LR in autoimmune diagnostics and beyond

Personal experience with LR in practice

Xavier Bossuyt
UZ KU Leuven, Belgium

Financial disclosure

- Thermo Fisher Scientific: lecture fees
- Werfen: scientific advisory committee

Introduction

What does a weak pos. autoantibody test result mean?

"Medicine is a science of uncertainty and an art of probability."

~ William Osler (1849-1919)

Probability for disease based on laboratory test results

Vermeersch P, Bossuyt X. Arch Intern Med. 2010;170:734-5.

Likelihood ratio (LR)

Pre-test odds X LR = post-test odds

$$\frac{\text{Prob.}}{\text{1-prob.}} = \text{odds}$$

Pre-test odds X LR = post-test odds

$$\frac{\text{odds}}{\text{1+odds}} = \text{prob.}$$

LR for single cutoff

Anti-CCP	Interval	Fraction of patients	Fraction of controls	LR
	Positive	0.67	0.05	13.4
	Negative	0.33	0.95	0.35

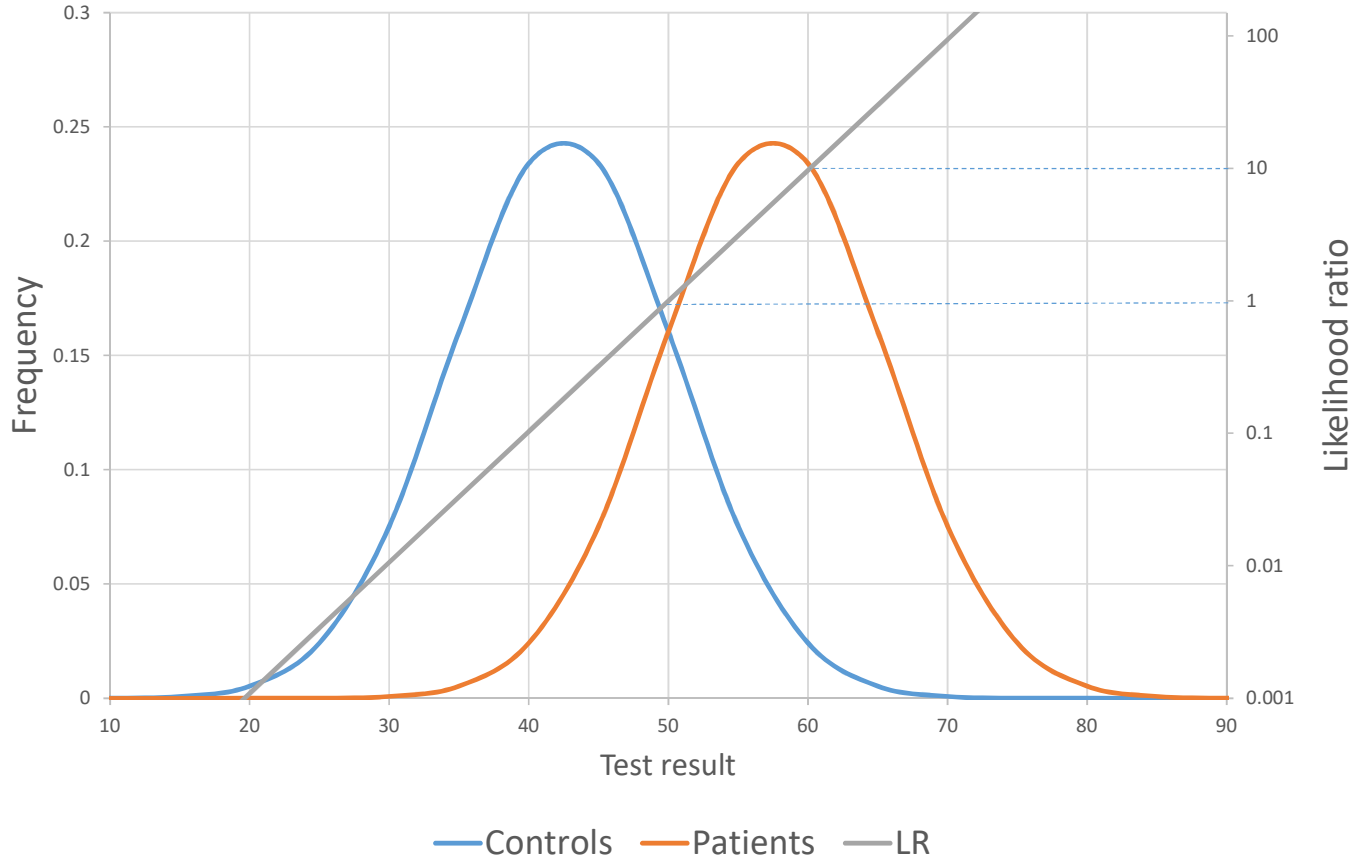
Bossuyt X. Autoimmunity Reviews 2009;8:543-548

Test result interval-specific LR

PR3-ANCA - MPO-ANCA (cut-off)	**Interval**	**Fraction of patients**	**Fraction of controls**	**LR**	**95% CI**
FEIA EliA, Thermo-Fisher	0.0, 2.1	0.099	0.950	0.10	0.07, 0.15
PR3: equivocal 2–3 IU/l	2.1, 5.0	0.083	0.025	3.4	1.9, 6.0
MPO: equivocal 3.5–5 IU/l	5.0, 16.0	0.179	0.015	11.8	6.6, 21.1
	16.0, 142.0	0.571	0.010	58.73	30.4, 113.5
	142.0, 180.0	0.067	0.000	∞	7.5, ∞

Bossuyt X, et al. Rheumatology (Oxford). 2017;56:1533-1541.

Test result-specific LR



Fierz W, Bossuyt X. Likelihood Ratios as Value Proposition for Diagnostic Laboratory Tests. J Appl Lab Med. 2020;5:1061-1069.

Fierz W, Bossuyt X. Likelihood Ratio Approach and Clinical Interpretation of Laboratory Tests. Front Immunol. 2021 Apr 16;12:655262

Reporting LR in a clinical setting

Ideal situation

Pre-test probability

Pre-test odds X test result-specific LR = post-test odds

Post-test probability

Ideal situation

only few studies available
requires structured data

Pre-test probability

Pre-test odds X test result-specific LR = post-test odds

Post-test probability

should be automated
graphical representation

Pragmatic approach

Test result interval-specific LR

Straightforward calculation

Interval thresholds based on predefined specificity level

allows consistency between assays and studies

Pragmatic approach

Test result interval-specific LR

Intuitive diagnostic information

Includes information on antibody level

No need to calculate post-test probability

Independent of the specific test

Pragmatic approach

How to establish LRs?

Consecutively diagnosed patients *(sample obtained at diagnosis)* *and disease controls*

Ideally multicenter, multinational

Examples of LR values on lab reports

ANCA: clinical suspicion AAV

PR3-ANCA

MPO-ANCA

LR reporting

Box 2: Clinical indications for ANCA testing

- Glomerulonephritis, especially rapidly progressive glomerulonephritis
- Pulmonary haemorrhage, especially pulmonary renal syndrome
- Cutaneous vasculitis with systemic features
- Multiple lung nodules
- Chronic destructive disease of the upper airways
- Long-standing sinusitis or otitis
- Subglottic tracheal stenoses
- Mononeuritis multiplex or other peripheral neuropathy
- Retro-orbital mass
- Scleritis

Bossuyt X, et al. Nat Rev Rheumatol. 2017;13:683-692

ANCA: follow-up

PR3-ANCA or MPO-ANCA

ANCA: IBD

IIF

ANCA: clinical suspicion AAV

ANCA identification		
PR3-ANCA	<0.6	U/mL
<2: negative, 2-3: equivocal, >3: positive		
MPO-ANCA	12.0	U/mL
<3.5: negative, 3.5-5: equivocal, >5 positive		
Likelihood ratio for ANCA-associated vasculitis at diagnosis	11.8	
(*Rheumatology 2017; 56:1533-1541*)	(95% CI: 6.6-21.1)	

Reporting LR in RA

Rheumatoid factor	
RF – IgM	37 U/mL
<3.5: negative, 3.5-5.0: equivocal, >5.0: positive	
Likelihood ratio for rheumatoid arthritis at diagnosis	7.5 (95% CI: 4.9-11.45)
(RMD Open 2022 Mar;8:e002099)	

ACPA	
Anti-cyclic citrullinated peptide (CCP)	55 U/mL
<7: negative, 7-10: equivocal, >10: positive	
Likelihood ratio for rheumatoid arthritis at diagnosis	8.9 (95% CI: 1.6-48.4)
(RMD Open 2022 Mar;8:e002099)	

ACPA	
Anti-cyclic citrullinated peptide (CCP)	375 U/mL
<7: negative, 7-10: equivocal, >10: positive	
Likelihood ratio for rheumatoid arthritis at diagnosis	106.9 (95% CI: 2.58-4425.96)
(RMD Open 2022 Mar;8:e002099)	

Reporting LR for ANA / CTD Screen

Antinuclear antibodies screening (IIF)

Nucleus	positive
Pattern	fine speckled
Titer	1:320
Cytoplasm	negative
Fluorescence intensity	626 LIU
>48: positive	
LR for ANA-associated rheumatic disease at diagnosis	5.2 (95% CI: 3.2-8.6)
(Autoimmun Rev 2018;17:533-540)	

Connective tissue disease (CTD) screen

(dsDNA, SSA/Ro 52, SSA/Ro 60, SSB/La, U1-RNP (RNP-70, A, C), Sm, centromere B, Jo-1, Scl-70, Rib-P, fibrillarin, RNA Pol III, PM-Scl, PCNA, and Mi-2)

CTD screen	0.8 ratio
<0.7: negative, 0.7-1.0: equivocal, >1.0: positive	
LR for ANA-associated rheumatic disease at diagnosis	0.75 (95% CI: 0.33-1.73)
(Autoimmun Rev 2018;17:533-540)	

Reporting LR for celiac disease

IgA anti-tissue transglutaminase	
IgA anti-tTG	320 CU
>20: positive	
Likelihood ratio for celiac disease at diagnosis *(Clin Chem Lab Med. 2015;53:1537-46)*	668 (95% CI: 94-4754)

Reporting LR: personal experience

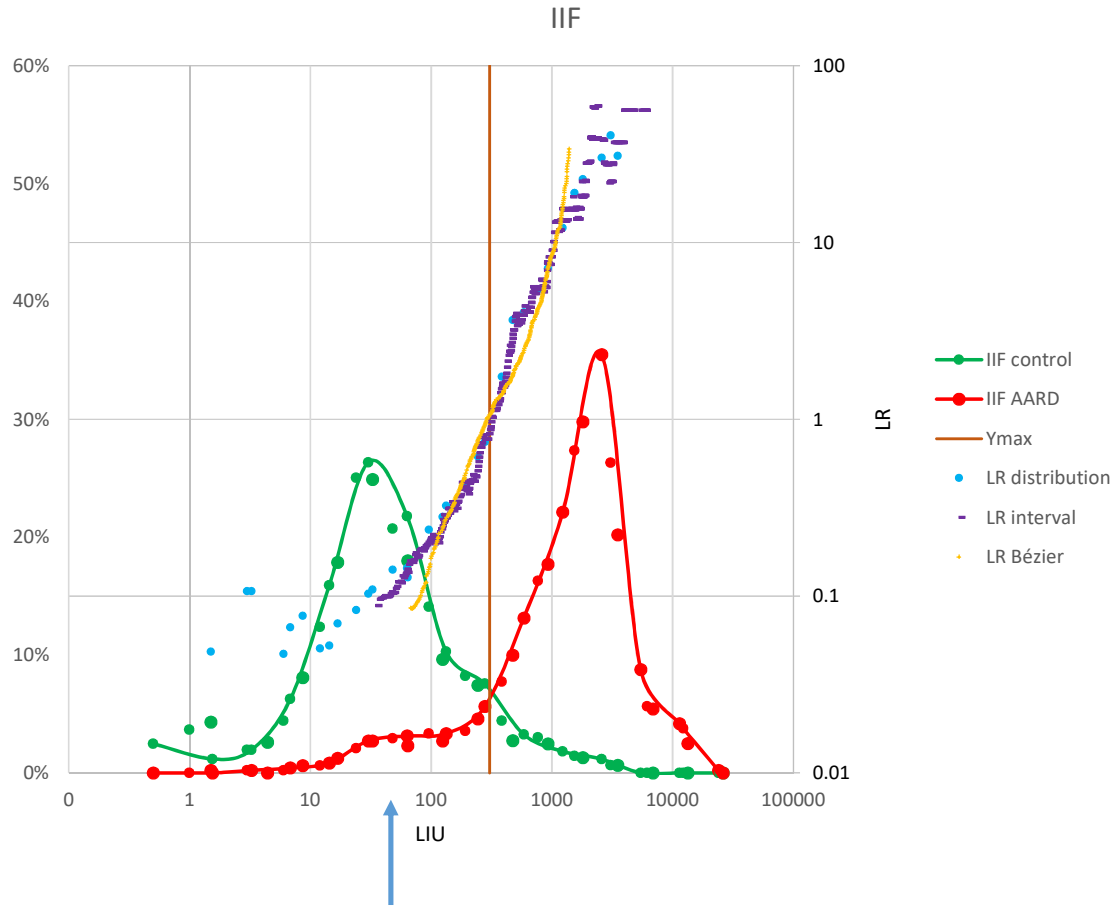
LR: personal experience

Useful intuitive diagnostic information

Request to introduce LR for test combinations

Assay-independent diagnostic information

Request to introduce LR for allergy tests



Bossuyt X et al. Autoimmun Rev. 2019;18:102386

LR: personal experience

Useful intuitive diagnostic information

Request to introduce LR for test combinations

Assay-independent diagnostic information

Request to introduce LR for allergy tests

LR: personal experience

Useful intuitive diagnostic information

Request to introduce LR for test combinations

Assay-independent diagnostic information

Request to introduce LR for allergy tests

LR: personal experience

Useful intuitive diagnostic information

Request to introduce LR for test combinations

Assay-independent diagnostic information

Request to introduce LR for allergy tests

LR in allergy testing

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

Defining thresholds of specific IgE levels to grass pollen and birch pollen allergens improves clinical interpretation

Erna Van Hoeyveld [a,1], Silvie Nickmans [a,1], Jan L. Ceuppens [b], Xavier Bossuyt [a,*]

[a] Laboratory Medicine, Immunology, University Hospitals, KU Leuven, Belgium
[b] Allergy and Clinical Immunology, University Hospitals, KU Leuven, Belgium

Clinical Commentary Review

Evolving Interpretation of Screening and Diagnostic Tests in Allergy

Elissa M. Abrams, MD, FRCPC, MPH[a], Edmond S. Chan, MD, FRCPC[b], and Jay Portnoy, MD[c] *Winnipeg, MB and Vancouver, BC, Canada; and Kansas City, Mo*

Correspondence and Replies

The added value of reporting likelihood ratios to laboratory test results in allergy and clinical immunology

To the Editor:

It was with much interest that we have read the article by Abrams et al[1] on using the Bayesian approach in reporting laboratory test results in allergy diagnostics. In their report, the authors make a case to include likelihood ratios (LRs) in the reports of laboratory tests, an idea we fully support.

Reporting LRs allows one to estimate the posttest probability for disease based on the pretest probability and the LR. Even if the pretest probability is not exactly known, the LR gives the

Finally, LRs express the clinical value of a test result independent of the unit used by the assay. This is especially useful for autoantibody tests for which good reference materials are unavailable and different units are applied by the manufacturers. It was shown that LRs harmonize ANCA[6] and antinuclear antibody[7] testing across assays.

Adding LRs to laboratory reports adds value to the field of allergy and clinical immunology. These reports can be supplemented with a graphical representation of posttest probability as a function of pretest probability and the laboratory result (eg, for a specific IgE result[2,3]). Therefore, in agreement with Abrams et al,[1] we encourage further research in this area.

Xavier Bossuyt, MD, PhD[a,b]
Glynis Frans, PhD[a]

Reply to "The added value of reporting likelihood ratios to laboratory test results in allergy and clinical immunology"

To the Editor:

laboratories and from investigators who study the performance of diagnostic tests.

Jay Portnoy, MD[a]
Elissa M. Abrams, MD, FRCPC, MPH[b]
Edmond S. Chan, MD, FRCPC[c]

[a]Department of Allergy and Immunology, Children's Mercy Hospital Kansas City, Miss
[b]Department of Allergy and Immunology, University of Manitoba, Winnipeg, Manitoba,

"If laboratories (or perhaps the US FDA) were to demand LR values for tests before they could be licensed, investigators would have an incentive to determine and report them rather than generating a confusion matrix to determine sensitivity, specificity, and predictive values for a single cutoff value."

Conclusions

Likelihood ratio

- provides intuitive diagnostic information
- gives an idea how much more or less likely a particular test result occurs in patients compared to controls
- is unit-independent

Acknowlegdments

1. Lieve Van Hoovels
2. M. Infantino
3. B. Van der Cruyssen, P. Verschueren, S. Vanden Brempt
4. J. Claessens, T. Belmondo, E. De Langhe, R. Westhovens, K. Poesen, S. Hüe, D. Blockmans, M. J. Fritzler, M. Mahler, W. Fierz, S. Broeders
5. N. Rasmussen, P. van Paassen, B. Hellmich, B. Baslund, P. Vermeersch, D. Blockmans, JW Cohen Tervaert, J. Damoiseaux, E. Csernok
6. L. Nevejan, P. Dobbels, G.Norman, A. Voreck
7. G. Steiner, D. Sieghart, C. Bonroy, N. Eszter N, R. Pullerits, S. Čučnik, C. Dahle, I. Heijnen, L. Bernasconi, F. Benkhadra, L. Bogaert, A. Van Liedekerke, G. Vanheule, J. Robbrecht, L. Studholme, C. Wirth, R.B. Müller, D. Kyburz D, C. Sjöwall, A. Kastbom, R. Ješe, B. Jovancevic, K. Emese, P. Jacques, D. Aletahah
8. L. Bogaert, M. Cauchie, P. Vermeersch, W. Fierz, G. De Hertogh, I. Hoffman
9. E. Van Hoeyveld, J. Ceuppens.
10. In vitro diagnostic companies: Orgentec, Euroimmun, BioRad, Thermo Fisher, Werfen, Svar Diagnostics, Generic Assays, Roche Siemens, Abbott, Diazym , Cambridge Life Science, Abbott, Ortho-Clinical diagnostics, Beckman Coulter, Siemens, Diazym, Werfen

ANCA

Bossuyt X, Rasmussen N, van Paassen P, Hellmich B, Baslund B, Vermeersch P, Blockmans D, Cohen Tervaert JW, Csernok E, Damoiseaux J. A multicentre study to improve clinical interpretation of proteinase-3 and myeloperoxidase anti-neutrophil cytoplasmic antibodies. Rheumatology (Oxford). 2017;56:1533-1541.

ACPA - RF

Van Hoovels L, Vander Cruyssen B, Sieghart D, Bonroy C, Nagy E, Pullerits R, Čučnik S, Dahle C, Heijnen I, Bernasconi L, Benkhadra F, Bogaert L, Van Den Bremt S, Van Liedekerke A, Vanheule G, Robbrecht J, Studholme L, Wirth C, Müller R, Kyburz D, Sjöwall C, Kastbom A, Ješe R, Jovancevic B, Kiss E, Jacques P, Aletaha D, Steiner G, Verschueren P, Bossuyt X. Multicentre study to improve clinical interpretation of rheumatoid factor and anti-citrullinated protein/peptide antibodies test results. RMD Open. 2022;8:e002099.

ANA

Claessens J, Belmondo T, De Langhe E, Westhovens R, Poesen K, Hüe S, Blockmans D, Mahler M, Fritzler MJ, Bossuyt X. Solid phase assays versus automated indirect immunofluorescence for detection of antinuclear antibodies. Autoimmun Rev. 2018 Jun;17(6):533-540.

Bossuyt X, Claessens J, De Langhe E, Belmondo T, Westhovens R, Hue S, Poesen K, Blockmans D, Mahler M, Fritzler MJ. Antinuclear antibodies by indirect immunofluorescence and solid phase assays. Ann Rheum Dis. 2020;79:e65.

IgA tissue transglutaminase – DGP

Oyaert M, Vermeersch P, De Hertogh G, Hiele M, Vandeputte N, Hoffman I, Bossuyt X. Combining antibody tests and taking into account antibody levels improves serologic diagnosis of celiac disease. Clin Chem Lab Med. 2015;53:1537-46.