DIAGNOSTIC ACCURACY OF CEREBROSPINAL FLUID LACTATE FOR DIFFERENTIATING BACTERIAL MENINGITIS FROM ASEPTIC MENINGITIS: A META-ANALYSIS

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Summary (Abstract)

Objectives:

Cerebrospinal fluid (CSF) lactate is produced by bacterial anaerobic metabolism and is not affected by blood lactate concentration, an advantage over CSF glucose in differentiating bacterial meningitis from aseptic meningitis. However, the previous investigations have shown mixed results of the sensitivity and specificity. Our study's purpose was to assess the utility of CSF lactate in differentiating bacterial meningitis from aseptic meningitis.

Methods:

We searched MEDLINE and EMBASE for clinical studies that included CSF lactate measurement in bacterial meningitis and aseptic meningitis. Test characteristics were pooled using hierarchical summary ROC curve and random effects model.

Results:

Thirty three studies were included. The pooled test characteristics of CSF lactate were sensitivity 0.93 (95%CI: 0.89-0.96), specificity 0.96 (95% CI: 0.93-0.98), likelihood ratio positive 22.9 (95%CI: 12.6-41.9), likelihood ratio negative 0.07 (95%CI: 0.05-0.12), and diagnostic odds ratio 313 (95%CI: 141-698). Pretreatment with antibiotics lowered the sensitivity 0.49 (95% CI: 0.23-0.75). CSF lactate of around 35 mg/dl (34-36 mg/dl) had higher sensitivity and specificity than those of around 27 mg/dl (26-28 mg/dl).

Conclusions:

CSF lactate's high negative likelihood ratio may make it useful for ruling out bacterial

meningitis though pretreatment with antibiotics reduces clinical accuracy. CSF lactate of 35 mg/dl could be optimal cut-off value for distinguishing bacterial meningitis from aseptic meningitis.

Key words: meningitis, cerebrospinal fluid, lactate, meta-analysis

INTRODUCTION

Bacterial meningitis is an infectious disease of the central nervous system (CNS) characterized by significant mortality and morbidity despite advances in antibiotics. [1] The mortality of bacterial meningitis varies from 3-21%, by type of organism. [2] Furthermore, survivors of bacterial meningitis have a high risk of cognitive impairment or other neurological deficits. [3, 4] In addition to antibiotics, an adjunctive steroid therapy have been shown to improve mortality and reduce neurological complications in both children and adults. [5, 6] However, timing is important, steroids should be administered before or concurrent with antibiotics. [7] Therefore, rapid differentiation between bacterial meningitis and aseptic meningitis, a self-limiting infection, is important for appropriate treatment.

Polymorphonuclear leukocytosis, decreased glucose concentration and cerebrospinal fluid (CSF)/serum glucose ratio, and an increased protein concentration in CSF are characteristics of bacterial meningitis. But, bacterial meningitis sometimes presents with atypical CSF manifestations such as predominance of monocytes or glucose more than 40 mg/dl. [8] While a bacterial culture is the most reliable test for bacterial meningitis, it requires a few days for growth. These CSF characteristics may result in under or delayed treatment of bacterial meningitis or overtreatment of aseptic meningitis.

CSF lactate is a potential marker for bacterial meningitis that could provide early diagnostic information. CSF lactate is produced by bacterial anaerobic metabolism or ischemic brain tissue. An advantage of CSF lactate over CSF glucose is that the value

of CSF lactate is not affected by blood lactate concentration.[9, 10] However, the previous investigations have shown mixed results of the sensitivity and specificity of CSF lactate. [11-14] The purpose of our review is to assess the test characteristics of CSF lactate for the diagnosis of bacterial meningitis.

METHODS

Data Sources and Searches

We conducted a systematic literature search of MEDLINE from 1966 to December 2009 and EMBASE from 1968 to December 2009 on January 2010 using the Medical Subject Headings (MeSH) and text keywords meningitis and lactate. We restricted our search to English language studies and hand-searched bibliographies of retrieved articles. Literature search was performed by two of the investigators (K.S, T.K) independently.

Study selection

We used three inclusion criteria: 1) CSF lactate was measured in patients suffering from bacterial meningitis and aseptic meningitis in clinical practice, 2) absolute numbers of true positive (TP), false negative (FN), true negative (TN), and false positive (FP) were abstractable from the text, figures or tables, 3) cut-off points for positivity were given by authors or available from figures or tables.

Data Extraction and Quality Assessment

We abstracted the following variables; publication year, name of the author, patients demographics, methods of CSF lactate measurement, pathogens of bacterial meningitis (bacteria only, fungi and tuberculosis also included), pretreatment with antibiotics, number of TP (bacterial meningitis with CSF lactate elevation), FN (bacterial meningitis without CSF lactate elevation), TN (aseptic meningitis without CSF lactate elevation), FP (aseptic meningitis with CSF lactate elevation). Data were extracted and analyzed based on the number of cases. We evaluated study quality using

the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) method. [15] QUADAS contains 14 domains (spectrum of patients representative, selection criteria clarity, reference standard, period between reference standard and index test, verification bias, completeness and consistency of verification, independence between index test and reference standard, index test description, reference standard description, clinical review bias of index test, clinical review bias of reference standard, similarity to practice, uninterpretable tests, and withdrawals). Data extraction and QUADAS scoring were conducted independently by two of investigators (K.S and T.K), differences were resolved by consensus.

Data Synthesis and Analysis

We assessed for potential threshold effects by assessing the correlation between sensitivity and specificity and by plotting ROC curves. While there was no statistical evidence of a threshold effect, ROC curves suggested a relationship prompting us to calculate sensitivities, specificities, likelihood ratio and diagnostic odds ratios (a single indicator of diagnostic test performance consists of the ratio of the odds of positivity in disease relative to the odds of positivity in the non-disease) fitting a two-level mixed logistic regression model and a hierarchical summary ROC (HSROC) curve, [16] with independent binomial distributions for the true positives and true negatives on the sensitivity and specificity in each study, and a bivariate normal model for the logit transform of sensitivity and specificity between the studies. [17] In order to assess for potential publication bias and to perform subgroup analyses, we also pooled sensitivity, specificity, and likelihood ratios using a random effect model [18] to derive

estimates and their 95% confidence intervals (CI). For this pooled analysis, we calculated standard errors using exact binomial methods. We used the Agresti-Coull (adjusted Wald) method [19] for articles reporting sensitivities and specificities of 1 or 0. Heterogeneity was assessed by I^2 statistic. [20] We evaluated potential sources for heterogeneity using meta-regression [21] and stratified analyses. Potential sources of heterogeneity explored included: (i) quality (using both a components and scored analysis approach and using a QUADAS score greater than 12); (ii) positivity criteria of CSF lactate; (iii) age of patients with bacterial meningitis; (iv) disease spectrum defined as bacterial meningitis only or including bacterial meningitis, tuberculous meningitis, and fungal meningitis; and (v) whether antibiotics were given before CSF sampling. Planned a priori subgroup analysis included whether or not the patient received pretreatment with antibiotics before CSF was obtained. We integrated studies collecting only untreated patients by antibiotics and studies with figures of patients with or without pretreatment. Subgroup analysis of untreated and pretreated patients could perform in bacterial meningitis because aseptic meningitis with or without pretreatment were not abstractable from collected studies. We also added subgroup analyses including studies with bacterial meningitis proven by culture or gram stain and studies with frequently used cut-off value in collected studies.

There are no formal tests for publication bias of meta-analyses of diagnostic tests, as both the Begg's and Egger's tests [22] were developed for meta-analyses of randomized controlled trials. However, we examined funnel plots and applied the Begg's test. P values less than 0.05 were taken as statistically significant. All analyses

were performed using STATA version 10.1 (STATA Corporation, College Station, TX, USA).

RESULTS

Study Selection and Data Extraction

Our systematic search of MEDLINE and EMBASE found 171 potential articles on CSF lactate in meningitis. Based on review of titles and abstracts, we narrowed this to 73 studies on meningitis diagnosis. Of these 73, 40 were excluded: 21 studies did not sufficiently differentiate between bacterial and aseptic meningitis, 10 studies were reviews or letters without data, 8 studies evaluated only the difference of mean CSF lactate levels between bacterial and aseptic meningitis, and one study provided sensitivity and specificity, but had insufficient information to abstract data into a 2x2 table (Figure 1). This left 33 studies involving a total of 1885 patients that consisted of 852 with TP, 82 with FN, 54 with FP, and 897 with TN. The number of patient who had bacterial meningitis and pretreatment by antibiotics was 67 (34 with TP and 26 with FN). Study characteristics of included studies are given in Table 1.

Most of the studies were published in 1970's and 1980's and conducted in developed countries. Almost all studies reported age range of subjects. There were 14 studies (42%) included only pediatric patients, 4 (12%) only adults, and 10 (30%) included both adults and children. The clinical outcome of meningitis was not described in most studies. The mean QUADAS score was 10.4 (range, 8-14). Nearly all studies reported on subject generation of subjects, but many elements of quality were not sufficiently described (Table 2). Only 9 studies described the spectrum of subjects adequately and collected CSF samples consecutively. Selection of subjects varied, some were limited to patients with suspected CNS infections, and others included

neurological diseases that required CSF examination. Some studies identified bacterial meningitis by culture or microscopic examination (some of them included serological test, n=24), 6 studies based the diagnosis on routine CSF analysis (cell counts, protein, and glucose), and 3 provided no details on the method for categorizing the type of meningitis. All studies performed routine CSF examination, culture, and lactate measurement on the same specimen. Index-test, reference testing were performed on all specimens and the diagnosis of bacterial meningitis was not based on CSF lactate measures, so there was no diagnostic test bias present in any studies.

Diagnostic test performances of CSF lactate

Pooling using a hierarchical summary ROC curves (Figure 2) produced sensitivity of 0.93 (95% CI: 0.89-0.96), and a specificity of 0.96 (95% CI: 0.93-0.98). Additional diagnostic test characteristics included: likelihood ratio positive (LR+): 22.9 (95% CI: 12.6-41.9), likelihood ratio negative (LR-): 0.07 (95% CI: 0.05-0.12), and diagnostic odds ratio: 313 (95% CI: 141-698). Pooling with random effects model (see Supplementary Figure 1) provided similar results with sensitivity 0.94 (95% CI: 0.92-0.96, I2=68.8%) and specificity 0.97 (95% CI: 0.96-0.99, I2=43.5%).

In subgroup analysis (Table 3), patients with bacteria proven by culture or gram stain had equivalent sensitivity of 0.96 (95% CI: 0.93-0.98 I^2=58.2%) and specificity of 0.97 (95% CI: 0.96-0.99 I^2=46.6%) compared with overall analyses. patients pretreated with antibiotics had lower sensitivity (Figure 3-A), 0.49 (95% CI: 0.23-0.75, I^2=91.1%), compared to those not receiving pretreatment (Figure 3-B): 0.98 (95% CI: 0.96-1.00, I^2=11.1%). To reveal the optimal cut-off value, two subgroups of patients

with around 35 mg/dl (34-36 mg/dl) cut-off value and around 27 mg/dl (26-28 mg/dl) were analyzed because those were first and second most used cut-off value in collected studies. Patients with around 35 mg/dl cut-off value had better sensitivity of 0.93 (95% CI: 0.89-0.97, I^2=76.2%) and specificity of 0.99 (95% CI: 0.97-1.00, I^2=32.1%) than those with around 27 mg/dl cut-off value.

Analyses evaluating other confounding variables, including QUADAS score, cut-off value, disease spectrum, and whether or not the population was adult or children found that none contributed more than 10% of the variance to either sensitivity or specificity.

There is no formal test for publication bias for systematic reviews of diagnostic tests. While the Begg's test suggested the possibility of publication bias for both sensitivity (sensitivity bias p=0.001) and specificity (specificity bias p=0.001), this was due to the fact that both sensitivity and specificity are limited to 1.0 as an upper value and the Begg test for asymmetry was positive because the cluster of studies was asymmetric around 1.0. In other words, the test was positive because all studies were less than 1.0, reflecting one problem with the current set of tests for publication bias in diagnostic test meta-analyses.

Discussion

Our study confirms three important findings in using CSF lactate to diagnose bacterial meningitis. First, CSF lactate has high sensitivity and specificity in distinguishing between bacterial and aseptic meningitis. Second, like other CSF markers, lactate is less sensitive if patients receive antibiotics before CSF sampling. Third, the good diagnostic test performance of CSF lactate was confirmed both adults and children.

Fortunately, bacterial meningitis is less common than aseptic meningitis, in one series of 3295 children with pleocytosis, only 4% had bacterial meningitis. [23] The neurological outcomes of bacterial meningitis are often poor making early diagnosis and treatment important. [5] Classical clinical characteristics of bacterial meningitis include fever, nuchal rigidity, and change in mental status. However, only two-fifth to two-thirds of patients with bacterial meningitis present with all three symptoms.[4, 8] Proportions of fever, nuchal rigidity, and change in mental status were 77-95%, 83-88%, and 60-78%, respectively. [4, 8] Triad of these symptoms was observed only 44% in patients with bacterial meningitis. [4] Consequently the clinical history and physical examination have low diagnostic accuracy. [24] Other methods to distinguish between bacterial and aseptic meningitis, including gram stain of the cerebrospinal fluid, CSF cell counts and glucose levels, have been studied. One systematic review found only three studies on the diagnostic accuracy of gram stains reporting sensitivities ranging from 56-86%. Only one study reported specificity, finding it to be 100%. [25] This same systematic review found only one study meet their quality criteria

evaluating leukocytosis (CSF WBC>500/ml) with a LR+ of 15 (95% CI: 10-22) and a LR- of 0.3 (95% CI: 0.2-0.4); two studies of blood CSF/serum glucose ratios < 0.4 found widely varied LR+ (18 and 145), with LR- of 0.31 and 0.25. The lack of accuracy of any single test has prompted creation and testing of decision rules, combining clinical and lab features with only moderate success, notably none of these decision rules incorporate CSF lactate. [23, 26] These atypical manifestation of CSF examination including culture negative and gram stain negative can result in a missed diagnosis of bacterial meningitis. Combination CSF lactates and routine CSF examination provides can estimate the chance of bacterial meningitis more satisfactory in very short time.

Our meta-analysis pooled a large number of studies, thirty three, and found that CSF lactate had good likelihood ratios. The very low negative likelihood ratio means that lack of CSF lactate is particularly good for ruling out bacterial meningitis. For example, given a prevalence of 4%, a negative CSF lactate reduces the probability of bacterial meningitis to 3/1000. This negative likelihood ratio is lower than CSF white blood cell count, glucose, or blood glucose ratio. [25]

In subgroup analysis, patients with bacterial meningitis proven by culture or gram stain had similar results with overall analyses. These results find the robustness of the reliability of CSF lactates in bacterial meningitis. However, reduction of sensitivity in pretreated bacterial meningitis was observed, similar to CSF glucose. [27] It is well known that early antibiotic treatment improves clinical outcomes. However, this can modify CSF findings, making both CSF glucose and lactate less sensitive. [28] The

effects of treatment on CSF leukocytosis is mixed, some investigator have found that prior antibiotic therapy does not reduce the total number of white blood cell, or the percentage of polymorphonuclear leukocytes. [29, 30] Our study suggests that a CSF lactate in the normal range cannot rule out bacterial meningitis among patients pretreated with antibiotics.

Optimal cut-off value derived from our meta-analysis is around 35 mg/dl to distinguish bacterial meningitis from aseptic meningitis. Since, recommended cut-off value is 35 mg/dl or 3.9 mmol/l in clinical practice.

One strength of our analysis is the inclusion of varying age groups. The epidemiology of bacterial meningitis differs by age. [31] Our data suggests that the diagnostic value of CSF lactate is similar between children and adults.

There are several limitations in this study. First, included studies varied in quality. Our meta-regression based on QUADAS score found no effect of quality on our pooled values for sensitivity or specificity for CSF lactate in infectious meningitis. Second, this meta-analysis could not discriminate between bacterial meningitis only and those with bacterial, fungal, and tubercular meningitis, but meta-regression analysis indicated that this might not cause significant heterogeneity. Finally, a ceiling effect appeared in funnel plot, distorting the formal statistical test for publication bias Therefore, the possibility of publication bias cannot be excluded. Currently there are no standard methods for evaluation publication bias in diagnostic studies.

In conclusion, CSF lactate is reliable distinguishing bacterial meningitis from aseptic meningitis in combination with other CSF characteristics for clinical practice.

Because of its high negative likelihood ratio (LR-), this test is especially useful for ruling out bacterial meningitis. Pretreatment of antibiotics reduces the clinical value of CSF lactate.

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Conflict of interest:

We have no conflict of interest for this article.

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Table 1. Background of studies included in this meta-analysis

Author	Year	Country	Age	Number of patients	Type of outcome *	Cutoff point	QUADUS score	lactate measurement method †
Bland[32]	1974	USA	child	55	BMonly	35	10	enz
Controni[33]	1977	USA	child	77	BMonly	25	11	enz
Furguson[34]	1977	UK	both	25	N/A	35	10	GLchro
Lauwers[35]	1978	Belgium	N/A	66	BMTMFM	35	11	GLchro
D'souza[36]	1978	UK	N/A	35	BMonly	35.1	9	enz
Boon[37]	1978	Singapore	N/A	24	BMonly	21	8	enz
Brook[28]	1978	USA	both	53	BMonly	35	14	GLchro
Aragon[13]	1979	Mexico	child	44	BMonly	35	8	enz
Gastrin[38]	1979	Sweden	both	55	BMonly	36	11	GLchro
Lannigan[11]	1980	Canada	adult	33	BMTMFM	35	11	enz
Gould[39]	1980	England	N/A	32	BMTMFM	35	8	GLchro
Knight[40]	1981	USA	child	88	BMonly	30	10	enz
Curtis[41]	1981	UK	both	41	BMTMFM	25.2	14	enz
Eross[42]	1981	Australia	child	155	BMonly	34.2	11	enz
Rutledge[43]	1981	USA	child	42	BMonly	27	10	enz
Berg[44]	1982	Sweden	both	141	BMTMFM	27	14	enz
Dwivedi[45]	1983	USA	child	12	BMonly	35	9	enz
Ponka[46]	1983	Finland	both	38	BMonly	27	11	enz
Mandal[47]	1983	UK	N/A	85	BMonly	35.1	11	enz
Vanprapar[48]	1983	Thailand	child	31	BMonly	40	8	enz
Briem[12]	1983	Sweden	child	137	BMTMFM	31.5	10	enz
Jordan[49]	1983	USA	both	15	BMTMFM	27	12	enz
Ruuskanen[50]	1985	Finland	child	62	N/A	27	8	enz
Lester[51]	1985	Denmark	both	31	BMonly	31.5	12	enz
Low[14]	1986	Singapore	child	80	BMonly	25	8	enz
Donald[52]	1986	S.Africa	both	71	BMTMFM	35.1	11	enz
Nelson[53]	1986	Sweden	child	46	BMonly	21.6	12	enz
Komorowski[54]	1986	USA	adult	47	BMTMFM	27	8	other
Shaltout[55]	1989	Kuwait	child	30	BMTMFM	27	11	other
Genton[56]	1990	Switzerland	adult	60	N/A	37.8	12	other
Cameron[57]	1993	UK	child	26	BMTMFM	36	10	enz
Abro[58]	2009	UAE	adult	95	BMonly	34.2	11	enz
de Almeida[59]	2009	Brazil	both	53	Bmonly	31.5	9	other

*BMonly indicates studies including only bacterial meningitis; BMTMFM, Study including bacterial meningitis, tuberculous meningitis, and fungal meningitis ; N/A indicates studies without information about including tuberculous meningitis and fungal meningitis or not.

enz: lactate was measured by enzymatic method

†Glchro indicates lactate was measured by Gas/Laquid chromatogyraphy

Table 2. Quality Problems According to QUADAS

Studies	Patients Represented in Clinical Practice	Clearly Described Selection Criteria	Reference Standard Classifies Target Correctly	Period Between Reference and Index Tests Short Enough	Whole or Random Samples Receive Verification	Same Reference Regardless of Index	Reference Independence Index*	Detailed Described Index	Detailed Described Reference	Blind Interpretation of Index Test	Blind Interpretation of Reference Test	Same Clinical Data Available in Practice	Intermediate Result Report	Withdrawals Explained
Bland(1974)	−	−	+	+	+	+	+	+	+	+	+	+	?	?
Controni(1977)	−	+	+	+	+	+	+	+	+	+	+	+	?	?
Furguson(1977)	+	+	?	+	?	+	+	+	+	+	+	+	+	?
Lauwers(1978)	−	+	?	+	?	+	+	+	+	+	+	+	+	+
D'souza(1978)	−	+	?	+	?	+	+	+	+	+	+	+	?	?
Boon(1978)	−	−	?	+	?	+	+	+	+	+	+	+	?	?
Brook(1978)	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Aragon(1979)	−	−	−	+	?	+	+	+	+	+	+	+	?	?
Gastrin(1979)	−	−	+	+	+	+	+	+	+	+	+	+	+	?
Lannigan(1980)	−	−	+	+	+	+	+	+	+	+	+	+	+	?
Gould(1980)	−	−	−	+	?	+	+	+	+	+	+	+	?	?
Knight(1981)	−	−	+	+	+	+	+	+	+	+	+	+	?	?
Curtis(1981)	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Eross(1981)	−	+	+	+	+	+	+	+	+	+	+	+	?	?
Rutledge(1981)	−	−	+	+	+	+	+	+	+	+	+	+	?	?
Berg(1982)	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Dwivedi(1983)	−	+	?	+	?	+	+	+	+	+	+	+	?	?
Ponka(1983)	−	+	+	+	+	+	+	+	+	+	+	+	?	?
Mandal(1983)	−	+	+	+	+	+	+	+	+	+	+	+	?	?
Vanprapar(1983)	−	−	?	+	?	+	+	+	+	+	+	+	?	?
Briem(1983)	−	−	+	+	+	+	+	+	+	+	+	+	−	−
Jordan(1983)	+	?	+	+	+	+	+	+	+	+	+	+	?	+
Ruuskanen(1985)	−	−	?	+	?	+	+	+	+	+	+	+	?	?
Lester(1985)	+	−	+	+	+	+	+	+	+	+	+	+	?	+
Low(1986)	−	−	?	+	?	+	+	+	+	+	+	+	?	?
Donald(1986)	−	+	+	+	+	+	+	+	+	+	+	+	?	?
Nelson(1986)	+	+	?	+	?	+	+	+	+	+	+	+	+	+
Komorowski(1986)	−	−	?	+	?	+	+	+	+	+	+	+	?	?
Shaltout(1989)	−	−	+	+	+	+	+	+	+	+	+	+	?	?
Genton(1990)	+	+	+	+	+	+	+	+	+	+	+	+	?	−
Cameron(1993)	−	−	+	+	+	+	+	+	+	+	+	+	?	?
Abro(2009)	−	+	+	+	+	+	+	+	+	+	+	+	?	?
Almeida(2009)	−	−	?	+	+	+	+	+	+	+	+	+	?	?

Table 3. Summary of overall analyses and subgroup analyses

	Sensitivity (95% CI)	Specificity (95% CI)
Overall analysis		
HSROC model	0.93 (0.89-0.96)	0.96 (0.93-0.98)
Random effect model	0.94 (0.92-0.96)	0.97 (0.96-0.99)
Subgroup analysis		
Bacteria proven BM *	0.96 (0.93-0.98)	0.97 (0.96-0.99)
Pretreated BM	0.49 (0.23-0.75)	NA †
Untreated BM	0.98 (0.96-1.00)	NA †
Cut off around 35mg/dl	0.93 (0.89-0.97)	0.99 (0.97-1.00)
Cut off around 27mg/dl	0.90 (0.85-0.94)	0.94 (0.90-0.98)

* Bacterial Meningitis proven by culture or gram stain

† Not Available because of unabstractable data

Figure Legends

Figure 1.

Flow of studies through the retrieval and inclusion process in the meta-analysis

Figure 2.

Hierarchical summary receiver operating characteristic (HSROC) curve of all included studies shows high sensitivity and specificity with small 95% confidence region.

Figure 3.

(A) Pooled sensitivity of the cases with administration of antibiotics before CSF test

(B) Pooled sensitivity of studies included patients without antibiotics before CSF test

Supplementary Figure 1.

(A) Pooled sensitivity of all included studies by the random effect model

(B) Pooled specificity of all included studies by the random effect model

Figure 1.

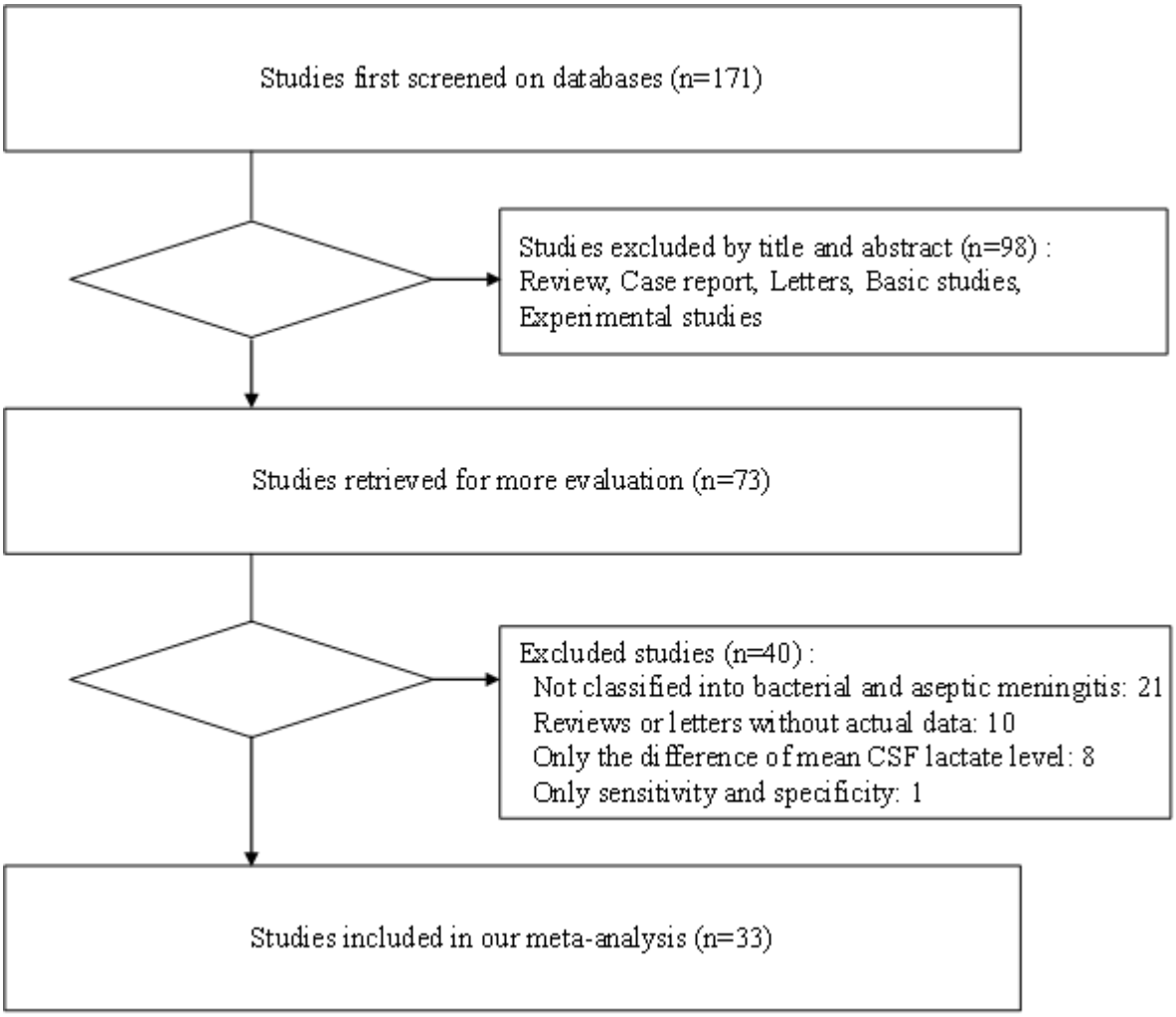

Studies first screened on databases (n=171)
Studies excluded by title and abstract (n=98) :
Review, Case report, Letters, Basic studies,
Experimental studies
Studies retrieved for more evaluation (n=73)
Excluded studies (n=40) :
Not classified into bacterial and aseptic meningitis: 21
Reviews or letters without actual data: 10
Only the difference of mean CSF lactate level: 8
Only sensitivity and specificity: 1
Studies included in our meta-analysis (n=33)

Figure 2.

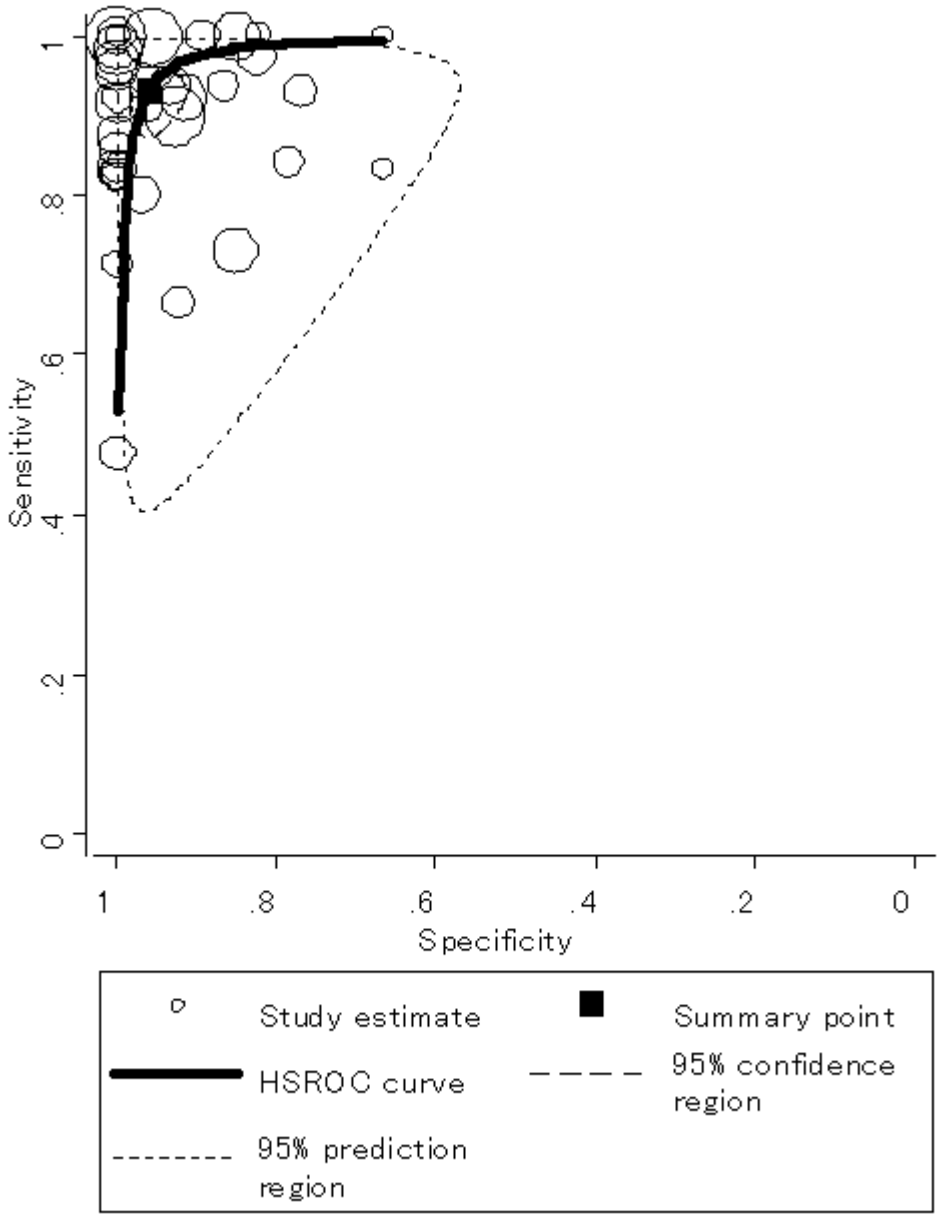
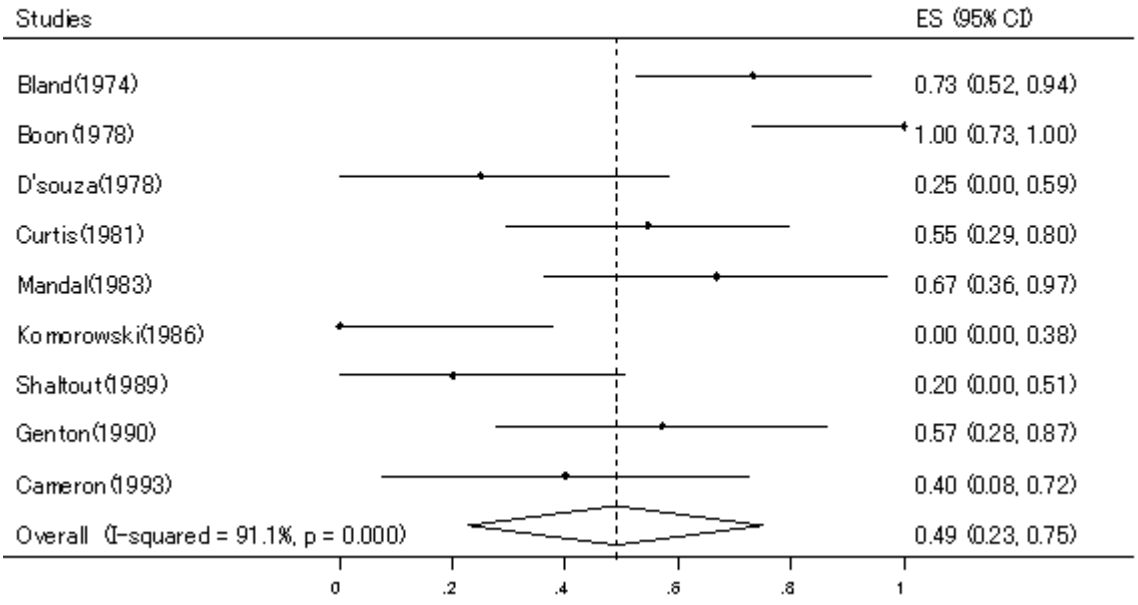
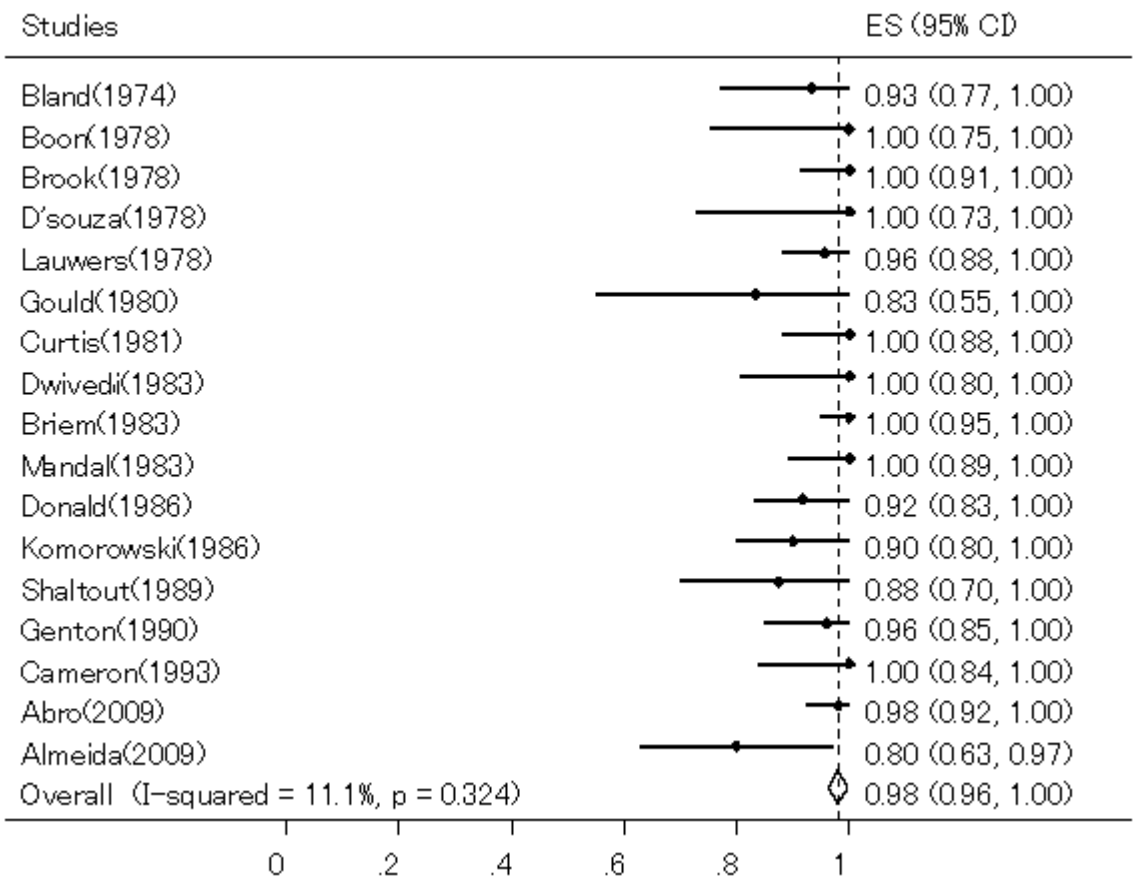

Sensitivity
0
.2
.4
.6
.8
1
1
.8
.6
.4
.2
0
Specificity
Study estimate
Summary point
HSROC curve
95% confidence region
95% prediction region

Figure 3.

(A)

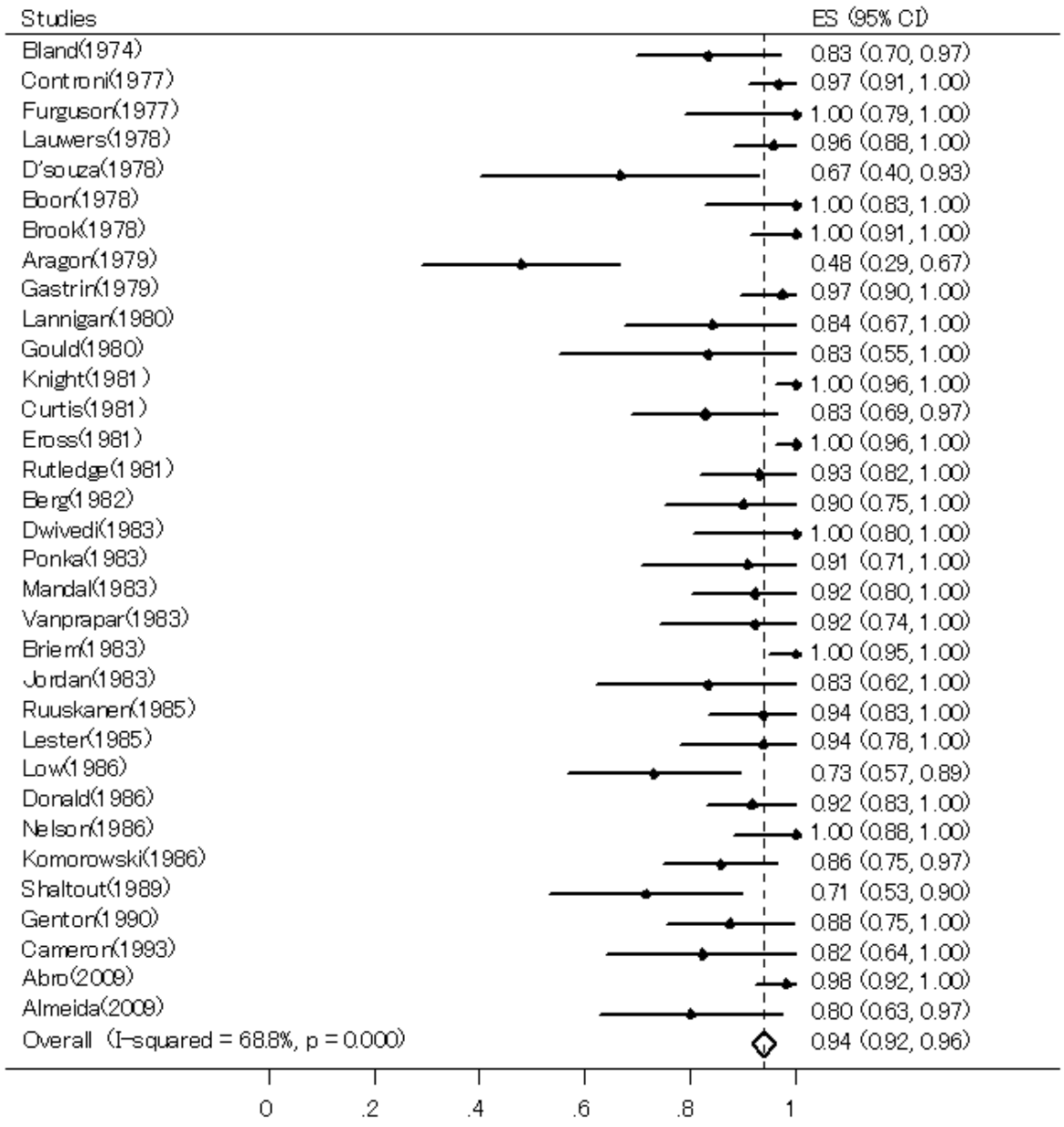

Studies
ES (95% CI)
Bland(1974)
0.73 (0.52, 0.94)
Boon(1978)
1.00 (0.73, 1.00)
D'souza(1978)
0.25 (0.00, 0.59)
Curtis(1981)
0.55 (0.29, 0.80)
Mandal(1983)
0.67 (0.36, 0.97)
Komorowski(1986)
0.00 (0.00, 0.38)
Shaltout(1989)
0.20 (0.00, 0.51)
Genton(1990)
0.57 (0.28, 0.87)
Cameron(1993)
0.40 (0.08, 0.72)
Overall (I-squared = 91.1%, p = 0.000)
0.49 (0.23, 0.75)
0
.2
.4
.6
.8
1

(B)

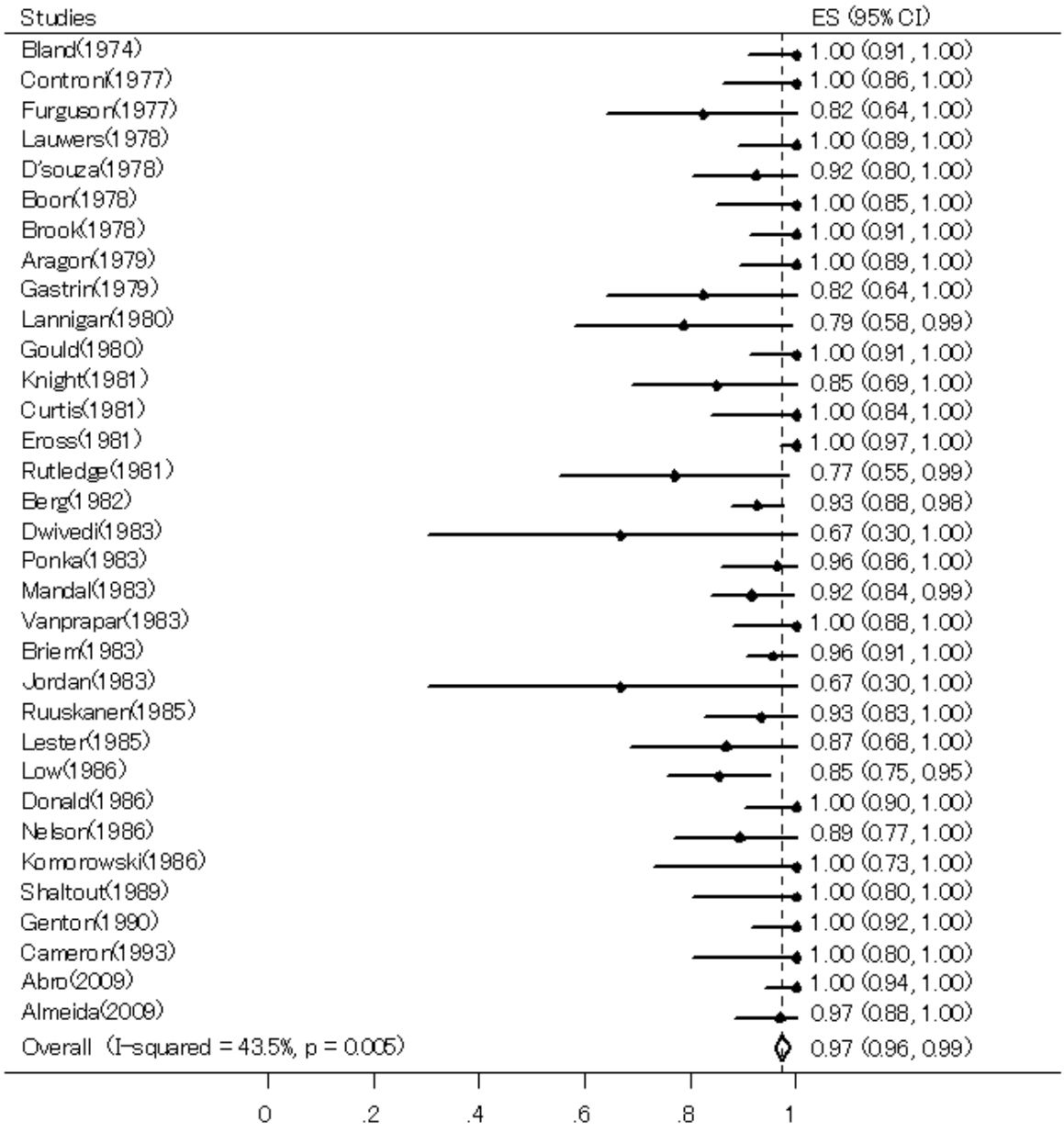

Studies
ES (95% CI)
Bland(1974)
0.93 (0.77, 1.00)
Boon(1978)
1.00 (0.75, 1.00)
Brook(1978)
1.00 (0.91, 1.00)
D'souza(1978)
1.00 (0.73, 1.00)
Lauwers(1978)
0.96 (0.88, 1.00)
Gould(1980)
0.83 (0.55, 1.00)
Curtis(1981)
1.00 (0.88, 1.00)
Dwivedi(1983)
1.00 (0.80, 1.00)
Briem(1983)
1.00 (0.95, 1.00)
Mandal(1983)
1.00 (0.89, 1.00)
Donald(1986)
0.92 (0.83, 1.00)
Komorowski(1986)
0.90 (0.80, 1.00)
Shaltout(1989)
0.88 (0.70, 1.00)
Genton(1990)
0.96 (0.85, 1.00)
Cameron(1993)
1.00 (0.84, 1.00)
Abro(2009)
0.98 (0.92, 1.00)
Almeida(2009)
0.80 (0.63, 0.97)
Overall (I-squared = 11.1%, p = 0.324)
0.98 (0.96, 1.00)
0
.2
.4
.6
.8
1

Supplementary Figure 1.

(A)



(B)


Studies
ES (95% CI)
Bland(1974) 1.00 (0.91, 1.00)
Contron(1977) 1.00 (0.86, 1.00)
Furguson(1977) 0.82 (0.64, 1.00)
Lauwers(1978) 1.00 (0.89, 1.00)
D'souza(1978) 0.92 (0.80, 1.00)
Boon(1978) 1.00 (0.85, 1.00)
Brook(1978) 1.00 (0.91, 1.00)
Aragon(1979) 1.00 (0.89, 1.00)
Gastrin(1979) 0.82 (0.64, 1.00)
Lannigan(1980) 0.79 (0.58, 0.99)
Gould(1980) 1.00 (0.91, 1.00)
Knight(1981) 0.85 (0.69, 1.00)
Curtis(1981) 1.00 (0.84, 1.00)
Eross(1981) 1.00 (0.97, 1.00)
Rutledge(1981) 0.77 (0.55, 0.99)
Berg(1982) 0.93 (0.88, 0.98)
Dwivedi(1983) 0.67 (0.30, 1.00)
Ponka(1983) 0.96 (0.86, 1.00)
Mandal(1983) 0.92 (0.84, 0.99)
Vanprapar(1983) 1.00 (0.88, 1.00)
Briem(1983) 0.96 (0.91, 1.00)
Jordan(1983) 0.67 (0.30, 1.00)
Ruuskanen(1985) 0.93 (0.83, 1.00)
Lester(1985) 0.87 (0.68, 1.00)
Low(1986) 0.85 (0.75, 0.95)
Donald(1986) 1.00 (0.90, 1.00)
Nelson(1986) 0.89 (0.77, 1.00)
Komorowski(1986) 1.00 (0.73, 1.00)
Shaltout(1989) 1.00 (0.80, 1.00)
Genton(1990) 1.00 (0.92, 1.00)
Cameron(1993) 1.00 (0.80, 1.00)
Abro(2009) 1.00 (0.94, 1.00)
Almeida(2009) 0.97 (0.88, 1.00)
Overall (I-squared = 43.5%, p = 0.005) 0.97 (0.96, 0.99)
0
.2
.4
.6
.8
1