ORIGINAL 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
J Ayub Med Coll Abbottabad 2014;26(2):118–22

INTRODUCTION

Rheumatoid arthritis, a chronic deforming Polyarthritis is a challenging problem for the healthcare providers' worldwide.[1] The exact prevalence of the disease is largely unknown in Pakistan but it is more common in the north compared to the south.[2]

The diagnosis of RA is often difficult due to wide spectrum of clinical presentation and progressive changes in the disease over time.[3] 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.[4] The 1987 ARA criteria used till date have significant limitations with respect to both sensitivity and specificity and hence detection of early disease.[5]

Recently, the American college of rheumatology has devised new criteria for diagnosis of RA at early stage.[3] Whether or not these criteria can be applied to Asians, need to be further explored. The Bayesian probabilistic approach[6] 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.[7] If there is a high pre-test probability for a particular disorder, the physician should start treatment without further tests.[8]

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.[9] 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.[10] 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

rheumatologists' early.[11] This would imply that the ability to estimate pre-test probability and use of likelihood ratios to obtain post-test probability will help early diagnosis of RA. Moreover, screening relatives of RA patients is vital as genetic factors contribute to development of RA.[12]

This study will help us to find out whether our physicians are using the Bayesian probabilistic approach for diagnosis of RA and whether this can be an important tool for early diagnosis of RA especially in setups where anti-CCP antibodies are not available.

MATERIAL AND METHODS

This cross-sectional study was conducted at Shifa International Hospital Islamabad from April to December, 2010. Two hundred participants from clinical health sciences including doctors of different clinical cadres and final (fifth) year medical students were included. The curriculum of the students included, involves introduction to the basic principles of epidemiology, clinical trials, bayes` theorem[13] and use of probabilistic approach in clinical diagnosis. Doctors who did not give consent for participation were excluded from study. Consecutive sampling technique was used and study design was descriptive.

Institutional review board approval was obtained before data collection. After taking consent, participants were asked to fill a questionnaire. Three scenarios for Rheumatoid arthritis were provided (Table-1). For each scenario, five questions were asked: {**1.**The pretest probability for Rheumatoid arthritis in this case is: a) Low (20%, b) Intermediate (50%), c) High (80%) **2.** The post-test probability for detecting Rheumatoid arthritis in this case after 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 ($preProb_{REF}$) were defined by a panel of experts for each scenario. Reference estimates of post-test probability ($postProb_{REF}$) 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 ($postProb_{INT}$= 44.46±26.22% vs $postProb_{REF}$ =60%, difference= -15.54±26.22% [p<0.0001]) while Group-2 estimated it as ($postProb_{INT}$=33.57±22.39% vs $postProb_{REF}$ =60%, difference= -26.43±22.39% [p<0.0001]). Group 3 estimated post-test probability as ($postProb_{INT}$= 22.34±13.88% vs $postProb_{REF}$ = 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 ($postProb_{INT}$=70.75±21.91% vs $postProb_{REF}$ =80%, difference= -9.25±21.91%

[p<0.0039]) while Group-2 estimated it as ($postProb_{INT}$=68.41±16.22 % vs $postProb_{REF}$ =80%, difference= -11.59±16.22 % [p<0.0001]). Group 3 estimated post-test probability as ($postProb_{INT}$= 66.30±13.71% vs $postProb_{REF}$ =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 ($postProb_{INT}$=79.75±19.64% vs $postProb_{REF}$ =96%, difference= -16.25±19.64% [p<0.0039]) while group-2 estimated it as ($postProb_{INT}$=77.80±14.70% vs $postProb_{REF}$ =96%, difference= -18.20±14.70 % [p<0.0001]). Group-3 estimated post-test probability as ($postProb_{INT}$=80.34±15.11% vs $postProb_{REF}$ =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

1	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%)
2	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%)
3	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%)

Table-2: Baseline characteristics of the subjects

Number of subjects	145 (100%)
Mean age±SD	31.86±10.45
Females	71 (48.96 %)
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%)

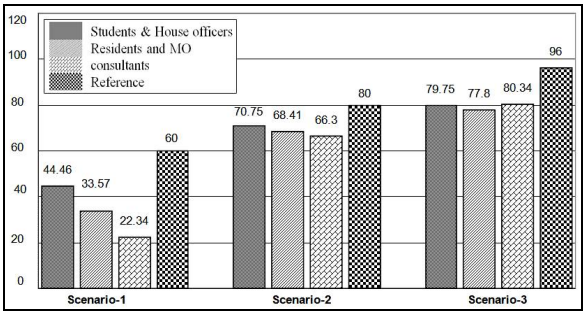

Figure-1: Post-test probability of the respondents with reference post-test probability in percentage

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.[15] Here it is important point 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.[9] 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.[16,17] 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.[18] 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.[19] 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[5] 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.

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