J Bras Pneumol. 2022;48(1):e20210337
https://dx.doi.org/10.36416/1806-3756/e20210337

Diagnostic performance of VEGF-D for lymphangioleiomyomatosis: a meta-analysis

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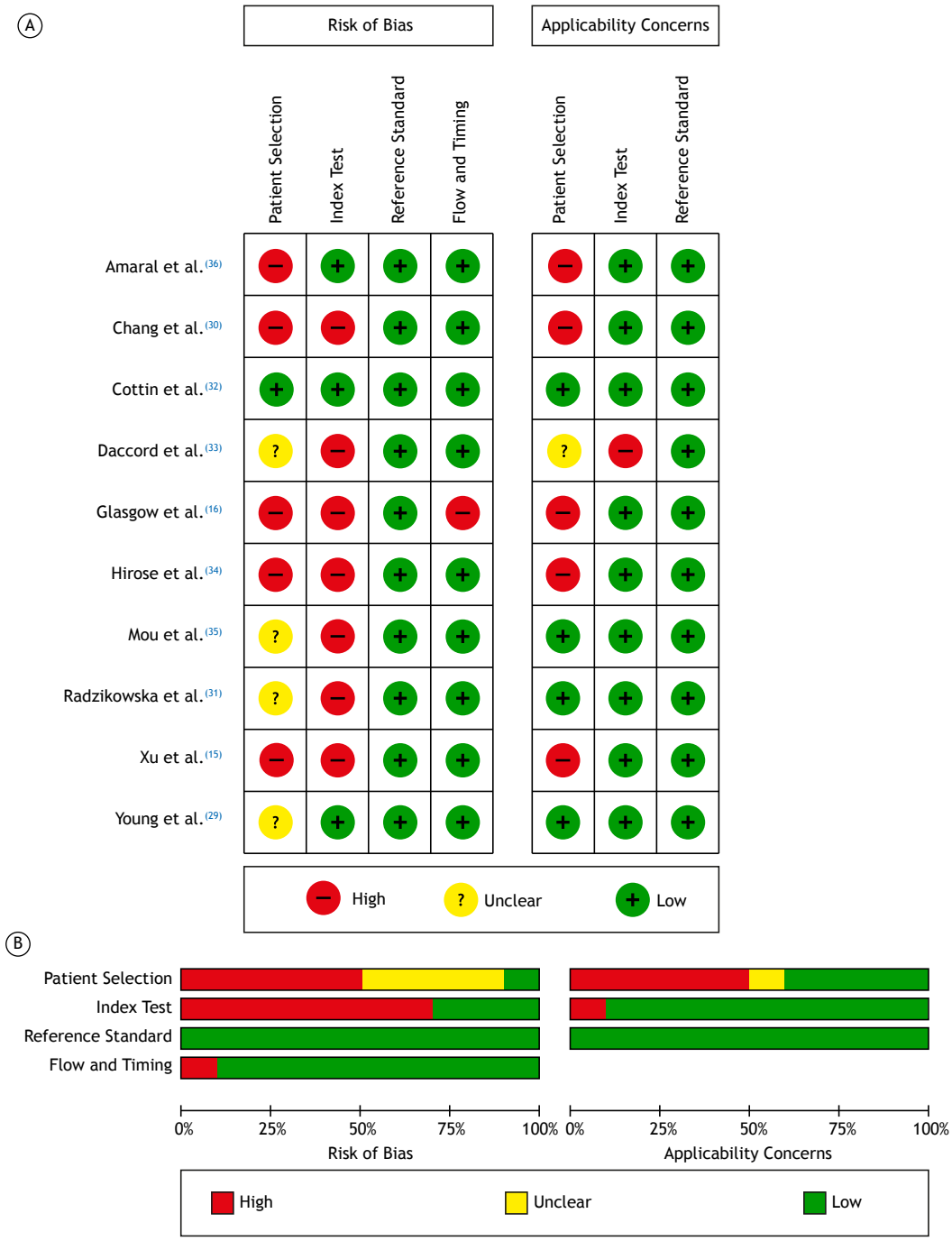

Figure S1. Methodological quality assessment of included studies based on Quality Assessment of Diagnostic Accuracy Studies-2. A. Graph of risk of bias and applicability concerns. B. Summary of risk of bias and applicability concerns.

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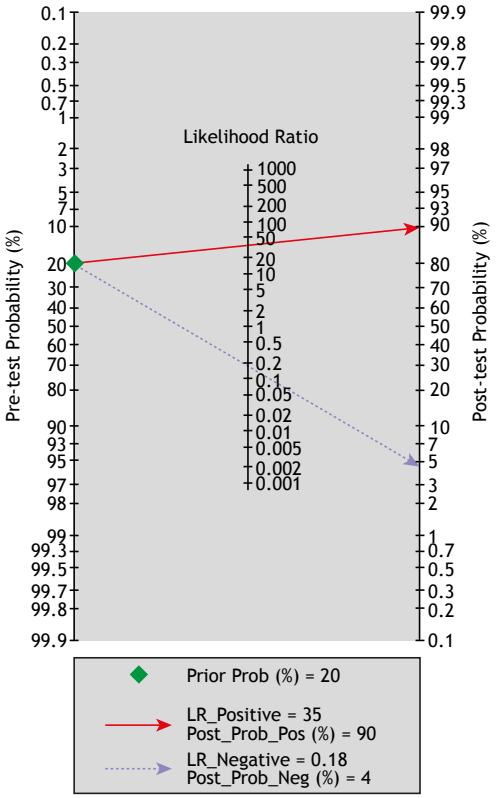

Figure S2. Fagan's nomogram for the diagnostic performance of VEGF-D for lymphangioleiomyomatosis. Prob: probability; LR: likelihood ratio; Post_Prob_Pos: post-test probability positive; and Post_Prob_Neg: post-test probability negative.

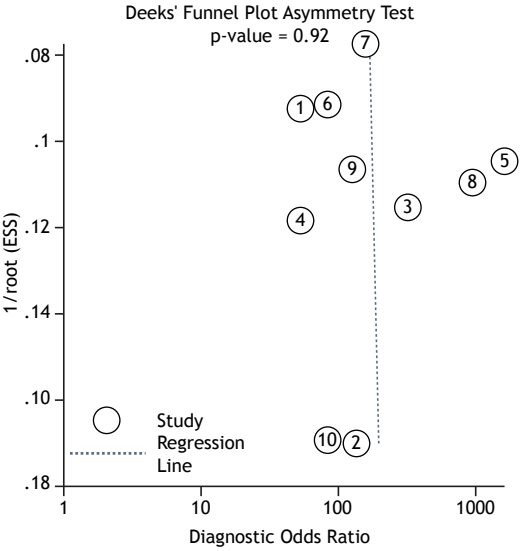

Figure S3. Deeks' funnel plot of publication bias of included studies. ESS: effective sample size.

Chart S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[18]

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2,3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3

Continue...▶

Chart S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[18] (Continued...)

Section/Topic	#	Checklist Item	Reported on Page #
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5,6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6,7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6,7
Section/Topic	#	Checklist Item	Reported on age #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5,6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6,7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8,9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9,10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group; (b) effect estimates and confidence intervals, ideally with a forest plot.	10
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	9,10

Continue...▶

Chart S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[18] (Continued...)

Section/Topic	#	Checklist Item	Reported on Page #
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10,11
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14, 15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

Chart S2. Description of lymphangioleiomyomatosis in accordance with the American Thoracic Society/Japanese Respiratory Society (ATS/JRS) guidelines[6] and in the International Classification of Diseases (ICD), 11th edition.

ATS/JRS	- It is a rare, systemic neoplastic disease associated with cystic lung destruction, chylous fluid accumulation, and abdominal tumor development, including angiomyolipomas and lymphangioleiomyomas - It occurs almost exclusively in adult women, affecting approximately five per million individuals, but has also been reported in adult men and children - It occurs sporadically and especially in patients with tuberous sclerosis complex, an inherited neoplastic syndrome associated with seizures, cognitive impairment, and tumor formation in multiple organs
ICD-11	- It is a multiple cystic lung disease characterized by progressive cystic destruction of the lungs and abnormalities of the lymphatic system frequently associated with renal angiomyolipomas - It occurs sporadically or as a manifestation of tuberous sclerosis complex

Chart S3. Diagnostic criteria of lymphangioleiomyomatosis in accordance with the European Respiratory Society guidelines.[9]

Definite LAM	Probable LAM	Possible LAM
Characteristic[a] or compatible[a] lung HRCT AND lung biopsy fitting the pathological criteria for LAM[a] OR 2. Characteristic[a] lung HRCT and any of the following: Angiomyolipoma (kidney)[b] Thoracic or abdominal chylous effusion[c] Lymphangioleiomyoma[d] or lymph node involvement by LAM[d] Definite or probable TSC	Characteristic[a] HRCT and compatible clinical history[e] Compatible[a] HRCT and any of the following Angiomyolipoma (kidney)[b] Thoracic or abdominal chylous effusion[c]	Characteristic or compatible HRCT[a]

LAM, lymphangioleiomyomatosis; and TSC> tuberous sclerosis complex. [a]Characteristic lung HRCT findings: multiple (> 10) thin-walled round well-defined air-filled cysts with a preserved or increased lung volume with no other significant pulmonary involvement, specifically no interstitial lung disease, with the exception of possible features of multifocal micronodular pneumocyte hyperplasia in patients with TSC; compatible lung HRCT findings: few (> 2 and < 10) present cysts. [b]Diagnosed on the basis of characteristic CT features and/or on pathological examination findings. [c]Based on visual and/or biochemical characteristics of the effusion. [d]Based on pathological examination findings. [e]Compatible clinical features include pneumothorax (especially multiple and/or bilateral) and/or altered lung function test results, as in LAM.

Table S1. Supplementary quality assessment of the included studies on VEGF-D levels in relation to the diagnosis of lymphangioleiomyomatosis.[a]

Author	Study registration	IRB	Prospective	Consecutive	Sample size calculation	Multicenter	Real-world design	Inclusion/ exclusion criteria	Conflict of interest
Glasgow et al.[16]	No	Yes	Unclear	No	No	No	No	Lenient	No
Young et al.[29]	No	Yes	Yes	Unclear	No	No	No	Stringent	Yes
Cottin et al.[32]	Unclear	Unclear	Yes	Yes	No	No	No	Lenient	No
Chang et al.[30]	No	Yes	No	No	No	Yes	No	Lenient	No
Radzikowska et al.[31]	No	Unclear	Unclear	Unclear	No	No	No	Lenient	No
Xu et al.[15]	No	Yes	Unclear	No	No	No	No	Lenient	No
Daccord et al.[33]	Unclear	Unclear	Unclear	Unclear	No	No	No	Lenient	No
Amaral et al.[36]	No	Yes	Unclear	No	No	No	No	Stringent	No
Hirose et al.[34]	No	Yes	Unclear	No	No	No	No	Lenient	Yes
Mou et al.[35]	No	Yes	Unclear	Unclear	No	No	No	Lenient	No

IRB: institutional review board. [a]Studies that had inclusion/exclusion criteria with more than three items were defined as stringent.

Table S2. Grading of Recommendations Assessment, Development, and Evaluation of the quality of VEGF-D levels in relation to the diagnosis of lymphangioleiomyomatosis.

Outcome	Studies (patients), n	Study design	Factors that may decrease certainty of evidence					Quality
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	
TP FN	10 studies (945 patients)	Cross-sectional study	Serious*	No	Serious†	Serious††	None	Very low
TN FP	10 studies (945 patients)	Cross-sectional study	Serious*	No	Serious†	Not serious	None	Low

TP: true positive; FN: false negative; TN: true negative; and FP: false positive. *Risk of bias was evaluated on the basis of the Quality Assessment of Diagnostic Accuracy Studies-2 results. †$I^2 > 0.5$ and $p < 0.1$. ††The width of the 95% CI was 10-20%.