Acta Pædiatrica ISSN 0803–5253

REVIEW ARTICLE

Understanding diagnostic tests 2: likelihood ratios, pre- and post-test probabilities and their use in clinical practice

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Keywords
Bayes theorem, Fagan's nomogram, Likelihood ratio, Post-test probability, Pre-test probability

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Received
8 June 2006; revised 4 December; accepted 8 December 2006.

DOI:10.1111/j.1651-2227.2006.00179.x

Abstract

The sensitivity and specificity of a test cannot be used to estimate probability of disease in individual patients. They can, however, be combined into a single measure called the likelihood ratio which is, clinically, more useful than sensitivity or specificity. Likelihood ratios provide a summary of how many times more (or less) likely patients with a disease are to have a particular result than patients without the disease. Using the principles of the Bayes theorem, likelihood ratios can be used in conjunction with pre-test probability of disease to estimate an individual's post-test probability of disease, that is his or her chance of having disease once the result of a test is known. The Fagan's nomogram is a graphical tool which, in routine clinical practice, allows one to combine the likelihood ratio of a test with a patient's pre-test probability of disease to estimate post-test probability.

Conclusion: Likelihood ratios summarize information about a diagnostic test by combining sensitivity and specificity. The Fagan's nomogram is a useful and convenient graphical tool that allows likelihood ratios to be used in conjunction with a patient's pre-test probability of disease to estimate the post-test probability of disease.

LIKELIHOOD RATIO

The sensitivity and specificity of a test can be combined into one measure called the likelihood ratio (1). The likelihood ratio for a test result is defined as the ratio between the probability of observing that result in patients with the disease in question, and the probability of that result in patients without the disease (2).

Likelihood ratios are, clinically, more useful than sensitivity and specificity. They provide a summary of how many times more (or less) likely patients with the disease are to have that particular result than patients without the disease, and they can also be used to calculate the probability of disease for individual patients (3). For these reasons, likelihood ratios are becoming increasingly popular for reporting the usefulness of diagnostic tests.

When test results are reported as being either positive or negative, two types of likelihood ratios can be described, the likelihood ratio for a positive test (LR+) and the likelihood ratio for a negative test (LR−).

Likelihood ratio for a positive test (LR+)

LR+ is defined as the probability of an individual *with* disease having a positive test divided by the probability of an individual *without* disease having a positive test. The formula for calculating LR+ is

$$\text{LR+} = \frac{\text{The probability of an individual } with \text{ disease having a positive test}}{\text{The probability of an individual } without \text{ disease having a positive test}}$$

You will notice that the numerator in this equation is exactly the same as the sensitivity of the test, and the denominator is the converse of specificity (1 − specificity). Thus the LR+ of a test can simply be calculated by dividing the sensitivity of the test by 1− specificity (Sensitivity/1 − specificity).

Interpretation of LR+

In the first article of the series (4), I described a hypothetical test, Test A, which was used to diagnose Disease A. The sensitivity of Test A was 80% or 0.8, and the specificity was 94% or 0.94. Thus the LR+ of this test is calculated as 0.8/1 − 0.94 = 0.8/0.06 or 13.3. This means that a person with Disease A is about 13 times more likely to have a positive test than a person who has not got Disease A.

LR+s greater than 1 mean that a positive test is more likely to occur in people with the disease than in people without the disease. LR+s less than 1 mean that a positive test is less

likely to occur in people with the disease compared to people without the disease. Generally speaking, for patients who have a positive result, LR+s of more than 10 significantly increase the probability of disease ('rule in' disease) whilst very low LR+s (below 0.1) virtually rule out the chance that a person has the disease 5).

Likelihood ratio for a negative test

LR− is defined as the probability of an individual *with* disease having a negative test divided by the probability of an individual *without* disease having a negative test. The formula for calculating LR− is:

$$\text{LR}- = \frac{\text{The probability of an individual } with \text{ the disease having a positive test}}{\text{The probability of an individual } without \text{ the disease having a positive test}}$$

The numerator in this equation is the converse of sensitivity (1 − sensitivity), and the denominator is equivalent to specificity. Thus the LR− of a test can be calculated by dividing 1 − sensitivity by specificity (1 − Sensitivity/Specificity).

Interpretation of likelihood ratio for a negative test

The sensitivity of our hypothetical test, Test A, was 80% or 0.8, and the specificity was 94% or 0.94. Thus LR− for Test A is $1 - 0.8/0.94 = 0.2/0.94$ or 0.21. This means that the probability of having a negative test for individuals with Disease A is 0.21 times or about one-fifth of that of those without the disease. Put in another way, individuals without the disease are about five times more likely to have a negative test than individuals with the disease.

LR−s greater than 1 mean that a negative test is more likely to occur in people with the disease than in people without the disease. LR−s less than 1 mean that a negative test is less likely to occur in people with the disease compared to people without the disease. Generally speaking, for patients who have a negative test, LR−s of more than 10 significantly increase the probability of disease (rule in disease) whilst a very low LR− (below 0.1) virtually rule out the chance that a person has the disease (5).

ESTIMATING PROBABILITY OF DISEASE

A major advantage of likelihood ratios is that they can be used to help the clinician adapt the sensitivity and specificity of tests to individual patients. When you see a patient in your clinic, you may decide to perform a particular test after taking a history and examining the patient. You decide to perform that test because, based on the patient's symptoms and signs and your personal experience, you suspect a certain diagnosis and would like to either rule in or 'rule out' this diagnosis. Before you request the test, you usually have a rough estimate of your patient's chance or probability of having that disease. The estimated probability of disease *before* the test result is known is referred to as the **pre-test probability**, which is usually estimated on the basis of the clinician's personal experience, local prevalence data and published reports (6).

The most important reason why you perform the test is to try and obtain further information which may modify the pre-test probability of disease. A positive test may increase the pre-test probability and a negative test may reduce the pre-test probability. The patient's probability or chance of having the disease *after* the test results is known is referred to as the **post-test probability**. The post-test probability of disease is what clinicians and patients are most interested in as this can help in deciding whether to confirm a diagnosis, rule out a diagnosis or perform further tests.

The results of clinical tests are usually used not to categorically make or exclude a diagnosis but to modify the pre-test probability in order to generate the post-test probability. The Bayes theorem is a mathematical relationship which allows the estimation of post-test probability.

Bayes theorem

The Bayes theorem, named after Reverend Thomas Bayes, an 18th century mathematician, describes how to update or revise beliefs in the light of new evidence. Applied to diagnostic tests, the theorem describes how the result of a test (positive or negative) changes our knowledge of the probability of disease (3, 7). This is done by combining the pre-test probability of disease (estimated from clinical experience, local disease prevalence etc.) with the likelihood ratio of the test. In routine clinical practice, there are two ways of using the Bayes theorem to estimate post-test probability: by direct mathematical calculation and by using the Fagan's nomogram (3).

Mathematical calculation

According to the Bayes theorem, the post-test odds that a patient has a disease is obtained by multiplying the pre-test odds by the likelihood ratio of the test (3).

$$\text{Post} - \text{test odds} = \text{pre} - \text{test odds} \times \text{likelihood ratio}$$

The use of odds rather than probabilities in this equation makes the calculation a little bit complex because pre-test probabilities must be converted to pre-test odds which is multiplied by the likelihood ratio to get the post-test odds which is then converted into post-test probabilities (8). For this reason, I will not dwell too much on the mathematical calculation but will describe in detail how the Fagan's nomogram allows a much easier way of using the likelihood ratio of a test to update or revise a patient's pre-test probability in order to provide a post-test probability of disease.

The Fagan's nomogram

The Fagan's nomogram (Fig. 1) is a graphical tool which, in routine clinical practice, allows one to use the results of a diagnostic test to estimate a patient's probability of having disease (9). In this nomogram, a straight line drawn from a patient's pre-test probability of disease (left axis) through the likelihood ratio of the test (middle axis) will intersect with the post-test probability of disease (right axis).

A hypothetical example

In the hypothetical population described in the first article of the series (4), the prevalence of Disease A was 10%, which

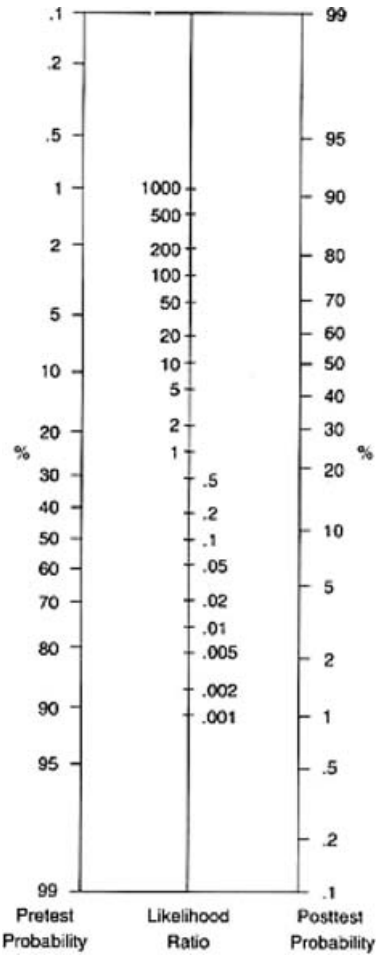

Figure 1 The Fagan's nomogram.

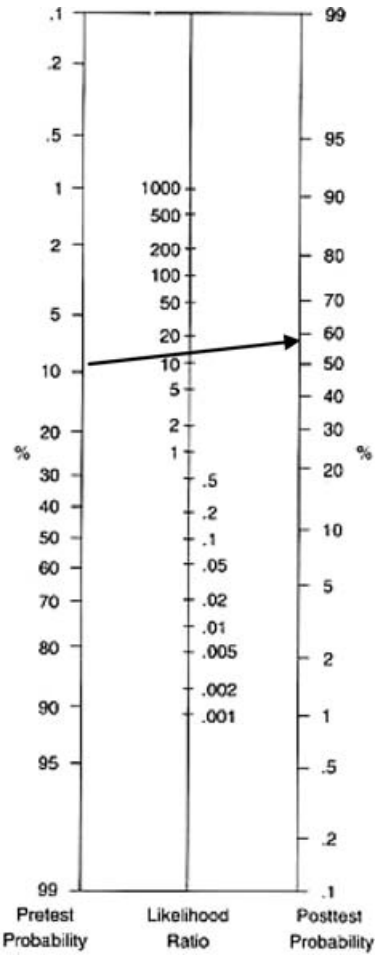

Figure 2 The use of the Fagan's nomogram (a straight line through the pre-test probability of 10% and the LR+ and the LR+ of 13 yields a post-test probability of 60%).

means that when we randomly select a person from this population, his or her chance of having Disease A (pre-test probability) is 10%. The LR+ of Test A was earlier calculated to be about 13. As shown in Figure 2, when we draw a straight line from the pre-test probability of 10% through the likelihood ratio of 13, the line intersects with the post-test probability of about 60%. This means that the probability of Disease A for a person in this hypothetical population increases from 10% to 60% when he or she has had a positive result for Test A.

In the same way, we can also estimate the post-test probability of a person in this population who has a negative result. You will recall that the LR− of Test A was earlier calculated to be 0.21. Joining the pre-test probability of 10% to the likelihood ratio of 0.21 on the Fagan's nomogram, we read off a post-test probability of about 2% (Fig. 3). This means that after a negative test, a person in this population's chance of having Disease A reduces from 10% to 2%.

DIAGNOSTIC TESTS IN PRACTICE

To further understand the practical application of these concepts, consider the use of serological testing in children with coeliac disease (CD), which is a condition characterized by a permanent intolerance to gluten and mucosal disease of the small bowel. The definitive diagnosis of the disease is based on small intestinal biopsy (10). Intestinal biopsy is, however, an invasive procedure and serological testing has become a significant adjuvant in the screening and diagnosis of CD. Serological tests could be used to select which patients need a biopsy and may also be helpful in preventing unnecessary biopsies being performed. One such serological test is the IgA endomyseal antibody test. In a recent study, Rostom et al. found the sensitivity and specificity of the IgA endomyseal antibody test to be 96% and 97%, respectively in the paediatric population (11).

Note that for reasons explained in the first article of the series (4), the sensitivity and specificity of this test cannot be used to predict the probability of CD in an individual patient who has a positive or a negative endomyseal antibody test. We can, however, use the sensitivity and specificity values to calculate likelihood ratios which can be used to help adapt the results of the test to individual patients. The LR+ of the test is calculated as Sensitivity/1 − Specificty = 0.96/1 − 0.97 = 0.96/0.03 or 32. This means that a person with CD is 32 times more likely to have a positive test result than a

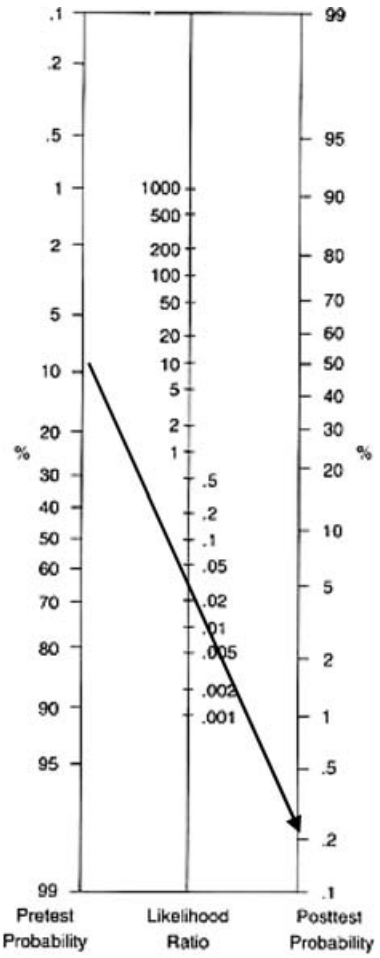

Figure 3 The use of the Fagan's nomogram (a straight line through the pre-test probability of 10% and the LR− of 0.21 yields a post-test probability of about 2%).

person without CD. The LR− is calculated as 1 − Sensitivity/Specificity = 0.04/0.97 or 0.04. This means that a person with CD is 0.04 times less likely to have a negative test result than a person without CD.

Using the Fagan's nomogram, I will now apply the concepts outlined to three children with different pre-test probabilities of CD who were referred to a paediatrician. I will explain how the results of the IgA endomyseal antibody test could be used by the paediatrician to estimate post-test probabilities, which may influence decisions on whether to subject the children to small intestinal biopsies.

Real-life examples

Patient 1

A 12-month-old white girl is seen in a Manchester general paediatric clinic with a 7-month history of diarrhoea and failure to thrive.

On the basis of the paediatrician's experience, he estimated the pre-test probability of CD to be 40%. What would be the child's post-test probability of having CD if she has a positive IgA endomyseal antibody test? To estimate this, the paediatrician could use the Fagan's nomogram (Fig. 1). A straight line drawn from the pre-test probability of 40% through the LR+ of 32 will intersect with a post-test probability of about 95%. Thus after testing positive for the IgA endomyseal antibody test, this child's probability of having CD will increase from 40% to 95%. The paediatrician may then decide that the post-test probability is so high that CD is very likely, and small intestinal biopsies may be recommended.

What about if the child had a negative result? The LR− is 0.04, so when we draw a straight line on the nomogram to connect the pre-test probability of 40% with the likelihood ratio of 0.04, the post-test probability will be about 2.5%. This means that if the patient tests negative, her chance of having CD would decrease from 40% to a very low risk of 2.5%. This may make the paediatrician decide not to recommend small intestinal biopsies.

Patient 2

A 9-year-old boy with insulin dependent diabetes mellitus (IDDM) was seen in a paediatric diabetic clinic in London. He was well and had no gastrointestinal symptoms. Since the risk of CD in children with diabetes is higher than the general population, the paediatrician decided to routinely screen with the IgA endomyseal antibody test.

The prevalence of CD in children with IDDM has been estimated to be about 4.5% (12). Thus the paediatrician estimated this boy's pre-test probability of having CD as 4.5%. When this child returns a positive IgA endomyseal antibody test, we can estimate his post-test probability on the Fagan's nomogram by drawing a straight line from the pre-test probability of 4.5% on the left axis through the LR+ of 32 and read off the post-test probability as about 60%. Thus by testing positive, this child's chances of having CD has increased from 5% to 60%. This may make the paediatrician decide to recommend small intestinal biopsies.

Likewise, if this child tests negative, we can join his pre-test probability of 4.5% through the LR− of 0.04 and read off as his post-test probability as 0.2%. This means that after testing negative, this child's chance of having CD has reduced from 4.5% to 0.2%. A small intestinal biopsy may not be recommended.

Patient 3

A 10-year-old Turkish boy who was healthy with no gastrointestinal symptoms and no family history of CD had a positive IgA endomyseal antibody test when the test was performed 'by mistake' at the general practitioner's surgery in Ankara.

The prevalence of biopsy proven CD in healthy Turkish school children has been estimated to be about 0.6% (13). Thus this child's pre-test probability of having CD is 0.6%. Joining this pre-test probability to the LR+ of 32 will yield a post-test probability of about 16%. Thus after testing positive, this child's chance of having CD is 16%. The paediatrician will then have to decide after consultation with the parents whether the risk of 16% is high enough to subject the child to biopsies.

If this child had tested negative, we could join his pre-test probability of 0.6% through the LR− of 0.04 and read off as his post-test probability as being well below 0.1%. Thus by testing negative, this child's chance of having CD becomes virtually non-existent.

CONCLUSION

Sensitivity, specificity and disease prevalence interact to determine a test's ability to predict the presence or absence of disease. Likelihood ratios derived from sensitivity and specificity could be used in conjunction with a patient's pre-test probability of disease to estimate the post-test probability of disease. The Fagan's nomogram allows a simple estimation of post-test probability of disease and I will recommend its use in routine clinical practice.

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