Ciência & Saúde Coletiva
ISSN: 1413-8123
cienciasaudecoletiva@fiocruz.br
Associação Brasileira de Pós-Graduação em Saúde Coletiva
Brasil

Rosa, Maria Ines; Fernandes dos Reis, Maria; Simon, Carla; Dondossola, Eduardo; Alexandre, Maria Cecília; Colonetti, Tamy; Oliveira Meller, Fernanda
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Ciência & Saúde Coletiva, vol. 22, núm. 12, diciembre, 2017, pp. 4001-4012
Associação Brasileira de Pós-Graduação em Saúde Coletiva
Rio de Janeiro, Brasil

DOI: 10.1590/1413-812320172212.14112016

IgM ELISA for leptospirosis diagnosis: a systematic review and meta-analysis

ELISA IgM para diagnóstico de leptospirose: revisão sistemática e meta-análise

Maria Ines Rosa [1]
Maria Fernandes dos Reis [2]
Carla Simon [3]
Eduardo Dondossola [3]
Maria Cecília Alexandre [3]
Tamy Colonetti [2]
Fernanda Oliveira Meller [1]

Abstract *A systematic review with meta-analysis was performed to estimate the accuracy of IgM ELISA for Leptospirosis diagnosis. A search of Medline, Lilacs, Embase, Cochrane Central Register of Controlled Trials and Grey literature (Google Scholar and British Library) was conducted. The medical subject headings (MeSHs) and the words "leptospirosis", "human leptospirosis" and "IgM ELISA" were used. Fifty-two studies were analyzed, which included 10,775 samples. The pooled sensitivity of all the studies was 86% (CI 95%, 85%-87%) and specificity was 90% (CI 95%, 89%-91%). In studies of the acute phase, the sensitivity and specificity were 84% (CI 95%, 82%-85%) and 91% (CI 95%, 90%-91%), respectively. In conclusion, IgM ELISA is sensitive for use as an initial screen for leptospiral infections.*

Key words *Human leptospirosis, IgM ELISA, Leptospirosis diagnosis, Meta-analysis*

Resumo *O objetivo desta revisão sistemática e meta-análise foi avaliar a acurácia do ELISA IgM para o diagnóstico precoce da leptospirose em humanos. A busca foi realizada nas seguintes bases de dados: Medline, PubMed, LILACS, Embase e Cochrane Central Register of Controlled Trials e Grey literature (Google Scholar and British Library). As palavras-chaves usadas foram: "leptospirosis", "human leptospirosis" e "IgM ELISA". Foram analisados 52 estudos, que incluíram 10.775 amostras. A sensibilidade e especificidade combinada de todos os estudos foram 86% (CI 95%, 85%-87%) e 90% (CI 95%, 89%-91%), respectivamente. Nos estudos de fase aguda, a sensibilidade e especificidade foram, respectivamente, 84% (CI 95%, 82%-85%) e 91% (CI 95%, 90%-91%). Conclui-se que o ELISA IgM é um teste sensível para rastreamento inicial da leptospirose.*

Palavras-chave *Leptospirose humana, ELISA IgM, Diagnóstico, Meta-análise*

[1] Programa de Pós-Graduação em Saúde Coletiva, Universidade do Extremo Sul Catarinense (UNESC). Av. Universitária 1105, Bairro Universitário. 88806-000 Criciúma SC Brasil. mir@unesc.net
[2] Programa de Pós-Graduação em Ciências da Saúde, UNESC. Criciúma SC Brasil.
[3] Laboratório de Epidemiologia, UNESC. Criciúma SC Brasil.

Introduction

Leptospirosis is a neglected infectious disease caused by spirochetes from the genus *Leptospira*. It constitutes the most widespread zoonosis and is emerging as a major public health problem with outcomes ranging from subclinical infections to fatal pulmonary hemorrhage and Weil´s syndrome[1].

Leptospirosis has a broad geographical distribution, occurring in both rural and urban areas of tropical, subtropical and temperate regions. The disease outbreaks in developed countries are usually associated with occupational exposure, tourism or sporting events[1].

Leptospirosis is transmitted by contact of abraded skin or mucous membranes with water or soil contaminated with urine from reservoir animals, such as rodents[2]. More than 500.000 cases of severe leptospirosis are reported each year, with mortality rates exceeding 10%[3]. A new global estimate estimates that the overall annual incidence is 1 million cases and 60,000 deaths[4].

The microscopic agglutination test (MAT) is most often used as a reference test[5]. Standard tests are tedious, laborious and require well-equipped laboratories with experienced staff and are therefore restricted to a few centers. Because the initial presentation of leptospirosis may be difficult to discern from other infectious diseases, rapid and accurate diagnosis is essential to prevent the progression of the more severe form of the disease, particularly in developing countries[2].

Traditional serological methods, such as the ELISA, are widely used to diagnose leptospirosis. Antileptospires IgM may be detected 4 to 5 days after the onset of symptoms, before detection of IgG and agglutinating antibodies, and persist at least 5 months in patients[6]. ELISA can be performed with minimal training and typically provides results in 2–4 hours. The aim of this study was to perform a systematic review and meta-analysis of the literature to verify the accuracy of the IgM ELISA for leptospirosis diagnosis.

Methods

All methods for analysis, inclusion/exclusion criteria, data extraction and quality assessment were specified in advance. It was performed a systematic review according to a prospective protocol using PRISMA–statement guidelines[7,8]. The review protocol is registered at PROSPERO (International prospective register of systemic reviews, http://www.crd.york.ac.uk/prospero; CRD42014009784).

The electronic databases Medline via Pubmed, Lilacs (through Scielo interface), Cochrane Central Register of Controlled Trials, Embase and Grey literature (Google Scholar and British Library) were searched for papers published from January 1969 to July 2014. The following terms were used, both as text words and, as appropriate, Medical Subjects Heading (MeSH), or equivalent subject heading/thesaurus terms: *Leptospirosis, Human Leptospirosis* and *IgM ELISA*.

This sensitive filter was created by combining three filters to identify diagnostic studies via the Boolean operators "OR" and "AND". The search was limited to human studies and had no language restrictions. Reference lists of all available primary studies were reviewed to identify additional relevant citations. The complete search strategy is available on request.

Abstracts/titles identified from the search were screened by two reviewers. Disagreements about study inclusion or exclusion were initially solved by consensus, and if agreement was not possible, they were arbitrarily resolved by a third reviewer.

Cross-sectional and cohort studies, prospective and retrospective, which evaluated IgM enzyme-linked immunosorbent assay (Elisa) in Leptospirosis diagnosis were included. Studies that used the index test IgM Elisa to diagnose leptospirosis in patients were analyzed. The diagnostic *reference standard* was the result of the MAT with confirmation based on the result on the same serum sample as used for the index test. Therefore, the primary outcome analyzed was the presence of Leptospirosis.

It was extracted data on the studies, patients and test characteristics using a standardized form. Data were abstracted as 2 x 2 tables regarding IgM Elisa *vs* MAT in leptospirosis diagnosis (positive *vs* negative by cut-off). It was also calculated the sensitivities, specificities, and Odds Ratio diagnostic (DOR). Studies that lacked the data needed to construct 2 x 2 contingency tables were excluded. The assessment of non–English–language articles was performed independently following translation (if necessary). Any disagreement was resolved by consensus for studies published in all languages. Final inclusion or exclusion was made with reference to a selection criteria checklist.

Disagreements about study inclusion or exclusion were initially solved by consensus, and if agreement was not possible, they were arbitrarily

resolved by another reviewer. The agreement statistics among reviewers were computed.

The methodological quality assessment for diagnostic accuracy was performed according to criteria from the Quality Assessment of Diagnostic Accuracy Studies (QUADAS 2)[9]. QUADAS-2 is designed to assess the quality of primary diagnostic accuracy studies, and it consists of four domains: patient selection, index test, reference standard, and flow of patients through the study and timing of the index tests(s) and reference standard "flow and timing". Signaling questions are included to help judge the risk of bias[8]. The Quality assessment of studies was independently performed using the Review Manager 5.2 software[10].

The rates were calculated as true positive (TPR, sensitivity), false positive (FPR, 1 – specificity), true negative (TN) and false negative (FN)[11]. If any cell containing "0" was present in the contingency table, 0,5 was added to each cell to facilitate the calculations; if the study contained two cells with "0", the study was excluded from the analysis[12].

Bivariate analysis was used to calculate pooled estimates of sensitivity, specificity, and DOR in addition to 95% confidence intervals (CIs) for the summary estimates[13]. The bivariate model preserves the 2-dimensional nature of diagnostic data by analyzing the logit transformed sensitivity and specificity of each study in a single model and considers both within-study and between-study variability, in contrast to the Littenberg and Moses method that departs from a fixed effects model[14]. To detect cut-off threshold effects, the relationship between sensitivity and specificity was evaluated by the Spearman's correlation coefficient. Pooled estimates were only calculated for studies showing sufficient clinical and statistical homogeneity. I^2 or Q tests (commonly used in meta-analysis) are not recommended for assessing statistical homogeneity in diagnostic reviews because they do not consider the association between sensitivity and specificity[15]. The DOR can relate to different combinations of sensitivities and specificities and describes the odds of the positive test resulting in participants with the disease compared with the odds of a positive test resulting in those without disease. A single diagnostic odds ratio corresponds to a set of sensitivities and specificities depicted by the SROC. It can change according to the threshold and to the ROC curve used to define an abnormal examination resulted in the expected trade-off between sensitivity and specificity.

A summary receiver operating characteristic curve was generated using data from all thresholds using the Littenberg and Moses method. Additionally, the area under the curve (AUC) can summarize the inherent capacity of a test for discriminating a diseased from a non-diseased subject. Accurate tests usually have AUCs close to 1, and poor tests usually have AUCs close to 0.5[16]. Sensitivity analyses were performed to assess excluding studies with a high risk of verification bias according to QUADAS 2. To analyze publication bias, inverted funnel plots of the logarithmic odds ratio (OR) of individual studies were plotted against sample size[15].

The statistical analysis was performed with the software Stata 11[17], Meta-DiSc®[18] (version 1.4), and Review Manager 5.2[10].

Results

A total of 545 studies were identified: 510 studies were identified using the database search and 35 additional records were identified through other sources. Seventy-nine full-text articles were retrieved; 27 were excluded after further scrutiny. Fifty-two primary studies, including 10,775 serum samples, met the criteria for inclusion and were included in the meta-analysis 19-69 (Figure 1).

Details of the participants and interventions are summarized in Table 1[18-69]. Most studies were prospective, except for two[41,44].

The quality assessment results are presented in Figure 2[19-69]. Thirteen studies fulfilled all criteria of QUADAS 2[19,20,27,28,36,41,52,56,57,59,61,63,70]. In five studies, the risk of bias was in the patient selection[31,44,55,58,62]. Two studies showed unclear risk of bias in the reference standard[22,44] and two studies showed unclear risk of bias in the flow timing[39,45]. Two studies have indicated high risk of bias in the patient selection in the applicability criteria[50,51], and two studies demonstrated a high risk of bias in evaluating the index test[48,65]. In the other studies, there were some unclear applicability criteria in the index test and reference standard[19,21,23-26,29,30,32,34,35,38,40,42,43,46,47,49,53,54,57,64,67-69].

The robustness of the results was tested by repeating the analysis using a different statistical model (random effects model). Some studies were identified as outliers, and one re-analysis was performed without them. However, no significant difference was found in the sensitivity or specificity; therefore, those papers were not excluded from the meta-analysis.

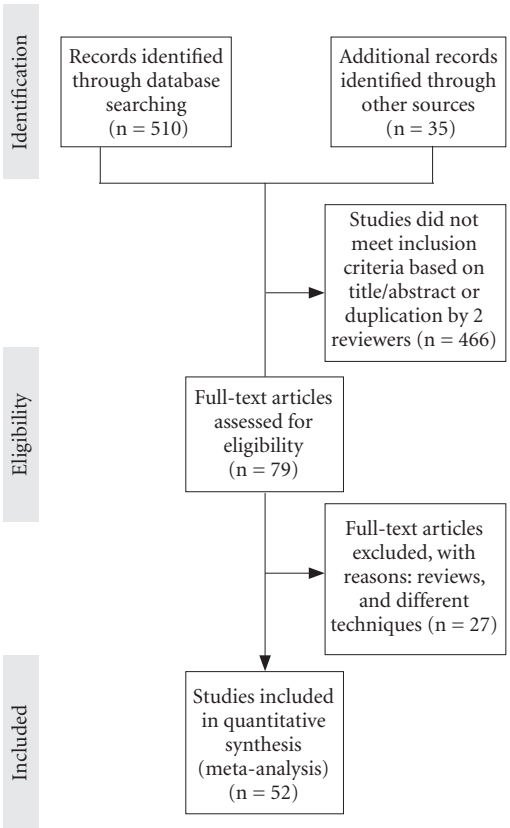


Figure 1. Flow diagram of the study selection process.

All 52 studies selected were included in the meta-analysis. Statistical analyses were performed on both the acute and unspecific phase and only the acute phase. Analysis with excluding particular studies with high risk of bias [48,65] in relation to the index test were conducted, and because there was no significant change they were maintained the meta-analysis.

IgM ELISA for the diagnosis of human Leptospirosis had a pooled sensitivity in all studies of 0.86 (95% CI, 0.85 – 0.87). The pooled specificity in all studies was 0.90 (95% CI, 0.89 – 0.91). The estimates for heterogeneity were highly consistent across studies: sensitivity: QT = 914.77, *P*-value < 0.0001; inconsistency I^2 = 94.4%; and specificity: QT = 738.48, *P*-value < 0.0001; inconsistency I^2 = 93.1% (Figure 3).

IgM ELISA for the diagnosis of human leptospirosis had a pooled sensitivity in the acute phase of 0.84 (95% CI, 0.82 – 0.85), and the specificity of Leptospirosis in the acute phase was 0.91 (95% CI, 0.90 - 0.91). The estimates for heterogeneity were highly consistent across studies: sensitivity: QT = 764.77, *P*-value < 0.0001; I^2 = 95.3%; and specificity: QT = 435.55, *P*-value < 0.0001; I^2 = 91.7% (data not shown).

The DOR was 82.06 (95% CI, 45.77-147.12), QT=595.94, *P*-value = 0.001 in all studies and 67.11 (95% CI, 33.53-134.29), QT = 426.33, *P*-value = 0.001 in the acute phase (data not shown).

SROC curves were constructed due to heterogeneity in the DOR. The AUC for the ROC curve was estimated by a trapezoidal rule 95. The resulting summary ROC curves are shown with operating points for sensitivity and specificity. The AUC was 0.960 in all studies and 0.952 in the acute phase respectively (Figure 4).

Covariable-type studies were separated into prospective and retrospective design, and the meta-regression analysis indicated no association between type of studies and outcome (P = 0.32).

Begg's funnel plot and Egger's test were performed to assess the publication bias of the literature in all comparison models. The shape of the funnel plot reveals any evidence of obvious asymmetry. Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry for total phase (P for bias = 0.001) and acute phase (P for bias = 0.008), indicating publication bias (data not shown).

Discussion

In summary, this systematic review showed that IgM ELISA in all phases had a sensitivity of 0.86 and specificity of 0.84, whereas the acute phase had a sensitivity of 0.90 and specificity of 0.91.

The results showed that IgM ELISA could be useful as a screening and a confirmatory test, especially in regions with small laboratories that have difficulty performing other techniques such as MAT.

A recent systematic review included 35 studies up to 2010 and analyzed ELISA (IgM, IgG and IgA). In the present study, 55 studies with IgM only were included and analyzed the accuracy of IgM in the acute phase of the disease. We found a higher sensitivity compared to IgM results Signorini et al.[71], 86 versus 80%, respectively.

It was found high heterogeneity between studies. It is expected in meta-analyses of diagnostic test accuracy because it comes from observational studies, study designs and different cutoff points. This high heterogeneity was also observed in the meta-analysis performed by Signorini et al.[71].

Table 1. Characteristics of the primary diagnostic studies.

Author/year	Country	N (samples)	Mean Age	Cut-off	Stage	TP	FP	FN	TN
Aviat et al. 2009	France	48	NR	0.5	Acute	12	3	26	7
Bajani et al. 2003	EUA	775	NR	NR	Unspecific	115	38	18	604
Bharadwaj et al. 2002	India	169	NR	NR	Acute	67	11	7	84
Blacksell et al. 2006	Laos	70	NR	NR	Acute	7	18	3	42
Blanco et al. 2008	Brazil	138	NR	NR	Acute	27	0.5	3	108
Bourhy et al. 2013	France	197	45,05	0,4	Unspecific	141	0.5	8	48
Brandão et al. 1998	Brazil	353	32(6-67)	NR	Acute	107	1	1	244
Céspedes et al. 2002	Perú	120	NR	0.6	Acute	39	1	1	79
Cinco et al. 1992	Italy	260	NR	0.245	Acute	110	08	25	117
Cumberland et al. 1999	United Kingdon	638	45.9(14-85)	NR	Acute	167	19	154	298
Da Silva et al. 1988	Brazil	142	NR	0.589	Acute	41	21	9	71
Da Silva et al. 1990	Brazil	71	NR	0.382	Acute	21	0.5	9	41
Da Silva et al. 1992	Brazil	57	30.9	0.630	Acute	26	0.5	0.5	31
Da Silva et al. 1997	Brazil	114	30.5(12-52)	NR	Acute	65	0.5	1	48
Desakorn et al. 2012	Thailand	214	NR	NR	Acute	56	36	51	71
Dey et al. 2008	India	136	NR	0.8	Unspecific	77	0.5	3	51
Effler et al. 2002	Hawaii	217	NR	NR	Acute	16	18	17	166
Fonseca et al. 2006	Brazil	124	34.4	NR	Acute	47	07	13	57
Honarmand et al. 2008	Iran	152	NR	NR	Unspecific	88	1	10	53
Kucerova et al. 2011	Czech Republic	45	44.24(19-82)	NR	Acute	10	4	0.5	31
Kumar et al. 2012	India	319	NR	NR	Acute	130	2	2	185
Levett et al. 2002	Barbados	48	NR	NR	Unspecific	24	9	4	11
Levett et al. 2001	Barbados	51	NR	NR	Acute	25	9	3	14
Mc Bride et al. 2007	Brazil	204	NR	NR	Acute	41	36	0.5	127
Mc Bride et al. 2007b	Brazil	72	NR	NR	Acute	25	0.5	4	38
Nakarin et al. 2004	Thailand	282	NR	0.9	Acute	79	0.5	6	197
Obregón et al. 2004	Cuba	71	NR	NR	Unspecific	37	2	1	31
Ooteman et al. 2006	Brazil	158	NR	NR	Unspecific	44	12	3	99
Pappas et al. 1985	EUA	172	NR	NR	Unspecific	93	14	4	61
Pol and Bharadwaj 2009	India	50	NR	0.41	Unspecific	17	2	3	28
Polanco et al. 1997	Venezuela	181	NR	NR	Unspecific	44	63	5	69
PremLtha et al. 2013	India	328	(3-75)	NR	Unspecific	32	50	31	215
Ribeiro et al. 1995	Brazil	89	NR	NR	Acute	23	24	3	39
Ribeiro et al. 1996	Brazil	89	NR	NR	Unspecific	23	28	1	37
Sehgal et al. 2003	India	117	NR	NR	Acute	35	10	35	37
Sekhar et al. 2000	Malaysia	70	NR	0.5	Acute	26	01	12	31
Shekathar et al. 2010a	India	110	NR	0.5	Acute	15	26	25	44
Shekatkar et al. 2010b	India	150	40.5(15-84)	NR	Acute	29	0.9	9	103
Silpasakorn et al. 2011	Thailand	161	NR	NR	Acute	54	0.5	35	72
Smits et al. 2000	Hawaii	686	NR	0.4	Acute	286	7	48	345
Smits et al. 2001	Hawaii	420	NR	0.1	Acute	120	17	15	268
Srimanote et al. 2007	Thailand	75	NR	0,75	Acute	32	04	14	25
Tanganuchitcharnchai et al. 2012	Laos	70	30(12-50)	NR	Acute	09	17	01	43
Tansuphasiri et al. 2005	Thailand	343	NR	NR	Acute	95	15	01	232
Terpstra et al. 1980	The Netherlands	313	NR	0,45	Unspecific	91	01	05	216
Trombert-Paolantoni et al. 2010	France	79	NR	NR	Acute	27	09	03	40
Vedhagiri et al. 2013	India	1289	NR	NR	Acute	1137	10	43	99
Velineni et al. 2006	India	32	NR	0,45	Unspecific	26	04	02	0,5
Vitale et al. 2003	Italy	71	NR	0,45	Acute	19	02	0,5	50
Winslow et al. 1997	Australia	274	NR	NR	Acute	41	16	0,5	217
Yersin et al. 1999	The Netherlands	161	NR	NR	Acute	36	03	01	121
Zochowski et al. 2001	UK	200	NR	0,40	Unspecific	96	07	04	93
TOTAL		**10775**				**4050**	**605**	**682**	**5438**

NR, not reported; TP, true-positive; FP, false-positive, FN, false-negative, TN, true-negative.

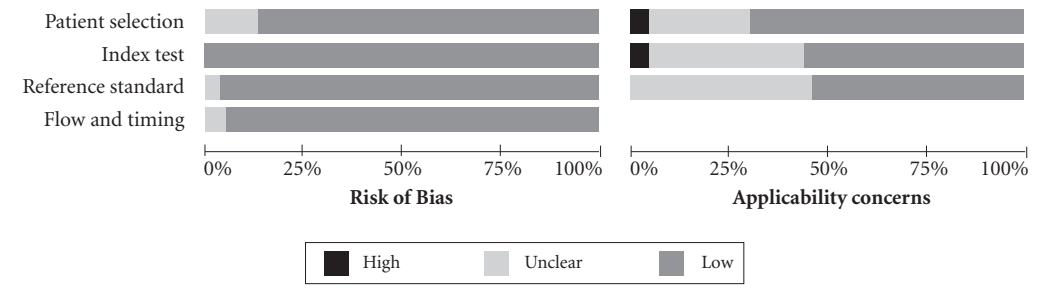


Figure 2. Results of the evaluation of each study according to QUADAS 2.

A rapid diagnostic test provides a quick test result but does not indicate an early test. The ideal rapid test should have high accuracy, be easy to perform, interpret, inexpensive, and stable and give the result within 2 hours[70].

There are two phases of Leptospira infection: (1) between 3-7 days or acute septicemic phase with nonspecific symptoms such as myalgia and headache. The leptospires are detectable in the blood stream, decrease until 15 days[72] and (2) the start in the second week after the onset of symptoms, and the antibodies usually persist for several months[6]. During this phase, leptospires are eliminated from the blood stream as IgM antibodies increase[73].

The rapid test depends on the detectable presence of anti-Leptospira antibodies already presented during the acute phase of the disease[74]. Molecular tests that detect the causative agent can be confirmed during the first 5 days after the onset of the disease[75]. It is very important that a test be rapid and sensitive, because the earlier the diagnosis the faster the treatment decision.

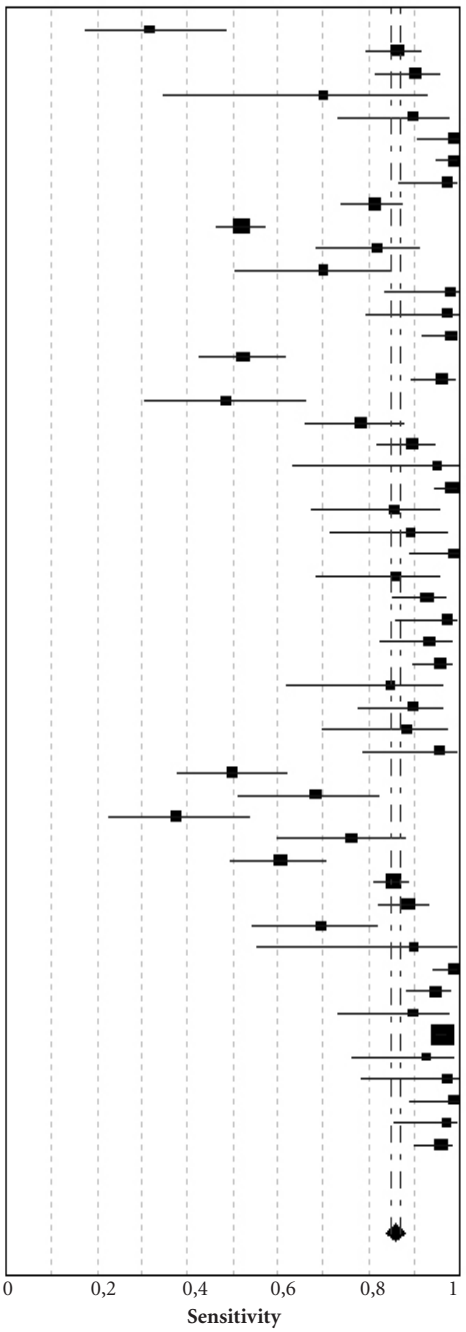
Whereas molecular tests, such as the polymerase chain reaction (PCR), that demonstrate the presence of the causative agent in a clinical sample mainly during the first 5 days after the onset of the disease (DPO), serological tests depend on the accumulation of detectable amounts of anti-Leptospira antibodies in the late acute to convalescent samples[74-76].

Rapid diagnostic tests should ideally be accurate, simple to use, relatively inexpensive, easy to interpret, stable under extreme conditions, require little or no processing, and give the results within 1–2 hours[70]. Again, it is very important that a test be rapid and sensitive, because the earlier the diagnosis the faster the treatment decision.

Often, an early diagnosis or reference standard is employed in referral centers where confirmation is performed by experts. The rapid diagnosis is highly useful at the peripheral facilities and might be integral for early outbreak warning and useful for monitoring outbreaks if a rapid unusual accumulation of cases might provide an early alert, provided that specimens are collected, transported, and stored in an adequate manner[76].

This review, which included retrospective and prospective studies, had the following limitations: i) high heterogeneity found between studies; ii) use of selected samples and the choice of case definition may be a source of bias; and iii) it is a misunderstanding that rapid tests are easy and therefore do not require experience; iv) it may reflect population-related differences, such as past exposure to leptospirosis, exposure to environmental leptospires, or infection with other infectious agents.

In conclusion, in the meta-analysis, the diagnosis of leptospirosis was ascertained by definite clinical criteria and standard MAT criteria. Also, IgM ELISA is sufficiently sensitive for use as an initial screen for leptospiral infections. The IgM ELISA showed higher sensitivity (84%) and specificity (91%) in the diagnosis of acute leptospiral infection and can be used as a rapid test for the detection of the disease, therefore improving the prognosis of patients and decreasing the lethality of leptospirosis.



Study	Sensitivity (95% Conf Interval)
Aviat et al. 2009	0,32 (0,18 – 0,49)
Bajani et al. 2003	0,86 (0,79 – 0,92)
Bharadwaj et al. 2002	0,91 (0,81 – 0.96)
Blacksell et al. 2006	0,70 (0,35 – 0,93)
Blanco et al. 2008	0,90 (0,73 – 0,98)
Bourhy et al. 2013	0,99 (0,91 – 1,00)
Brandão et al. 1998	0,99 (0,95 – 1,00)
Céspedes et al. 2002	0,98 (0,87 – 1,00)
Cinco et al. 1992	0,81 (0,74 – 0,88)
Cumberland et al. 1999	0,52 (0,46 – 0,58)
Da Silva et al. 1988	0,82 (0,69 – 0,91)
Da Silva et al. 1990	0,70 (0,51 – 0,85)
Da Silva et al. 1992	0,98 (0,84 – 1,00)
Da Silva et al. 1994	0,98 (0,79 – 1,00)
Da Silva et al. 1997	0,98 (0,92 – 1,00)
Desakorn et al. 2012	0,52 (0,42 – 0,62)
Dey et al. 2008	0,96 (0,89 – 0,99)
Effler et al. 2002	0,48 (0,31 – 0,66)
Fonseca et al. 2006	0,78 (0,66 – 0,88)
Honarmand et al. 2008	0,90 (0,82 – 0,95)
Kucerova et al. 2011	0,95 (0,63 – 1,00)
Kumar et al. 2012	0,98 (0,95 – 1,00)
Levett et al. 2002	0,86 (0,67 – 0,96)
Levett et al. 2001	0,89 (0,72 – 0,98)
Mc Bride et al. 2007	0,99 (0,72 – 0,98)
Mc Bride et al . 2007b	0,86 (0,68 – 0,96)
Nakarin et al. 2004	0,93 (0,85 – 0,97)
Obregón et al. 2004	0,97 (0,86 – 1,00)
Ooteman et al. 2006	0,94 (0,82 – 0,99)
Pappas et al. 1985	0,96 (0,90 – 0,99)
Pol and Bharadwaj 2009	0,85 (0,62 – 0,97)
Polanco et al. 1997	0,90 (0,78 – 0,97)
Ribeiro et al. 1996	0,88 (0,70 – 0,98)
Ribeiro et al. 1995	0,96 (0,79 – 1,00)
Sehgal et al. 2003	0,50 (0,38 – 0,62)
Sekhar et al. 2000	0,68 (0,51 – 0,82)
Shekathar et al. 2010b	0,38 (0,23 – 0,54)
Shekatkar et al. 2010a	0,76 (0,60 – 0,89)
Silpasakorn et al. 2011	0,61 (0,50 – 0,71)
Smits et al. 2000	0,86 (0,81 – 0,89)
Smits et al. 2001	0,89 (0,82 – 0,94)
Srimanote et al. 2007	0,70 (0,54 – 0,82)
Tanganuchitcharnchai et al. 2012	0,90 (0,55 – 1,00)
Tansuphasiri et al. 2005	0,99 (0,94 – 1,00)
Terpstra et al. 1980	0,95 (0,88 – 0,98)
Trombert-Paolantoni et al. 2010	0,90 (0,73 – 0,98)
Vedhagiri et al. 2013	0,96 (0,95 – 0, 97)
Velineni et al. 2006	0,93 (0,76 – 0,99)
Vitale et al. 2003	0,97 (0,78 – 1,00)
Winslow et al. 1997	0,99 (0,89 – 1,00)
Yersin et al. 1999	0,97 (0,86 – 1,00)
Zochowski et al. 2001	0,96 (0,90 – 0,99)

Pooled Sensitivity = 0,86 (0,85 to ,87)

Heterogeneity chi-squared = 873,87 (d.f.= 51) p = 0,0000
Inconsistency (I-square) = 94,2%

Figure 3. Forest plot of sensitivity (A) and specificity (B) of the all studies included in this review.

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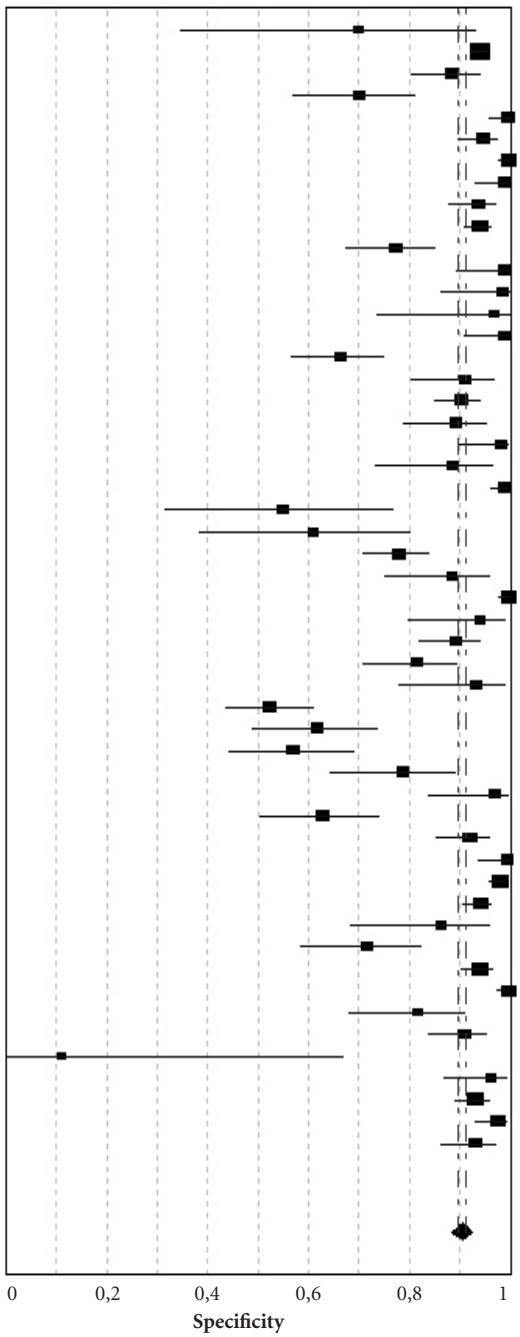

Study	Specificity (95% Conf Iterval)
Aviat et al. 2009	0,70 (0,35 – 0,93)
Bajani et al. 2003	0,94 (0,92 – 0,96)
Bharadwaj et al. 2002	0,88 (0,80 – 0,94)
Blacksell et al. 2006	0,70 (0,57 – 0,81)
Blanco et al. 2008	1,00 (0,96 – 1,00)
Bourhy et al .2013	0,95 (0,90 – 0,98)
Brandão et al. 1998	1,00 (0,98 – 1,00)
Céspedes et al. 2002	0,99 (0,93 – 1,00)
Cinco et al. 1992	0,94 (0,88 – 0,97)
Cumberland et al. 1999	0,94 (0,91 – 0,96)
Da Silva et al. 1988	0,77 (0,94 – 0,85)
Da Silva et al. 1990	0,99 (0,89 – 1,00)
Da Silva et al. 1992	0,98 (0,86 – 1,00)
Da Silva et al. 1994	0,97 (0,74 – 1,00)
Da Silva et al. 1997	0,99 (0,91 – 1,00)
Desakorn et al. 2012	0,66 (0,57 – 0,75)
Dey et al. 2008	0,91 (0,80 – 0,97)
Effler et al. 2002	0,90 (0,85 – 0,94)
Fonseca et al. 2006	0,89 (0,79 – 0,95)
Honarmand et al. 2008	0,98 (0,90 – 1,00)
Kucerova et al. 2011	0,89 (0,73 – 0,97)
Kumar et al. 2012	0,99 (0,96 – 1,00)
Levett et al. 2002	0,55 (0,32 – 0,77)
Levett et al. 2001	0,61 (0,39 – 0,80)
Mc Bride et al. 2007	0,78 (0,71 – 0,84)
Mc Bride et al. 2007b	0,88 (0,75 – 0,96)
Nakarin et al. 2004	1,00 (0,98 – 1,00)
Obregón et al. 2004	0,94 (0,80 – 0,99)
Ooteman et al. 2006	0,89 (0,82 – 0,94)
Pappas et al. 1985	0,81 (0,71 – 0,89)
Pol and Bharadwaj 2009	0,93 (0,78 – 0,99)
Polanco et al. 1997	0,52 (0,43 – 0,61)
Ribeiro et al. 1996	0,62 (0,49 – 0,74)
Ribeiro et al. 1995	0,57 (0,44 – 0,69)
Sehgal et al. 2003	0,79 (0,64 – 0,89)
Sekhar et al. 2000	0,97 (0,84 – 1,00)
Shekathar et al. 2010b	0,63 (0,50 – 0,74)
Shekatkar et al. 2010a	0,92 (0,85 – 0,96)
Silpasakorn et al. 2011	0,99 (0,94 – 1,00)
Smits et al. 2000	0,98 (0,96 – 0,99)
Smits et al. 2001	0,94 (0,91 – 0,96)
Srimanote et al. 2007	0,86 (0,68 – 0,96)
Tanganuchitcharnchai et al. 2012	0,72 (0,59 – 0,83)
Tansuphasiri et al. 2005	0,94 (0,90 – 0,97)
Terpstra et al. 1980	1,00 (0,97 – 1,00)
Trombert-Paolantoni et al. 2010	0,82 (0,68 – 0,91)
Vedhagiri et al. 2013	0,91 (0,84 – 0,96)
Velineni et al. 2006	0,11 (0,00 – 0,67)
Vitale et al. 2003	0,96 (0,87 – 1,00)
Winslow et al. 1997	0,93 (0,89 – 0,96)
Yersin et al. 1999	0,98 (0,93 – 0,99)
Zochowski et al. 2001	0,93 (0,86 – 0,97)

Pooled Specificity = 0,90 (0,90 to 0,91)

Heterogeneity chi-squared = 716,96 (d.f.= 51) p = 0,0000
Inconsistency (I-square) = 92,9%

Figure 3. continuation

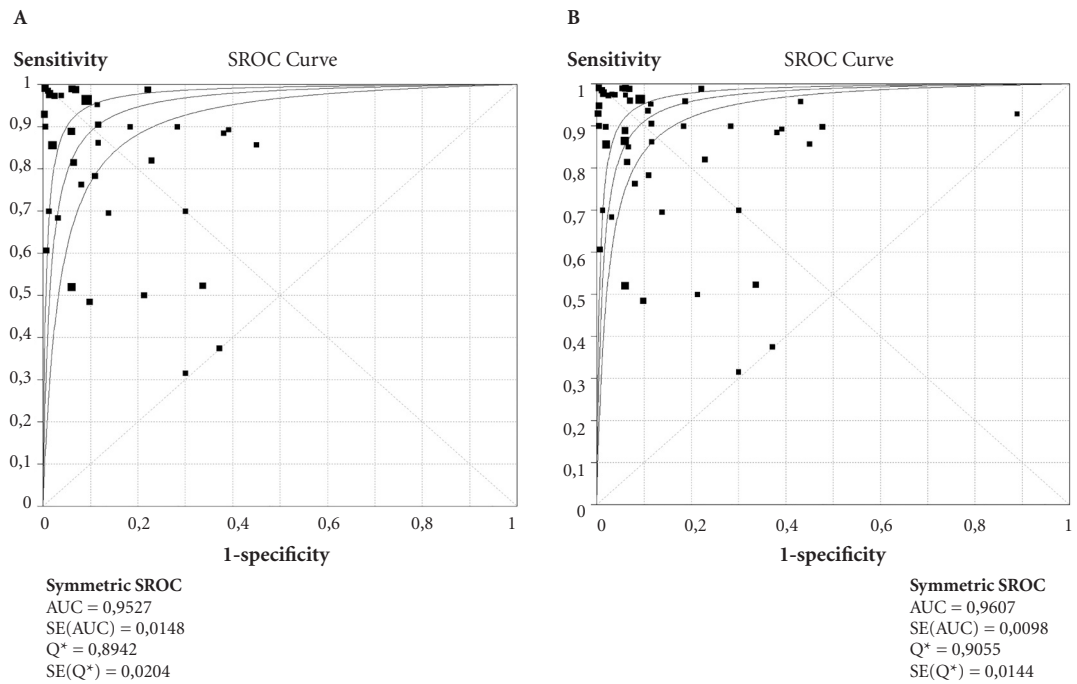

Figure 4. Summary receiver operating characteristic curves. A: all studies and B: acute phase.

Collaborations

MI Rosa was responsible for the literature review, results analysis, data interpretation, and writing of the final article. MF Reis, C Simon, E Dondossola, MC Alexandre, and T Colonetti conducted the data interpretation and writing of the final article. FO Meller contributed with the writing and critic review of the manuscript.

Acknowledgments

The study was supported by the University of Extremo Sul Catarinense.

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Artigo apresentado em 25/05/2016
Aprovado em 23/08/2016
Versão final apresentada em 25/08/2016