Diagnostic aid

How to use likelihood ratios in the daily routines of your laboratory

Introduction

Systemic autoimmune diseases are often difficult to diagnose. Healthcare providers (HCPs) expect a clear-cut response from laboratories, but autoantibody tests can give a hint, not a diagnosis. Clinicians are not always familiar with the diagnostic value of a specific autoantibody test result, and the interpretation of a test result might be challenging.[1–3] Likelihood ratio (LR) intervals enable interpretation of laboratory results, independent of a manufacturer's cut-off, thus allowing harmonization of test result interpretation and providing a clear indication of the connection of autoantibody titer and disease association.[1–3] Therefore, it is suggested that laboratories indicate the LR of a test result in their report in addition to units and manufacturer's cut-off.[1]

What is likelihood ratio (LR)

LR associated with the absence or presence of a disease

LR–	**Exclude a disease** A likelihood ratio **below 1.0 (LR-)** tells you how much the odds of having a disease decrease when a test is negative. The lower the LR- is, the more you can exclude a disease.[4]	<0.1	High association with absence of disease
		0.1 – 0.2	Moderate association with absence of disease
		0.2 – 0.5	Weak association with absence of disease
		0.5 – 2	No association with disease
LR+	**Confirm a disease** A likelihood ratio **above 1 (LR+)** tells you how much the odds of having a disease increase when a test is positive. The higher the LR+ is, the more you can confirm a disease.[4]	2 – 5	Weak association with presence of disease
		5 – 10	Moderate association with presence of disease
		>10	High association with presence of disease

Test result interval-specific LRs of EliA tests

Data for interval-specific LRs are calculated on the basis of clinical studies with diagnostic samples which are published in peer-reviewed journals. Studies are available for the following markers. With every new study, the list will expand.

Celiac disease (CeD)

EliA™ Celikey IgA test (for children)

Result interval	LR	Association with CeD in children
< 7 U/ml	**0.11**	9x more likely to be found in non-CeD patients than in CeD patients
7 – 70 U/ml	**48.20**	48.2x more likely to be found in CeD patients than in non-CeD patients
> 70 U/ml	∞	All children with an EliA Celikey IgA test result > 70 U/ml had CeD.

Reference: Bogaert L et al. Autoimmunity Reviews 2020; 19: 102513.

EliA™ Celikey IgA test

Result interval	LR	95% CI	Association with CeD
< 7 U/ml	**0.19**	0.14 – 0.27	5.26x more likely to be found in non-CeD patients than in CeD patients
7 – 21 U/ml	**7.40**	3.4 – 16.2	7.4x more likely to be found in CeD patients than in non-CeD patients
21 – 70 U/ml	**200**	28 – 1452	200x more likely to be found in CeD patients than in non-CeD patients
> 70 U/ml	**506**	71 – 3608	506x more likely to be found in CeD patients than in non-CeD patients

Reference: Oyaert M. Clin Chem Lab Med 2015; 53:1537-1546.

EliA™ Gliadin^{DP} IgG test

Result interval	LR	95% CI	Association with CeD
< 7 U/ml	**0.11**	0.07 – 0.17	9.1x more likely to be found in non-CeD patients than in CeD patients
7 – 21 U/ml	**7.0**	4.2 – 11.7	7x more likely to be found in CeD patients than in non-CeD patients
21 – 70 U/ml	**81**	25 – 259	81x more likely to be found in CeD patients than in non-CeD patients
> 70 U/ml	∞	∞	All individuals with an EliA Gliadin^{DP} IgG test result > 70 U/ml had CeD.

Reference: Oyaert M. Clin Chem Lab Med 2015; 53:1537-1546.

EliA Celikey IgA test combined with EliA Gliadin^{DP} IgG test

EliA Celikey IgA LR (95% CI)

EliA Gliadin^{DP} IgG test LR (95% CI)

Result interval	< 7 U/ml	7-21 U/ml	21-70 U/ml	>70 U/ml
< 7 U/ml	0.08 (0.05 – 0.14)	1.3 (0.3 – 5.7)	12 (1 – 137)	∞
7 – 21 U/ml	1.6 (0.7 – 3.9)	18 (2 – 179)	∞	56.2 (7 – 440)
21 – 70 U/ml	6.2 (1.3 – 30.6)	∞	∞	∞
> 70 U/ml	∞	∞	∞	∞

Reference: Oyaert M. Clin Chem Lab Med 2015; 53:1537-1546.

Rheumatoid arthritis (RA)

EliA™ CCP IgG test

Result interval	LR	95% CI	Association with RA
< 3.3 U/ml	**0.33**	0.29 – 0.39	3x more likely to be found in non-RA patients than in RA patients
3.3 – 9.5 U/ml	**0.90**	0.49 – 1.29	No association with RA
9.5 – 79.8 U/ml	**8.93**	1.65 – 48.42	8.93x more likely to be found in RA patients than in non-RA patients
79.8 – 324.6 U/ml	**27.30**	2.71 – 271.40	27.3x more likely to be found in RA patients than in non-RA patients
> 324.6 U/ml	**106.90**	2.58 – 4425.96	106.9x more likely to be found in RA patients than in non-RA patients

Reference: Van Hoovels L et al. RMD open 2021: 002099.

EliA™ RF IgM test

Result interval	LR	95% CI	Association with RA
< 5.0 IU/ml	**0.42**	0.37 – 0.48	2.4x more likely to be found in individuals without RA than in RA patients
5.0 – 7.5 IU/ml	**2.14**	1.25 – 3.65	2.14x more likely to be found in RA patients than in non-RA patients
7.5 – 15.0 IU/ml	**3.16**	1.95 – 5.12	3.16x more likely to be found in RA patients than in non-RA patients
15.0 – 45.0 IU/ml	**7.49**	4.90 – 11.45	7.49x more likely to be found in RA patients than in non-RA patients
> 45.0 IU/ml	**12.51**	8.25 – 18.97	12.51x more likely to be found in RA patients than in non-RA patients

Reference: Van Hoovels L et al. RMD open 2021: 002099.

ANCA-associated vasculitis (AAV)

The authors of this study calculated the interval-specific LRs only for PR3 and MPO ANCA together, as both tests should always be done in parallel. In AAV, only one of the two tests is positive. This positive result of one of the tests defines the interval-specific LR. If both tests are positive, studies indicate a low probability of having AAV.[8]

EliA™ PR3^S test or EliA™ MPO^S test

Result interval	LR	95% CI	Association with AAV
< 2.1 IU/ml	**0.10**	0.07 – 0.15	10x more likely to be found in non-AAV patients than in AAV patients
2.1 – 5.0 IU/ml	**3.35**	1.89 – 5.96	3.35x more likely to be found in AAV patients than in non-AAV patients
5.0 – 16 IU/ml	**11.80**	6.58 – 21.14	11.8x more likely to be found in AAV patients than in non-AAV patients
16 – 142 IU/ml	**58.73**	30.39 – 113.50	58.73x more likely to be found in AAV patients than in non-AAV patients
> 142 IU/ml	**∞**	7.52 – ∞	All individuals who had an EliA PR3^S or EliA MPO^S test result > 142 IU/ml had AAV.

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

Connective tissue diseases (CTD)

EliA™ CTD Screen test

Result interval	LR	95% CI	Association with CTD
< 0.4 Ratio	**0.17**	0.14 – 0.21	2.5x more likely to be found in non-CTD patients than in CTD patients
0.4 – 0.7 Ratio	**0.51**	0.28 – 0.92	No association with CTD
0.7 – 1.0 Ratio	**0.75**	0.33 – 1.73	No association with CTD
1.0 – 8.60 Ratio	**20.6**	13.1 – 32.4	20.6x more likely to be found in CTD patients than in non-CTD patients
> 8.60 Ratio	**∞**	28.1 – ∞	All individuals with an EliA CTD Screen result of >8.6 Ratio had a CTD.

Reference: Claessens J et al. Autoimmun Rev 2018;17:533-540.

How to report test result interval-specific LRs

The interval-specific LRs are calculated with data from huge studies using diagnostic samples. The data source is mentioned under the tables. The reference for the LR study should always be mentioned in your report.

Example – your result for EliA MPO[s]

12.0 IU/ml, which is in the interval 5.0 – 16 IU/ml (see table "ANCA-associated vasculitis" on page 3). The corresponding LR is 11.80, the 95% confidence interval is 6.58 – 21.14. With a LR above 10, there is a high association with AAV.

LRs for a result can be found in tables on pages 2 and 3, indicating the LRs of test result intervals. For every test result interval, the LR is calculated and can be reported in addition to the quantitative result and the cut-off.

Examples of how to incorporate LR into lab reports:

ANCA identification	
PR3 ANCA (FEIA) → <2: negative; 2–3: equivocal; >3 positive	<0.6 IU/ml
MPO ANCA (FEIA) → <3.5: negative; 3.5–5: equivocal; >5 positive	12.0 IU/ml
LR for ANCA-associated vasculitis*	11.8 (95% CI: 6.58–21.14) * Bossuyt X et al. Rheumatology 2017;56(9):1533-1541

Celiac serology	
Tissue transglutaminase IgA antibodies → <7: negative; 7–10: equivocal; >10 positive	15.0 U/ml
Deamidated gliadin IgG antibodies → <7: negative; 7–10: equivocal; >10 positive	12.0 U/ml
LR for celiac disease*	18 (95% CI: 2–179) * Oyaert M. Clin Chem Lab Med 2015; 53:1537-1546

References

1. Bossuyt X et al. Autoimmun Rev 2019;18:102386. **2.** Fierz W, Bossuyt X. Front Immunol 2021;12:655262. **3.** Bossuyt X et al. Clin Chem Lab Med 2021;59(2):e35-e39. **4.** Deeks JJ, Altman DG. Diagnostic tests 4: likelihood ratios. Br Med J 2004;329:168-169. **5.** Bogaert L et al. Autoimmunity Reviews 2020;19:102513. **6.** Oyaert M. Clin Chem Lab Med 2015;53:1537-1546. **7.** Van Hoovels L et al. RMD open 2021;002099. **8.** Chou J et al. J Clin Cell Immunol 2015;6:10.4172/2155-9899. **9.** Bossuyt X et al. Rheumatology (Oxford) 2017;56:1533-1541. **10.** Claessens J et al. Autoimmun Rev 2018;17:533-540.

Find out more at **thermofisher.com/elia**

Thermo Fisher Diagnostics GmbH, Munzinger Str. 7, D-79111 Freiburg, Germany, Tel. +49 761 47-805-0