REVIEW

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Scoping Review: Effectiveness of NDO-LID as new biomarker for leprosy diagnosis

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ABSTRACT

Leprosy is a chronic infectious disease that continues to be prevalent in over 120 countries worldwide, with over 200,000 cases of leprosy. The challenge in controlling leprosy cases is early diagnosis and identification of new cases. It is very important to diagnose quickly and precisely to prevent further disability due to nerve damage. This scoping review aims to assess the effectiveness of NDO-LID as a diagnostic test. The search strategy covered three main databases: PubMed, Science Direct, and Google Scholar, focusing on peer-reviewed studies published from 2019 to 2023. PRISMA guidelines were followed during the literature search. The keywords "NDO-LID" and "NDO-LID Leprosy" were used in the search to find relevant studies. The review included three articles out of 370 relevant ones. The review encompassed 1953 participants across three studies. Part of the review reported on 11 diagnostic test assessments. NDO-LID can detect leprosy patients in both MB and PB cases. Although NDO-LID has higher sensitivity and specificity values than its comparators, further studies are needed to test the accuracy of the diagnostic test more comprehensively to provide stronger and more convincing evidence.

Keywords: diagnosis, leprosy, NDO-LID.
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INTRODUCTION

Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae*. The disease commonly affects the skin and peripheral nerves, leading to neuropathy and various associated long-term consequences, including deformities and disability.[1-6] More than 200,000 new cases of leprosy, a tropical disease that is frequently ignored, are reported annually in more than 120 nations.[7-9] Based on data from the World Health Organization (WHO) in 2021, Indonesia became the third country with the highest number of leprosy cases worldwide. Indonesia reported 10,976 leprosy cases during that year.[7] Leprosy can be classified into five distinct forms based on the host's immune response against *Mycobacterium leprae*. These classifications are characterized by a clinical pathological spectrum, which ranges from tuberculoid-tuberculoid leprosy (TT), borderline tuberculoid (BT), borderline-borderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL).[3,7,10] WHO simplifies the diagnosis of leprosy and aligns it with treatment guidelines by recommending an operational classification based on the number of skin lesions and nerves involved. Leprosy cases are divided into two main categories: paucibacillary (PB) and multibacillary (MB). Paucibacillary cases are tuberculoid-tuberculoid (TT) and borderline tuberculoid (BT) cases, while multibacillary cases include borderline-borderline (BB), borderline lepromatous (BL), and lepromatous leprosy (LL) cases. This classification system assists in determining the appropriate treatment approach for each type of leprosy. Patients with PB have one to five asymmetrical skin lesions and one nerve involved, but no bacilli are found on a skin smear. In contrast, MB patients have at least one involved nerve and more than five skin lesions. MB patients present with higher bacteria indices (BIs) than PB patients.[6,7,11,12]

In the past, the diagnosis of leprosy relied on a combination of clinical manifestation, bacilloscopy, and histopathology.[4,13,14] In any case, the conclusion of leprosy disease is fundamentally founded on clinical assessment. Leprosy commonly manifests through skin lesions and involvement of the peripheral nerves. Pale or reddish numb patches, swelling or enlargement of peripheral nerves (with loss of sensation and/or weakness of muscles controlled by those nerves), or detection of microscopic bacilli on a skin smear sample are all key signs that can be used to make a diagnosis of leprosy. At least one of these critical signs must be recognized to diagnose leprosy.[5,7] Healthcare professionals can diagnose leprosy and initiate appropriate treatment and management for the affected individual.[7] It is very important to diagnose quickly and precisely to prevent further disability due to nerve damage.[6,15,16] Recently, many researchers have been researching the early detection of leprosy. This aligns with WHO's mission to eliminate leprosy from the world.[6] Several biomarkers have been tested, including NDO-LID, a conjugate form of Leprosy IDRI Diagnostic 1 (LID-1) with Natural Disaccharide Octyl (NDO).[17] Numerous studies have evaluated NDO-LID conjugates and consistently shown positive outcomes.[18-21]

Table 1. Criteria for the inclusion of studies

	Inclusion	Exclusion
Population	Leprosy patients	Patients with human immunodeficiency virus (HIV)
Intervention	Serological test for NDO-LID	No NDO-LID as index test
Comparator	Control group must exist	No Control group
Outcomes	Sensitivity and specificity value	There is no information on the number of patients, sensitivity, and specificity value
Design	Studies of diagnostic accuracy	Case report, Literature review

METHODS

Design

This was observational research with a scoping review. This research was started from July 17th up to August 17th, 2023.

Search strategy

Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines were followed during the literature search. The keywords "NDO-LID" and "NDO-LID Leprosy" were used in the search to find relevant studies. The search strategy covered three main databases: PubMed, Science Direct, and Google Scholar, focusing on peer-reviewed studies published from 2019 to 2023.

Research identification

The concept of PCC (Population, Concept, Context) was used to identify relevant research. The population was leprosy patients. The concept was the effectiveness of NDO-LID for leprosy diagnosis. The context was research and reports on the usefulness of NDO-LID in diagnosing leprosy patients.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are presented in Table 1.

Study selection

At first, titles and abstracts were assessed against the set inclusion criteria. The full-text papers that meet these criteria have been retrieved and evaluated for eligibility through complete reading.

Data extraction

Data extracted from each study included authors, year of publication, location, population, and study outcome.

Data analysis

The sensitivity and specificity values of test performance for NDO-LID and other comparison tests were reviewed for each study.

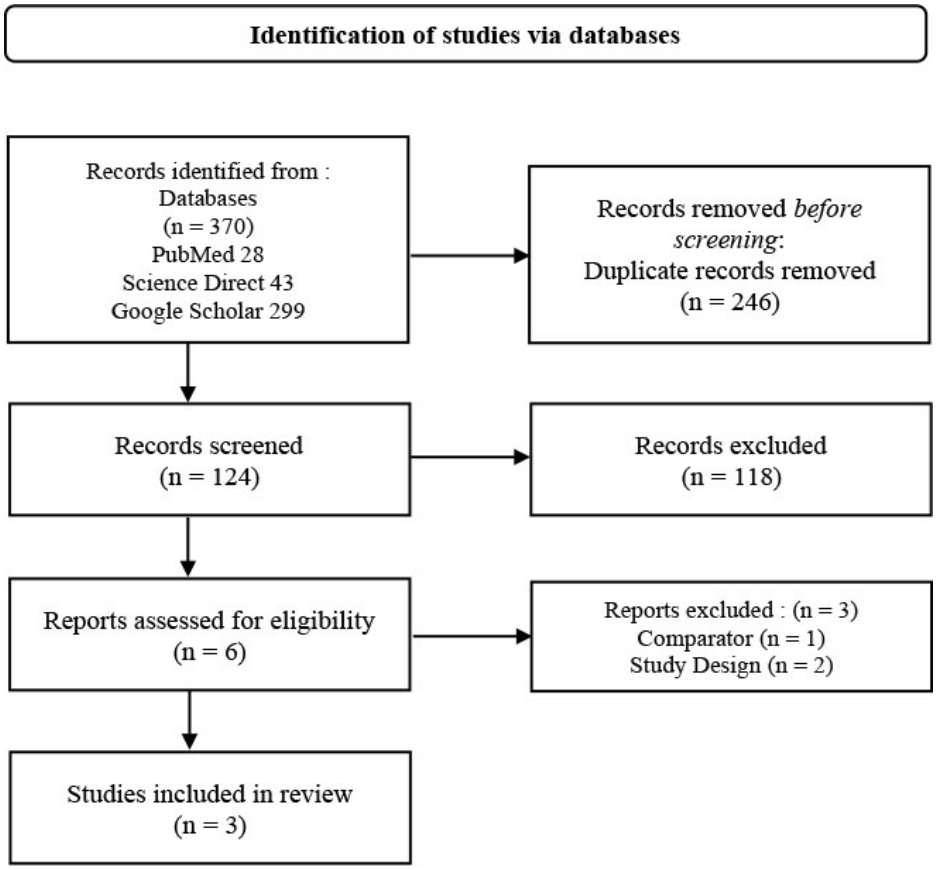

Figure 1. PRISMA 2020 flow diagram.

Ethical approval

It is not required.

RESULTS

From the search results using three international databases with predetermined keywords, 370 articles were found. Then, the articles were evaluated through the titles and abstracts to ensure their relevance. After initial screening, 6 articles were identified that met the criteria. These 6 articles underwent screening for eligibility, and subsequently, 3 articles were excluded during the process. Eventually, 3 articles were included in the review. A PRISMA flowchart diagram illustrating the complete search strategy can be seen in Figure 1.

The review encompassed 1953 participants across three studies. Part of the review reported on 11 diagnostic test assessments. The studies were conducted in two nations, Brazil and China. One study was conducted within public educational institutions, while the remaining were conducted within medical facilities. The study group size varied between 279 to 973 people in each study. The age of participants enrolled in the study ranged from 4 to 84 years. The participation of males made up 60.84 % of the subjects across three studies. Concerning the categorization of cases, instances of MB patients exceeded those of PB cases, with frequencies of 58.40%

Table 2. The characteristics of the three studies

Author, Year	Study Location	Study Population			Study Outcome					
		Sample Size	Characteristics of Study Population	Leprosy Classification	Detection by	Sensitivity	Specificity	Positive Predictive Value (PPV)	Negative Predictive Value (NPV)	Accuracy
Leturiondo, 2019	Brazil	701	171 leprosy patients and 530 healthy subjects	PB	NDO-LID	34.0%	81.7%	14.9%	92.9%	77.6%
					PGL-1	32.0%	75.9%	11.1%	92.2%	72.1%
				MB	NDO-LID	73.6%	81.7%	47.9%	93.1%	80.2%
					PGL-1	81.0%	75.9%	43.4%	94.6%	76.8%
Jian, 2020	China	279	113 leprosy patients and 166 controls	PB	NDO-LID	69.2%	60.4%	22.1%	92.4%	-
					LID-1	56.4%	57.1%	17.6%	89.0%	-
					NDO-BSA	74.4%	41.3%	17.1%	90.8%	-
				MB	NDO-LID	98.6%	76.1%	59.8%	99.4%	-
					LID-1	97.3%	74.1%	57.6%	98.7%	-
					NDO-BSA	97.3%	52.2%	42.4%	98.2%	-
Gobbo, 2022	Brazil	973	894 subjetcs are 706 school children and 188 household contact of school children, 79 subjects are 25 hospital new cases and 54 household contact of hospital new cases subjects	PB and MB in Public Schools	NDO-LID	33.0%	78.0%	-	-	73.0%
					LID-1	6.0%	95.0%	-	-	85.0%
					NDO-BSA	73.0%	31.0%	-	-	36.0%
				PB and MB in Hospital	NDO-LID	77.0%	78.0%	-	-	77.0%
					LID-1	63.0%	100.0%	-	-	88.0%
					NDO-BSA	77.0%	71.0%	-	-	73.0%

and 41.60%, respectively. The characteristics of the three studies are shown in Table 2.

DISCUSSION

Currently, NDO-LID is used for surveillance as a tool to detect Leprosy cases in patients and household contacts.[22,23] To assess the effectiveness of NDO-LID as a diagnostic test, sensitivity and specificity parameters were calculated for both categories of leprosy patients. In Leturiondo et al. (2019) and Jian et al. (2020) study, NDO-LID sensitivity for PB and MB cases were 51.6 % ± 17.6 % and 86.1 % ± 12.5 % respectively. Subsequently, NDO-LID specificity for PB and MB cases were 71.05 % ± 10.65 % and 78.9 ± 2.8 %. The test results of NDO-LID from two reviewed studies stated that NDO-LID has higher sensitivity and specificity values compared to its comparators, such as phenolic glycolipid I (PGL-1), natural disaccharide-octyl conjugated with bovine serum albumin (NDO-BSA), and Leprosy IDRI Diagnostic (LID)-1.

Leturiondo et al. (2019) stated that the accuracy of the NDO-LID test was superior to the PGL-1 test in the case of MB and PB leprosy patients. However, the NDO-LID and PGL1 test results showed a minimal capacity to identify true positive cases among PB patients, at only 14.9% and 11.1%, respectively, and among MB patients, at only 47.9% and 43.4%, respectively. Remarkably, the 93.1% negative predictive value (NPV) of NDO-LID indicates a high confidence level in excluding leprosy.[24] Jian et al. (2020) also showed the benefit of NDO-LID in diagnosing *Mycobacterium leprae* infection. This study stated that NDO-LID had the most significant area under the curve (AUC) for both MB and PB patients. Their research demonstrated that the NDO-LID ELISA is a promising instrument that can significantly aid in diagnosing leprosy.[25]

The two studies above show a weakness of NDO-LID in diagnosing PB leprosy. MB leprosy cases exhibited elevated levels of antigen-specific antibodies in circulation. These antibody levels decreased among PB patients.[13] This is seen in NDO-LID, which has higher accuracy in MB cases. This may happen because MB patients have humoral immunity, while PB patients have cellular immunity. POC immunochromatographic or immunoassay tests are difficult to evaluate the cellular immunity of PB patients.[13,26] Another challenge in diagnosing leprosy is the early diagnosis and identification of new cases.[27] Leprosy patient's household contacts are the population most likely to contract the disease.[28,29]

According to Gobbo et al. (2022), NDO-BSA had a higher capacity to distinguish leprosy infection cases through serology than NDO-LID and LID-1. NDO-BSA had the highest sensitivity value in public schools and hospitals. However, its specificity and accuracy values diminished for early leprosy cases. This finding indicates the limitation of using NDO-BSA for diagnosing early cases. NDO-LID showed similar results to NDO-BSA in all percentages for leprosy patients. However, the sensitivity of NDO-LID was noticeably lower in the case of public school subjects.[30] This result may occur because PB-type leprosy patients dominated the sample in this study. In addition, the current rapid diagnostic test for NDO-LID detects IgM antibodies against NDO and IgG antibodies against LID-1. The pilot study by Rumondor et al. (2019) concluded that examination of IgAMG anti-NDO-LID levels consistently showed higher levels than IgM and IgG levels separately. This finding implies that using

IgAMG may increase the sensitivity of NDO-LID for leprosy diagnostic tests.[4]

The limitation of our review is the number of journals reviewed. This is because the journals taken for review are published in the last 5 years (starting from 2019 up to 2023). Further studies are needed to test the accuracy of the diagnostic test more comprehensively to provide stronger and more convincing evidence. More studies are also required to prove that NDO-LID can detect subclinical symptoms of early leprosy cases and, at the same time, will be able to distinguish cases from uninfected endemic contacts.

CONCLUSION

This scoping review showed that NDO-LID has higher sensitivity and specificity values than its comparators. NDO-LID is effective enough to help diagnose leprosy. However, the challenge of NDO-LID in diagnosing leprosy is the low sensitivity in PB leprosy cases and the unproven effectiveness of NDO-LID in diagnosing subclinical leprosy.

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AUTHORS CONTRIBUTION

Study concept: RJ; data analysis and interpretation: RJ; article draft: RJ; final approval of the article to be published: RJ, RDP.

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CONFLICTS OF INTEREST

The writing of this scoping review does not involve any conflicts of interest.

REFERENCES

1. Salgado CG, Brito AC, Salgado UI, Spencer JS. Leprosy. In: Kang S, Amagai M, Bruckner AL, Enk AH, Margolis DJ, McMichael AJ, et al, editors. Fitzpatrick's Dermatology Ninth Edition Volume 1. New York: McGraw-Hill Education; 2019. p. 2892-919.
2. Jain S. Dermatology Second Edition. Switzerland: Springer International Publishing AG; 2017. p.220.
3. PERDOSKI. Panduan Praktik Klinis Bagi Dokter Spesialis Dermatologi Dan Venereologi Indonesia. Jakarta: PERDOSKI; 2021.
4. Rumondor BB, Prakoeswa AC, Trianita MN, Iswahyudi I, Herwanto N, Listiawan MY, et al. Immunoglobulin AMG Anti Natural Disaccharide Octyl - Leprosy IDRI Diagnostic (NDO-LID) Serologic Test for Leprosy Diagnosis: a Pilot Study. *Dermatol Reports* [Internet]. 2019 Mar. 29;11(s1). Available from:https://www.pagepress.org/journals/index.php/dr/article/view/8025.
5. Hooij, A. van. Development of immunodiagnostic tests for leprosy: from biomarker discovery to application in endemic areas. Netherlands: Universiteit Leiden; 2021. Retrieved from https://hdl.handle.net/1887/3240171.
6. Alinda MD, Geani S, Agusni RI, Kusumaputra BH, Reza NR, Prakoeswa CRS, et al. Diagnosis and Management of Leprosy. BIKK [Internet]. 2020 Jul. 31;32(2):149-57. Available from: https://e-journal.unair.ac.id/BIKK/article/view/14163.
7. WHO. Leprosy [Internet]. 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/leprosy.
8. Sarode G, Sarode S, Anand R, Patil S, Jafer M, Baeshen H, et al. Epidemiological aspects of leprosy. *Dis Mon*. 2020 Jul;66(7):100899.
9. Swe MMM, Phyo AP, Cooper BS, White NJ, Smithuis F, Ashley EA. A systematic review of neglected tropical diseases (NTDs) in Myanmar. *PLoS Negl Trop Dis*. 2023 Nov 1;17(11):e0011706.
10. Gautam S, Sharma D, Goel A, Patil SA, Bisht D. Insights into *Mycobacterium leprae* Proteomics and Biomarkers—An Overview. *Proteomes*. 2021; 9, 7.
11. Junior LARF, Sotto MN, Trindade MAB. Leprosy: clinical and immunopathological characteristics. *An Bras Dermatol*. 2022; 97(3): 338-47.
12. Gracino ME, Santos BM, Garbelin MV, Nishi V, Silva D, Kondo RN, et al. Leprosy: A systematic review. *Int J Dermatol Sci*. 2020; 2(1): 8-21.
13. Romero CP, Castro R, do Brasil PEA, Pereira DR, Pinheiro RO, Toscano CM, et al. Accuracy of rapid point-of-care serological tests for leprosy diagnosis: a systematic review and meta-analysis. *Mem Inst Oswaldo Cruz*. 2022;117:e220317.
14. Malhotra KP, Husain N. Laboratory perspectives for Leprosy: Diagnostic, prognostic and predictive tools. *Indian J Pathol Microbiol*. 2022;65, Suppl S1:300-9.
15. Silva KKdPe, Oliveira EE, Elias CMM, Pereira IE, Pinheiro RO, Sarno EN, et al. Serum IgA Antibodies Specific to M. leprae Antigens as Biomarkers for Leprosy Detection and Household Contact Tracking. *Front Med*. 2021; 8:698495.
16. Lockwood DNJ. In Griffiths CEM, Barker J, Bleiker T, Chaimer R, Creeamer D, editors, Rook's Textbook of Dermatology, 9th ed, Chichester: John Wiley & Sons, Ltd; 2016, p. 28.1-18.
17. Sengupta U. Recent Laboratory Advances in Diagnostics and Monitoring Response to Treatment in Leprosy. *Indian Dermatol Online J*. 2019;10(2):106-14.
18. Gama RS, Leite LA, Colombo LT, Fraga LAO. Prospects for new leprosy diagnostic tools, a narrative review considering ELISA and PCR assays. *Rev Soc Bras Med Trop*. 2020 Nov 25;53:e20200197.
19. Serrano-Coll H, Osorio-Leal Y, Escobar-Builes MV, Cardona-Castro N. Detection of *Mycobacterium leprae* infection in family clusters from six leprosy-endemic regions in Colombia. *Trans R Soc Trop Med Hyg*. 2022 May; 116(5): 501–8.
20. Trianita MN, Rumondor BB, Prakoeswa AC, Iswahyudi I, Adriaty D, Kusumaputra BH,et al. A simpler diagnostic method using blood collection on filter paper to determine anti-natural octyl disaccharide-leprosy infectious disease research institute diagnostic in household contacts of leprosy patients. *Dermatol Reports* [Internet]. 2019 Mar. 29 11(s1). Available from: https://www.pagepress.org/journals/index.php/dr/article/view/8048.
21. de Oliveira ALG, Fraga VG, Sernizon-Guimarães N, Cardoso MS, Viana AG, Bueno LL, et al. Diagnostic accuracy of tests using recombinant protein antigens of *Mycobacterium leprae* for leprosy: A systematic review. *J Infect Public Health*. 2020;13(8):1078-88.
22. Serrano-Coll H, Muñoz M, Beltrán JC, Cardona-Castro N. High seropositivity against NDO-LID in a group of household contacts of leprosy patients. Are we close to leprosy elimination in Colombia? *Pathog Glob Health*. 2023 Dec;117(8):727-34.
23. Gama RS, de Souza MLM, Sarno EN, de Moraes MO, Gonçalves A, Stefani MMA, et al. A novel integrated molecular and serological analysis method to predict new cases of leprosy amongst household contacts. *PLoS Negl Trop Dis*. 2019; 13:1–22.
24. Leturiondo AL, Noronha AB, do Nascimento MOO, Ferreira CdO, Rodrigues FdC, Moraes MO, et al. Performance of serological tests PGL1 and NDO-LID in the diagnosis of leprosy in a reference Center in Brazil. *BMC Infect Dis*. 2019;19(1):22.
25. Jian L, Xiujian S, Yuangang Y, Yan X, Lianchao Y, Duthie MS, et al. Evaluation of antibody detection against the NDO-BSA, LID-1 and NDO-LID antigens as confirmatory tests to support the diagnosis of leprosy in Yunnan province, southwest China. *Trans R Soc Trop Med Hyg*. 2020;114(3):193-9.
26. Ignotti E, Steinmann P. Perspectives for leprosy control and elimination. *Cad Saude Publica*. 2020; 36(7): 0-3.

27. Santos VS, de Souza CDF, Martins-Filho PRS, Cuevas LE. Leprosy: why does it persist among us? *Expert Rev Anti Infect Ther*. 2020; 18:613–5.
28. Barbosa AM, Silva SUD, Toledo ACCG, Abreu MAMM. Seroepidemiologic survey of the household contacts of leprosy patients. *Rev Assoc Med Bras*. 2022; 21;68(10):1389-93.
29. Wang N, Chu T, Li F, Wang Z, Liu D, Chen M, et al. The role of an active surveillance strategy of targeting household and neighborhood contacts related to leprosy cases released from treatment in a low-endemic area of china. *PLoS Negl Trop Dis*. 2020; 14:1–11.
30. Gobbo AR, Bouth RC, Moraes TMP, Pinto P, da Costa PF, Barreto JG, et al. NDO-BSA, LID-1, and NDO-LID Antibody Responses for Infection and RLEP by Quantitative PCR as a Confirmatory Test for Early Leprosy Diagnosis. *Front Trop Dis*. 2022; 3:850886.