An evidence-based approach to laboratory tests in usual care of patients with rheumatoid arthritis

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ABSTRACT

Laboratory tests often are regarded as the most important information in clinical care by patients and doctors, and dominate clinical decisions in many chronic diseases such as diabetes and hyperlipidemia. Most patients with rheumatoid arthritis (RA) have a positive test for rheumatoid factor or anti-cyclic citrullinated peptide antibodies (ACPA), or an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). However, about a third of RA patients, have negative tests for rheumatoid factor or ACPA, and more than 40% have a normal ESR or CRP at presentation (“false-negative” results). Furthermore, many normal people have a positive test for rheumatoid factor or ACPA but do not have RA, even among those with extensive musculoskeletal pain (“false-positive” results). Abnormal laboratory tests are the most significant predictor of high levels of radiographic progression, and therefore regarded as indicators of “poor prognosis RA”. By contrast, laboratory tests are far less predictive of severe long-term outcomes such as work disability and premature mortality than functional difficulties reported on a patient questionnaire. A patient questionnaire score is abnormal in 89% of RA patients at presentation, and therefore more useful than ESR or CRP to document subsequent clinical improvement or deterioration. In clinical practice, patient questionnaire scores and RAPID3, an index of physical function, pain, and patient global estimate of status, identify incomplete responses to methotrexate more effectively than ESR. Improved understanding of the limitations of laboratory tests in diagnosis and management of individual patients with RA (and all rheumatic diseases) could improve patient care and outcomes.

Laboratory tests often are regarded by most patients and doctors as the most important information collected in clinical care. The discovery in the 1940s of rheumatoid factor (1, 2) in most patients with rheumatoid arthritis (RA), and antinuclear antibodies (ANA) (3) in most people with systemic lupus erythematosus (SLE), led to hopes that laboratory tests could provide gold standard biomarkers in rheumatic diseases, as seen in hypertension, diabetes, and many chronic diseases, to apply to diagnosis, prognosis, and monitoring of all individual patients.

Most patients with RA have a positive test for rheumatoid factor or anti-cyclic citrullinated peptide antibodies (ACPA) (4-7), or an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) (8). Reduction in levels of rheumatoid factor, ESR or CRP often (but not always) accompanies clinical improvement in RA, suggesting control of pathophysiologic mechanisms. Changes in values of laboratory tests appear considerably more “scientific” than changes in other measures of RA status, such as tender joint counts or patient questionnaire scores for pain. Laboratory measures have contributed invaluably to understanding of pathogenesis and to development of new treatments for RA. However, laboratory tests cannot be applied to diagnosis, prognosis and monitoring of each individual patient with RA, unlike serum glucose or haemoglobin A1c. This article reviews and updates information concerning advantages and limitations of laboratory tests in routine clinical care of RA and rheumatic diseases (9-13).

Positive laboratory tests in RA

The majority of patients with RA do have positive tests for rheumatoid factor and anti-cyclic citrullinated peptide antibodies (ACPA) (4-7), both of which are prominent in revised classification criteria for RA. A meta-analysis indicated a positive likelihood ratio of 12.5 for RA in 37 studies of ACPA (using the

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former term anti-CCP antibodies) versus the general population, and a positive likelihood ratio of 4.9 for RA in 50 studies of rheumatoid factor (Table I) (7). Elevated levels of rheumatoid factor are associated with higher levels of radiographic progression (14), leading to a dictum that abnormal laboratory tests identify poor prognosis RA (15). The majority of patients with RA also have an elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (8) and an abnormal ESR or CRP often provides inclusion criteria for clinical trials (16). Reductions in ESR and CRP are seen in groups of patients in all successful clinical trials of RA therapies and contribute to improvement criteria which indicate efficacy of an active treatment compared to a control treatment. Furthermore, a normal ESR or CRP is required to meet RA remission criteria (17).

A perspective on laboratory tests in RA
No rheumatoid blood test is abnormal in 100% of individual patients with any rheumatic disease, and 100% within the normal range in all individuals who do not have that rheumatic disease, in contrast to serum glucose in diabetes, haemoglobin levels in anaemia, and other biomarkers in many other diseases. The meta-analysis noted above indicated that ACPA is found in 67% and rheumatoid factor in 69% of patients with RA (Table I) (7). Findings in a similar range are reported from most clinical sites, such as in 4 settings from the 1990s European Research on Incapacitating Diseases and Social Support (EURIDISS) project reported in 1996. Mean ESR levels reported in the rheumatology community, results for rheumatoid factor or anti-CCP is found in more than 30% of people with RA (Table II) (18). Therefore, about 1 in 3 patients, have negative tests for these serologic markers.

ESR or CRP are normal in about 40% of patients with RA, reported initially in 1994 by Wolfe and Michaud (19) (Table III). Mean ESR levels were 28–30 mm/Hr in data reported in 1996 from the 4 sites in the EURIDISS project (Table II) (18). A 2009 report from two sites, Nashville, TN, USA and Jyväskylä, Finland, indicated similar patterns, despite vastly different medical care systems. Mean ESR at presentation was 30 mm/Hr at both sites, and 45–47% of RA patients had ESR <28 mm/Hr (Table IV) (8).

Table I. Meta-analysis of features of autoantibodies in 37 reports concerning anti-cyclic citrullinated peptide antibodies (anti-CCP or ACPA), and in 50 reports concerning rheumatoid factor (RF).

<table>
<thead>
<tr>
<th>Anti-cyclic citrullinated peptide antibodies (anti-CCP or ACPA)</th>
<th>Rheumatoid factor (RF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies</td>
<td>37</td>
</tr>
<tr>
<td>Positive likelihood ratio</td>
<td>12.5</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>67%</td>
</tr>
<tr>
<td>Specificity</td>
<td>95%</td>
</tr>
<tr>
<td>% of patients with negative test result</td>
<td>33%</td>
</tr>
</tbody>
</table>


Table II. Percentage of patients who were positive for rheumatoid factor (RF) and mean erythrocyte sedimentation rate (ESR) levels in 4 locations in the European Research on Incapacitating Diseases and Social Support (EURIDISS) project reported in 1996.

<table>
<thead>
<tr>
<th>Location</th>
<th>n.</th>
<th>% RF positive</th>
<th>Mean ESR (mm/Hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oslo, Norway</td>
<td>237</td>
<td>73%</td>
<td>26 (20)</td>
</tr>
<tr>
<td>Nancy, France</td>
<td>135</td>
<td>62%</td>
<td>29 (26)</td>
</tr>
<tr>
<td>Groningen, Netherlands</td>
<td>283</td>
<td>81%</td>
<td>28 (24)</td>
</tr>
<tr>
<td>Belfast, N Ireland</td>
<td>51</td>
<td>71%</td>
<td>28 (27)</td>
</tr>
</tbody>
</table>


Table III. Percentages of 1556 patients with rheumatoid arthritis (RA) seen in usual care in Wichita KS USA, reported in 1994, whose values for erythrocyte sedimentation rate (ESR) were ≥28 mm/Hr versus <28 mm/Hr.

<table>
<thead>
<tr>
<th>ESR ≥28 mm/h</th>
<th>ESR &lt;28 mm/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>63%</td>
</tr>
<tr>
<td>Males</td>
<td>55%</td>
</tr>
</tbody>
</table>


“False negative” and “false positive” test results
The meta-analysis depicted in Table I indicates that a negative test, i.e. “false negative,” or “seronegative” as used by the rheumatology community, results for rheumatoid factor or anti-CCP is found in more than 30% of people with a diagnosis of RA. Furthermore, “false positive” results are seen in people who have other inflammatory diseases, and some who may not have any inflammatory rheumatic disease at all. The meta-analysis presents a specificity of 95% for ACPA (anti-CCP), i.e. 5% of people in the non-RA population have a positive test for ACPA, and 85% for rheumatoid factor, i.e. 15% of people in the non-RA population have a positive test for rheumatoid factor (7).

The prevalence of RA is about 0.5% (22, 23), or about 10 in 2,000 people.
If false-positive results among people positive, almost as many as with RA. will have fibromyalgia and be sero
of people (2% of 15%) or 6 in 2,000
are positive for rheumatoid factor, 0.3%
fibromyalgia in about 2% of the popu
ranges from 15–45% (22, 25) including
musculoskeletal symptoms in the population
Nonetheless, the prevalence of muscu
es in which the test was ordered (24).
the context of the clinical circumstanc
results of a test must be viewed in
ACPA are not ordered in all people, and
Of course, tests for rheumatoid factor or
rheumatoid factor (12).
eral population have a positive test for
about 300 people in 2,000 in the gen

Table IV. Number ( %) of rheumatoid arthritis patients at presentation with erythrocyte sedi
mentation rate (ESR) < or ≥28 mm/hr compared to C-reactive protein (CRP) < or ≥10 in:
a) 1744 patients in Jyväskylä, Finland, and
b) 170 patients in Nashville, TN, USA.

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</thead>
<tbody>
<tr>
<td></td>
<td>CRP ≥28 mg/L</td>
<td>CRP &lt;10 mg/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥28 mm/hr</td>
<td>&lt;28 mm/hr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>775 (44%)</td>
<td>202 (12%)</td>
<td>977 (56%)</td>
<td>1744 (100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>199 (11%)</td>
<td>568 (33%)</td>
<td>767 (44%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>974 (56%)</td>
<td>770 (44%)</td>
<td></td>
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</table>


If 70% have a positive rheumatoid factor test, about 0.35% or 7 in 2,000 people has RA and a positive rheuma
toid factor test. However, if 15% of the normal population has a positive test, about 300 people in 2,000 in the general population have a positive test for rheumatoid factor (12).

Of course, tests for rheumatoid factor or ACPA are not ordered in all people, and the results of a test must be viewed in the context of the clinical circumstances in which the test was ordered (24). Nonetheless, the prevalence of musculoskeletal symptoms in the population ranges from 15–45% (22, 25) including fibromyalgia in about 2% of the population (26, 27). If 2% of people have fibromyalgia and 15% of these people are positive for rheumatoid factor, 0.3% of people (2% of 15%) or 6 in 2,000 will have fibromyalgia and be sero-positive, almost as many as with RA. If false-positive results among people with soft tissue rheumatism and osteoarthritis also are considered, it appears likely that at least as many people with musculoskeletal symptoms and rheumatoid factor have RA as do not have RA, based on population data. The specific details of these analyses are less important than the evidence that a positive rheumatoid factor or ACPA test does not indicate a definitive diagnosis of RA and a negative test does not exclude this diagnosis. Furthermore, available data concerning the prevalence of positive laboratory tests in RA are derived from patients seen at rheumatology treatment centers. Patients are less likely to be referred by primary care physicians, if these tests are normal. Some patients who are se
onegative report to a rheumatologist that a physician has told them “Your test for rheumatoid arthritis was negative” which delayed referral. Evidence that more than 30% of patients with RA have negative tests for rheumatoid factor or ACPA, and 40% have normal ESR or CRP, may be underestimates, and may contribute to delays in diagnosis and treatment.

The likelihood of abnormal quantitative data at baseline for ESR versus other measures

Clinical decisions in RA are recognised to be guided primarily by a patient history and physical examination (28), in contrast to other chronic diseases, in which clinical decisions are guided by biomarkers such as blood pressure, laboratory tests, or imaging studies. However, the only quantitative data in the medical records of many patients with RA in usual care are laboratory tests. This practice reduces the capacity to monitor, recognise and document clinical improvement or deterioration in patient status according to quantitative data. Analyses of 287 RA patients seen in 3 clinical care centers indicated that at presentation ESR was abnormal in 57% and CRP in 58% (29) (Table VI). By contrast, scores on a patient questionnaire were abnormal for physical function in 70% and pain in 89% of patients (29). It is not possible to recognise and document clinical improvement according to a measure that is normal at baseline. Self-report scores also are as responsive to change over time as any of the RA Core Data Set measures (30, 31). Therefore, a strong case could be made that scores for physical function and pain, although only indirectly related to pathophysiological mechanisms, are at least as valuable as ESR to monitor the clinical status of patients with RA.

Documenting incomplete responses to methotrexate

ESR also is less likely than patient self-report questionnaire scores to recognise an incomplete response to methotrexate in RA patients, as demonstrated in an analysis of patients in whom methotrexate was initiated between 1996 and 2001 and for whom 5-year follow-up was available (Table VII). All patients had available ESR and the 3 patient self-report measures from the RA Core Data set on a multidimensional assess-
Table VI. Percentage of 287 patients with rheumatoid arthritis who have abnormal measures at presentation.

<table>
<thead>
<tr>
<th>Measure</th>
<th>% of patients with abnormal value at presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte sedimentation rate (ESR) &gt;28 mm/Hr</td>
<td>57%</td>
</tr>
<tr>
<td>C-reactive protein (CRP) &gt;10</td>
<td>58%</td>
</tr>
<tr>
<td>Rheumatoid factor positive</td>
<td>69%</td>
</tr>
<tr>
<td>ACPA positive</td>
<td>67%</td>
</tr>
<tr>
<td>Function score &gt;2/10</td>
<td>70%</td>
</tr>
<tr>
<td>Pain score &gt;2/10</td>
<td>89%</td>
</tr>
</tbody>
</table>


Table VII. Median levels of RA measures of erythrocyte sedimentation rate (ESR), and 3 patient self-report measures on a multidimensional health assessment questionnaire (MDHAQ), for physical function, pain, patient estimate of global status, and routine assessment of patient index data (RAPID3), in all patients at initiation of methotrexate in 1996-2001 compared to median levels of 63 “adequate responders” 2.6 years after initiation of methotrexate and 30 “incomplete responders” at the time of initiation of a biological agent at a mean of 2.6 years after initiation of methotrexate.

<table>
<thead>
<tr>
<th></th>
<th>63 Adequate Responders (“Controls”)</th>
<th>30 Incomplete Responders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At initiation of methotrexate</td>
<td>Follow-up at mean of 2.6 years later (no biologic agent)</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (0-150)</td>
<td>24</td>
<td>16</td>
</tr>
<tr>
<td>MDHAQ-Function (0-10)</td>
<td>2.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Pain (0-10)</td>
<td>4.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Patient Global estimate (0-10)</td>
<td>4.2</td>
<td>0.9</td>
</tr>
<tr>
<td>RAPID3 (0-30)</td>
<td>10.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>

MDHAQ: multidimensional health assessment questionnaire; RAPID3: routine assessment of patient index data.


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Pragmatic considerations

One final issue concerning laboratory tests is that they often are not available at the time at which a clinical decision is made. A clinician may arrange for a laboratory test in advance of a visit, or contact a patient at a later date, but these practices do not occur in most clinical settings at this time. Therefore, clinical decisions are made without laboratory data—often without any quantitative data at all.

Conclusions

Laboratory research is essential to provide new insights into pathogenesis and new treatments for rheumatic diseases. However, in usual clinical care, laboratory tests for RA often have limited sensitivity and specificity, high levels of false-positive and false-negative results, a lesser capacity than patient self-report questionnaire scores to provide a sensitive measure for documenting future improvement, recognize incomplete responses, and predict work disability and premature mortality. Laboratory tests are useful in many patients and essential in a few, but physicians and patients often attribute disproportionate importance to laboratory tests in rheumatic diseases. A more sophisticated understanding of rheumatology laboratory tests may help improve care and outcomes for patients with RA and all rheumatic diseases.

References:

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1. Literature Review:

- The clinical and reliability of laboratory tests in rheumatoid arthritis (RA) are essential for diagnosis and management.

2. Methodology:

- A pragmatic approach to cost-effective use of laboratory tests and imaging procedures in patients with musculoskeletal symptoms.

3. Discussion:

- The rheumatoid factor is a useful indicator of RA, especially in patients with musculoskeletal pain.

4. Conclusion:

- Effective use of laboratory tests and imaging procedures in patients with musculoskeletal symptoms can improve the diagnosis and management of RA.

5. References:


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