ORIGINIAL ARTICLE
RHEUMATOID ARTHRITIS: THE IMPORTANCE OF EVIDENCE BASED DIAGNOSTIC REASONING IN PREVENTING DEBILITATING CONSEQUENCES

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Background: The early diagnosis of Rheumatoid arthritis can improve clinical outcomes, in terms of morbidity and mortality. This study evaluates the role of evidence informed diagnostic reasoning in the early diagnosis of Rheumatoid arthritis. Methods: A cross-sectional survey was conducted on 200 respondents inclusive of doctors and medical students, at Shifa college of Medicine, Islamabad from April to December 2010. A questionnaire with three common clinical scenarios of low, intermediate and high pre-test probability for rheumatoid arthritis (RA) was provided to the respondents. The differences between the reference and respondents’ estimates of pre and post-test probability were used to assess the respondents’ clinical diagnostic reasoning process, as a tool to diagnose RA early. Respondents were also enquired about the cost effectiveness or potential harms of Rheumatoid factor (RF). Consecutive sampling technique was used and the data was analysed using SPSS-15. Results: In all scenarios, the pre-test probability was estimated close to the reference estimates suggesting respondents’ ability to rule in or rule out the disease. However, some over-estimation of the pre-test probability was noticed in low and intermediate pre-test probability settings. Post-test probabilities were significantly underestimated reflecting their inability to calculate post-test probabilities in all scenarios. More tests were ordered as the disease probability increased. Most respondents were of the opinion that RF is cost effective and safe. Conclusions: The significant underestimation of the post-test probability necessitates more emphasis on Bayesian probabilistic thinking in clinical practice to facilitate early diagnosis of rheumatoid arthritis.

Keywords: Rheumatoid arthritis. Rheumatoid factor, Probability, Early diagnosis

INTRODUCTION
Rheumatoid arthritis, a chronic deforming Polyarthritis is a challenging problem for the healthcare providers’ worldwide. The exact prevalence of the disease is largely unknown in Pakistan but it is more common in the north compared to the south.

The diagnosis of RA is often difficult due to wide spectrum of clinical presentation and progressive changes in the disease over time. Many cases may remain undiagnosed because of lack of identification of disease at early stage. The consequences are disability, lowered quality of life and early mortality. The 1987 ARA criteria used till date have significant limitations with respect to both sensitivity and specificity and hence detection of early disease.

Recently, the American college of rheumatology has devised new criteria for diagnosis of RA at early stage. Whether or not these criteria can be applied to Asians, need to be further explored. The Bayesian probabilistic approach is another important tool to diagnose RA early. According to this approach, physician generates a clinically plausible estimate of patient’s pre-test probability from personal experience, prevalence statistics or primary studies. The physician then orders tests which are available, affordable and precise in their settings. The physician would further assess whether the resulting post-test probability would affect management and help patient. If there is a high pre-test probability for a particular disorder, the physician should start treatment without further tests.

For decades, Rheumatoid factor has been considered primary serological marker for diagnosing RA. Recently, anti-cyclic citrullinated peptide antibodies (anti-CCP) have been identified as more important for diagnosis and subsequent prognosis in RA. Although anti-CCP antibodies offer more specificity than RF, the two tests have similar sensitivity for diagnosis. Again anti-CCP antibodies are more expensive and may be cost-effective only in those RF negative patients in whom there is a strong suspicion of RA. In addition, anti-CCP antibodies may not be available in primary care settings where most of cases can be identified. The ultimate diagnosis of RA however is based on history, physical examination supported by laboratory and imaging studies.

As early aggressive therapy has been proven to decrease morbidity and mortality, it is important that physicians diagnose and refer patients to
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sensitivity, specificity, positive and negative
into Bayes formula. 
substituting reference estimates of pre
Reference estimates of pre
3
proba
Respondents estimates were defined as pre
and the reference estimates of disease probability
respondents by two parameters i.e.
This test is cost effective? (Yes/No)}
Rheumatoid factor to this patient? (Yes/ No)
our figure e.g., 95%) 3. Would you suggest
Rheumatoid factor in this case after
Rheumatoid arthritis in this case is: a) Low (20%, b) Intermediate
(Rheumatoid factor (RF) is likely to be (mention your
own figure e.g., 95%) 3. Would you suggest
Rheumatoid factor to this patient? (Yes/ No) 4. Is there any potential harm associated with this test?
(Yes/No) 5. This test is cost effective? (Yes/No)
We assessed disease probability estimates of respondents by two parameters i.e., the respondents and the reference estimates of disease probability: 1) Respondents estimates were defined as pre-test probability (preProb RESP) and post-test probability (postProb RESP) estimates provided by respondents.2) Reference estimates of pre-test probability (preProbREF) were defined by a panel of experts for each scenario. Reference estimates of post-test probability (postProbREF) were calculated by substituting reference estimates of pre-test probability into Bayes formula. In literature, the pooled
sensitivity, specificity, positive and negative
likelihood ratios for RF are 69% (CI 65–73%), 85%
(CI 82–88%), 4.86 (CI 3.95–5.97), and 0.38 (CI
0.33–0.44) respectively.14 We used positive
likelihood ratio for estimating post-test probability
using Bayes’ nomogram.13
Statistical analysis was performed using
SPSS-16 and www.graphpad.com. Respondents’
estimates of pre-test probability and its mean
difference from corresponding reference estimates
were expressed in percentages. Measures of post-test
probability estimates were expressed as mean±SD
(Standard Deviation). Post test probabilities of
respondents were compared to actual post test
probability calculated in each scenario using Fagan’s
nomogram for Bayes’s theorem. Statistical
significance of difference in probability estimates
were checked by independent sample t test.
Difference in estimates between groups of doctors
was analyzed using Chi-square test.

RESULTS
This study included two hundred participants who were
asked to fill a Questionnaire. Total of 145 participants
responded. Base line characteristics of respondents are
given in table-2. The respondents were divided into
three groups based on their experience (Group-1:
Students and House officers, Group-2: Medical officers
and Residents and Group-3: Consultants).
In scenario one of low pretest probability,
correct answer (20%) was provided by 109 (75.2%)
while 34 (23.4%) reported it as 50% overestimating it
by 30% from the reference value. Only two (1.4%)
reported pre-test probability as 80%. Chi-square test was
used to see difference among the different level/groups
of doctors. There was no statistically significant
difference (p value=0.09) among the three groups with
respect to the pre-test probabilities. The respondents’
and the reference post-test probability estimates are
given in figure-1. Group-1 estimated the post-test
probability as (postProbINT= 44.46±26.22% vs
postProbREF =60%, difference= -15.54±26.22%
[p<0.0001]) while Group-2 estimated it as
(postProbINT=33.57±22.39% vs postProbREF =60%,
difference= -26.43±22.39% [p<0.0001]). Group 3
estimated post-test probability as (postProbINT=
22.34±13.88% vs postProbREF = 60%, difference= -
37.66±13.88% [p<0.0001]) Rheumatoid factor was
suggested to the patient in the scenario by 31 (21.37%).
In scenario no. 2 of intermediate pretest
probability, correct answer (50%) was provided by 75
(51.7%) while 7 (4.8%) under reported it as 20. Pre-test
probability was reported as 80%, by 63 (43.4%)
overestimating it by 30% from the reference estimates.
With respect to pre-test probability, there was no
statistically significant difference (p-value=0.27) among
the three groups. The post-test probability estimates in
the scenario are given in Figure-1. Group-1 estimated
the post-test probability as (postProbINT=70.75±21.91%
vs postProbREF =80%, difference= -9.25±21.91%
[p<0.0039]) while Group-2 estimated it as (postProbINT=68.41±16.22 % vs postProbREF =80%, difference= -11.59±16.22 % [p<0.0001]). Group 3 estimated post-test probability as (postProbINT=66.30±13.71% vs postProbREF =80%, difference=- 13.7±13.71% [p<0.0001]) Total of 132 (91.03%) participants suggested Rheumatoid Factor to the patient in the scenario.

In scenario 3 of high pretest probability, 121 (83.4%) correctly answered as 80%. The pre-test probability was reported as 20% by 3 (2.1%) while 21 (14.5%) reported it as 50%. There was no statistical significant difference (p-value=0.80) among the three groups of doctors. The post-test probability estimates in the scenario are given in figure-1. Group-1 estimated the post-test probability as (postProbINT=79.75±19.64% vs postProbREF =96%, difference= -16.25±19.64% [p<0.0039]) while group-2 estimated it as (postProbINT=77.80±14.70% vs postProbREF =96%, difference= -18.20±14.70 % [p<0.0001]). Group-3 estimated post-test probability as (postProbINT=80.34±15.11% vs postProbREF =96%, difference= -15.66±15.11% [p<0.0001]). Total of 115 (79.31%) participants suggested Rheumatoid Factor to the patient in the scenario. This shows that more tests were considered compared to scenario 1 and 2.

In all the three scenarios, 143 (98.62%) thought that there is no potential harm associated with this test while 2 (0.01%) were of the opposite opinion. In scenario 1, 2 and 3, 65 (44.82 %), 105 (72.41%) and 104 (71.72%) respectively, were of the opinion that it is a cost-effective procedure.

**Table-1: Clinical scenarios**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A 42 year old female presents with history of body aches and pains for one year. Systemic examination is normal. There is no evidence of active arthritis (Reference estimate of pre-test probability is 20%)</td>
</tr>
<tr>
<td>2</td>
<td>A 35 year old lady presents with joint pains and swelling of small and large joints of the body for the last 2 years. She gives history of morning stiffness for 30 minutes but on examination she has no active arthritis. (Reference estimate of pre-test probability is 50%)</td>
</tr>
<tr>
<td>3</td>
<td>A 48 year old lady presents with body aches and pains for which she is taking analgesics off and on. She has morning stiffness of joints for 2 hours. On examination she has deformities both hands and there is tenderness and swelling of small and large joints of upper and lower limbs. (Reference estimate of pre-test probability is 80%)</td>
</tr>
</tbody>
</table>

**Table-2: Baseline characteristics of the subjects**

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>145 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age±SD</td>
<td>31.8±10.45</td>
</tr>
<tr>
<td>Females</td>
<td>71 (48.96 %)</td>
</tr>
</tbody>
</table>

**Level/Groups of subjects**

- Final year students & house officers: 49 (33.8%)  
- Medical officers & Residents: 70 (48.3%)  
- Consultants: 26 (17.9%)  

**Experience (years)**

- <1: 31 (21.4%)  
- 1–5: 54 (37.2%)  
- 6–10: 14 (9.7%)  
- >10: 46 (31.7%)  

**DISCUSSION**

The significance of clinical decision making in diagnosis has been proven, however, with recent advances in diagnostic modalities, clinicians are perhaps relying more on investigations rather than clinical decision making. This study focused on early diagnosis of RA by assessing the physicians’ clinical decision making in the form of pre-test probability and the ability to generate post-test probability after application of the test. Evaluating this diagnostic reasoning process was important as this can be an important tool for early diagnosis of rheumatoid or any other inflammatory arthritis.

The most important finding reflected in this study was that most of the physicians estimated pre-test probabilities that were close to reference estimates in all three scenarios. This shows that respondents can easily rule out or rule in the disease based on historical data. However one fourth of the respondents in scenario 1 of low probability and one third in scenario 2 of intermediate pre-test probability respectively, overestimated pre-test probability.

In all the three scenarios, the moderately high likelihood ratio of RA factor (+LR=4.86) significantly increases post-test probability. However respondents significantly underestimated post-test probability of RA from reference estimates. This shows inability to generate an accurate post-test probability from pre-test estimates. The wide standard deviation in estimated post-test estimates further emphasizes this finding. Whether this finding is due to their underestimation of the sensitivity, specificity and likelihood ratio of the test (Rheumatoid factor) or their non-use of Bayesian probabilistic approach in clinical practice is not clear from study. This under estimation may lead to missing early cases of RA which may ultimately present with complications.

We found an increasing trend in the number of tests (RF) ordered as disease probability increased. Screening tests should not be ordered in low probability scenarios as they are perhaps not cost-effective.
effective. Here it is important to consider that with a positive likelihood ratio of 4.86 this test being of modest value should not have been ordered for those with pretest probability of 20% at all. Even in intermediate probabilities, although a positive test can increase the number of points in diagnostic criteria but its positivity in other autoimmune disorders makes it less specific for RA. The test however may be beneficial in our settings in high disease probability, i.e., 80% for confirmation prior to beginning treatment. This is in contradiction to the teachings of evidence based practice which guides us to stop testing if the pre-test probability is high enough to cross the test-treatment threshold. However this is one debilitating disease where disease modifying agents are also associated with significant morbidity and hence confirmatory tests need to be used to establish a diagnosis before using these agents. Hence in diagnosing RA in our outpatient settings, we should judiciously utilize resources by not ordering this test unless we have intermediate to high probability of diagnosis based on clinical data.

Several studies assessed the effects of test results on the estimation of disease likelihood using hypothetical scenarios previously. Our study was different in terms of the subjects and results and the outcome. In addition to the students, participants of different cadres who had clinical experience as well were included. Also both over and underestimation of test results was noticed in our study. Furthermore, this clinical diagnostic reasoning process was viewed as a tool for early diagnosis of RA.

Interestingly, there was no significant difference between the different levels of respondents. Students and house officers who have very little clinical experience performed almost similar to those with different level of experience. This however needs further evaluation.

Most of the subjects considered this test (RA Factor) as safe. For diagnostic purposes, RA factor is 3.3 times more cost-effective than Anti-CCP antibodies. When asked about the cost-effectiveness, most of the respondents considered it as a cost effective test, however they considered it as more and more cost-effective as the disease probability increased. This again goes against evidence based approach, according to which the need to order test decreases as disease probability increases. Their response might have been taken as correct, if they had ordered the test for prognostic purposes, which was not asked in the study.

Limitations of the study: Firstly, the test (RF) was asked for diagnostic purpose only and not for prognosis of the disease. Secondly, the respondents may not be familiar with the Probabilistic/Bayesian approach used in this study.

**CONCLUSION**

The significant underestimation of the disease probability may lead to missing of cases of Rheumatoid arthritis. Moreover, the recent 2010 classification criteria for diagnostic purposes although has increased sensitivity for early diagnosis of RA may need modifications in our set up, where anti-CCP antibodies are not available and the specificity of RF not high enough to rule out other autoimmune diseases. Hence, more emphasis on clinical decision making and incorporation of Bayesian probabilistic thinking in clinical practice will help in early diagnosis of Rheumatoid arthritis.

**REFERENCES**


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