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Accuracy of Diagnostics in Tegumentary Leishmaniasis: A Systematic Review

Sonia Igboanugo[1], Melissa S. Phuong[1], Rachel Lau[2], Robert Chris[1], Eric Shao[1], Ruwandi Kariyawasam[3], Hira Raheel[1], Sharmistha Mishra[4], Andrea K. Boggild[1,2,3]

[1]Tropical Disease Unit, Toronto General Hospital and University of Toronto, Toronto, ON, Canada,[2]Public Health Ontario, Toronto, ON, Canada,[3]Institute of Medical Sciences, Department of Medicine, University of Toronto, Toronto, ON, Canada, [4]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada

BACKGROUND

- Tegumentary leishmaniasis (TL) is characterized by cutaneous and mucocutaneous ulcerative skin lesions, caused by *Leishmania* parasites[1], that can potentially disfigure the midface.
- The clinical presentation of TL is similar to that of epidemiologically overlapping fungal and mycobacterial infections, thereby necessitating confirmatory diagnostics to inform appropriate treatment[1].
- Laboratory diagnostic techniques for TL include the leishmanin skin test (LST); microscopic identification of amastigotes from skin aspirates, biopsies and scrapings; culture; and molecular assays[1].
- Knowledge regarding the best-performing specimen and diagnostic assay for TL diagnosis is inadequate, leading to uncertainty as to what specimen to collect and which test to request when encountering a patient suspected to have TL.
- **Our objective was to conduct a knowledge synthesis to determine optimal methods to accurately and efficiently diagnose TL for the aim of diagnostic stewardship.**

METHODS

- We searched five databases from inception to October 28, 2019 including Ovid MEDLINE, Ovid Embase, LILACS, Cochrane Library and Scopus.
- The following search terms were used: ("cut* leish*" OR "muc* leish*" OR "teg* leish*") AND (diagnosis OR diagnostic accuracy OR sensitivity OR specificity OR stard OR test*) AND NOT (viscer*).
- All systematic reviews, diagnostic trials and observational studies were included.
- Titles, abstracts and full-texts are systematically doubled screened by two reviewers with a tertiary arbitrator.
- Full texts were excluded if they did not involve the diagnosis of cutaneous leishmaniasis (CL) and/or mucocutaneous leishmaniasis (ML). Full texts were also excluded if they did not include more than 10 human subjects, specify a reference comparator or use specimens taken from ulcers.
- Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[2] and Quality Assessment of Diagnostic Accuracy Studies (QUADAS)[3] are employed.

RESULTS

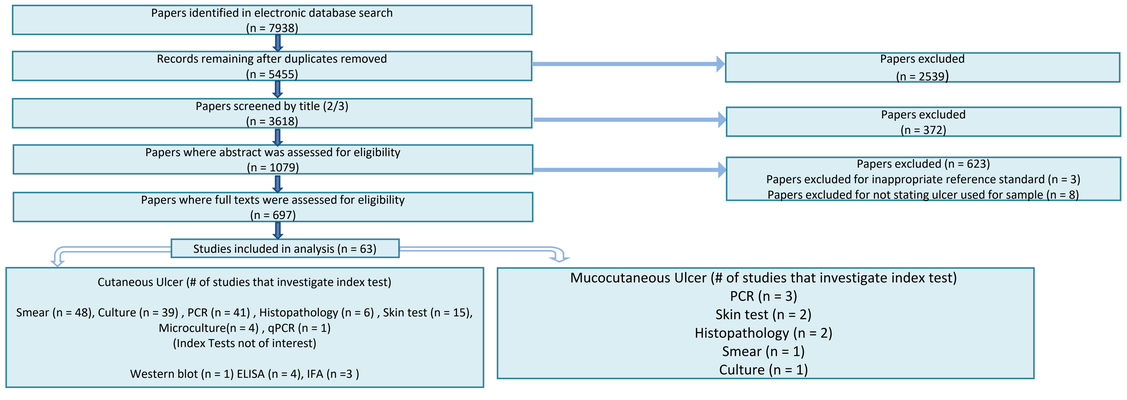

Figure 1. PRISMA flow diagram for database search from inception to October 28, 2019. Full texts found from July 2018 to October 2019 will undergo screening for eligibility. Therefore, the numbers of papers from that stage onwards reflect papers found in a search conducted on October 2019.

Table 1. Descriptive data for eligible full texts including patients with CL, MCL or both

Author, Published Year	Lesion Type	# of Patients	Country	Index Tests	Reference Comparator
Gomes et al., 2014	CL and MCL	52	Brazil	MST; indirect immunofluorescence (IIF); histopathologic examination (hematoxylin and eosin, Giemsa); culture (aspiration fluid, NNN media); smears (Giemsa); and PCR (filter paper imprints of lesion biopsy (FPILs), nasal swabs, saliva, and oral filter paper imprints)	2 positive immunologic tests (MST and IIF) or one positive test if there was a positive culture, histopathologic examination, smear, or FPIL
Pereira et al., 2008	CL and MCL	83	Brazil	Smear (May–Grunwald–Giemsa), culture (biopsy, NNN media), PCR (biopsy)	1/3 test(s) positive (culture, smear, and PCR all from biopsy specimens)
Satow et al., 2013	CL and MCL	128	Brazil	kDNA-PCR (biopsy)	1/3 test(s) positive (MST, direct investigation (biopsy, Giemsa stain), and culture (biopsy, Media 199)
Weigle et al., 1987	CL and MCL	124	Colombia	Aspirate sample: inoculation into hamster and culture (Senekjie's media) Biopsy sample: dermal scrapings, impression smears, and tissue sections (all Giemsa-stained); culture; inoculation into hamster	1/7 test(s) positive among the index tests
Boggild et al., 2011	MCL	28	Peru	Histopathology (biopsy); PCR (biopsy); LST; and non-invasive, cytology-brush based PCR (CerviSoft® or Histobrush®)	2/4 test(s) positive (biopsy with histopathology, biopsy PCR, LST, or cytology brush PCR
Ovalle-Bracho et al., 2007	MCL	61	Colombia	kDNA PCR and ITS rDNA PCR	Positive for clinical suspicion, histopathological findings, and therapeutic test. One of positive MST, scar presence, and history of exposure also required.
Ovalle-Bracho et al., 2016	MCL	60	Colombia	*Miniexon* gene PCR (biopsy – fresh and paraffin-embedded)	Positive for clinical suspicion, histopathological findings, and therapeutic test. One of positive MST, scar presence, and history of exposure also required

Table 2. Application of QUADAS for full texts investigating CL, MCL or both. There are minimal applicability concerns. However for some studies, the lack of information on patient selection and conduction of index test(s) and reference standard creates uncertainty in bias risk assessment.

Author, Published Year	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Test	Reference Standard
Gomes et al., 2014	☐	☐	☐	?	☺	☺	☺
Pereira et al., 2008	?	?	?	☺	☺	☺	☺
Satow et al., 2013	☐	?	☺	☐	☺	☺	☺
Weigle et al., 1987	?	?	?	☐	☺	☺	☺
Boggild et al., 2011	☺	☺	☺	☺	☺	☺	☺
Ovalle-Bracho et al., 2007	☐	☺	☺	☐	☺	☺	☺
Ovalle-Bracho et al., 2016	☐	☺	☺	☐	☺	☺	☺

☺ = low risk, ☐ = high risk, ? = unclear risk

Table 3. Reported diagnostic performances for papers investigating CL, MCL or both. All three papers which were found prior to March 2016 focused on evaluating the accuracy of PCR in detecting ML, albeit using different materials and protocols.

Author, Published Year	Skin Lesion Type	Reference Comparator	Index Test	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Gomez et al., 2014	MCL	2 positive immunologic tests (MST and IIF) or one positive test if there was a positive culture, histopathologic examination, smear, or FPIL	Montenegro skin test Indirect immunofluorescence Histopathology Microscopy Smear Culture kDNA PCR of Filter Paper Impression Lesion	93.8 68.8 13.3 27.3 10.0 61.5	62.1 75 100 100 100 100	57.7 64.7 100 100 100 100	94.7 78.3 71.1 79.5 76.9 85.7
Pereira et al., 2018	CL	1/3 test(s) positive (culture, smear, and PCR all from biopsy specimens)	Microscopy Smear Culture PCR	83.6 86.4 100	100 100 100	100 100 100	25.0 33.3 100
Satow et al., 2015	CL and MCL combined analysis	1/3 test(s) positive (MST, direct investigation (biopsy, Giemsa stain), and culture (biopsy, Media 199)	kDNA	98.8	33.3	73.2	93.8
Weigle et al., 1987	CL and MCL combined analysis	Montenegro skin test	Histopathology Microscopy on scraping Culture from aspirate Culture from biopsy	16.0 26.0 64.3 55.4	-	-	-
Boggild et al., 2011	MCL	2/4 test(s) positive (biopsy with histopathology, biopsy PCR, LST, or cytology brush PCR)	Biopsy with histopathology LST kDNA PCR of biopsy specimen kDNA PCR of CerviSoft® brushes kDNA PCR of Histobrush® brushes	21.7 69.6 95.7 95.7 91.3	100.0 100.0 100 90.0 90.0	100.0 100.0 100 95.7 95.5	21.7 41.7 83.3 90.0 81.8
Ovalle-Bracho et al., 2007	MCL	Positive for clinical suspicion, histopathological findings, and therapeutic test. One of positive MST, scar presence, and history of exposure also required.	kDNA PCR ITS rDNA PCR	68.6 40.0	92.0 96.0	92.3 93.3	67.6 53.3
Ovalle-Bracho et al., 2016	MCL	Positive for clinical suspicion, histopathological findings, and therapeutic test. One of positive MST, scar presence, and history of exposure also required.	Miniexon gene PCR (biopsy – fresh) Miniexon gene PCR (biopsy –paraffin-embedded)	83.00 87.50	100.00 95.00	100.00 95.45	81.25 86.36

DISCUSSION

- For diagnosis of CL from one study, PCR had the highest sensitivity (100%), followed by culture (86.4%) and microscopy smear (83.6%). All assays had specificity and PPV of 100%. NPV was highest by PCR (100%), with culture and microscopy having 33.3% and 25% respectively.
- For diagnosis of MCL, PCR had sensitivity with a range of 40 – 95.7%, specificity: 92 – 100%, PPV: 92.3 – 100%, and NPV: 53.3 – 90%.
- Leishmanin skin test had sensitivity of 69.6 – 93.8%, specificity: 62.1 – 100%, PPV: 57.7 – 100%, and NPV: 41.7 – 94.7%.
- Histopathology had sensitivity of 13.3 – 21.7%, specificity and PPV of 100%, and NPV of 21.7 – 71.1%.Microscopy smear, culture and indirect immunofluorescence had sensitivity of 27.3%, 10%, and 68.8% respectively.
- Two studies had a combined analysis of CL and MCL. PCR had the highest sensitivity of 98.8%, followed by culture of 55.4 – 64.3%, microscopy with 26%, and histopathology of 16%.
- Overall, PCR had the highest sensitivity and specificity with histopathology having the lowest sensitivity in the diagnosis of CL and MCL.

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For more information contact Dr.Andrea Boggild | andrea.boggild@utoronto.ca | www.boggildlab.ca | @boggildlab