Paesi Bassi e Belgio, si può stimare che quasi sette milioni di pazienti siano affetti da tali patologie.

OUTPUT 3 - Gap informativo

Quali dati o strumenti sarebbero necessari allo scopo di meglio definire il fenomeno del sottotrattamento;

Indagini epidemiologiche
OUTPUT 4 - Cause alla base dei fenomeni di sottot trattamento

Lo studio E&Y ha ipotizzato alcune cause alla base dei fenomeni di sottot trattamento. Quali possibili ulteriori cause possono essere individuate per descrivere il fenomeno del sottot trattamento?

Carica di Centri e specialisti territoriali di Reumatologia

Percorsi
OUTPUT 5 - Possibili soluzioni al sottotratamento

Quali strumenti, strategie ed approcci possono essere individuati al fine di ridurre il fenomeno di sottotratamento e o mancato/ritardato accesso alle terapie con biologici.
1. C’è necessità, prima di parlare di sottottrattamento dell’artrite reumatoide, di studi epidemiologici diretti ed aggiornati.

2. AIFA si impegna a proporre al Ministero di attivare appositi studi - attraverso le Società Scientifiche dei reumatologi italiani (SIR e CReI) - per verificare l’ipotesi di sottottrattamento.