Accepted Manuscript

The Accuracy of Ultrasonography for the Diagnosis of Carpal Tunnel Syndrome: A Systematic Review and Meta-analysis

Ana Torres-Costoso, PhD, Vicente Martínez-Vizcaíno, PhD, Celia Álvarez-Bueno, MSc, Asunción Ferri-Morales, PhD, Iván Cavero-Redondo, MSc

PII: S0003-9993(17)31115-2

DOI: 10.1016/j.apmr.2017.08.489

Reference: YAPMR 57026

To appear in: *ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION*

Received Date: 21 August 2017

Accepted Date: 21 August 2017

Please cite this article as: Torres-Costoso A, Martínez-Vizcaíno V, Álvarez-Bueno C, Ferri-Morales A, Cavero-Redondo I, The Accuracy of Ultrasonography for the Diagnosis of Carpal Tunnel Syndrome: A Systematic Review and Meta-analysis, *ARCHIVES OF PHYSICAL MEDICINE AND REHABILITATION* (2017), doi: 10.1016/j.apmr.2017.08.489.

Running title: Ultrasound and median neuropathy: review

Title: The Accuracy of Ultrasonography for the Diagnosis of Carpal Tunnel Syndrome: A Systematic Review and Meta-analysis

Ana Torres-Costoso PhD[1], Vicente Martínez-Vizcaíno PhD [2,3], Celia Álvarez-Bueno MSc[2*], Asunción Ferri-Morales PhD [1], Iván Cavero-Redondo MSc[2]

[1]Universidad de Castilla-La Mancha. School of Nursing and Physiotherapy, Toledo, Spain.

[2] Universidad de Castilla-La Mancha. Health and Social Research Center, Cuenca, Spain.

[3] Universidad Autónoma de Chile. Facultad de Ciencias de la Salud, Talca, Chile.

***Corresponding author:**

Celia Álvarez-Bueno, Social and Health Care Research Center (CESS), University of Castilla La Mancha, Ed/ Melchor Cano, C/Santa Teresa Jornet s/n, Cuenca 16071, Spain. Telephone: +34969179100. E-mail: Celia.AlvarezBueno@uclm.es

Funding

CAB is supported by a grant from the Spanish of Ministry of Education, Culture and Sport (FPU13/03137). ICR is supported by a grant from the University of Castilla-La Mancha (FPU13/01582).

Conflict of interest.

The authors declare no conflict of interest.

Review registration number

This systematic review and meta-analysis was registered through PROSPERO (registration number CRD42017057722).

The Accuracy of Ultrasonography for the Diagnosis of Carpal Tunnel Syndrome: A Systematic Review and Meta-analysis

ABSTRACT

Objetive: To evaluate the accuracy of inlet and outlet ultrasonography measurements for the diagnosis of carpal tunnel syndrome (CTS).

Data sources: We systematically searched MEDLINE, EMBASE, the Cochrane Library and the Web of Science databases, from inception to February 2017.

Study selection: Observational studies comparing the diagnostic accuracy of inlet and outlet ultrasonography measurements were selected.

Data extraction: Random effects models for the diagnostic odds ratio (dOR) values computed by Moses' constant for a linear model and 95% confidence intervals (CIs) were used to calculate the accuracy of the test. Hierarchical summary receiver operating characteristic curves (HSROC) were used to summarize overall test performance.

Data synthesis: Twenty-eight published studies were included in the meta-analysis. The pooled dOR values for the diagnosis of CTS were 31.11 (95%CI 20.42–47.40) for inlet and 16.94 (95%CI 7.58–37.86) for outlet level measurements. The 95% confidence region for the point that summarizes overall test performance of the included studies occurred where the cut offs ranged from 9.0 to 12.6 mm^2 for inlet and from 9.5 to 10.0 mm^2 for outlet level measurements.

Conclusions: Both ultrasonography measurements for the diagnosis of CTS showed sufficient accuracy for their use in clinical settings, though the overall accuracy was slightly higher for inlet than for outlet level measurements. The addition of outlet and inlet measurements doesn't increase the accuracy for the diagnosis. Therefore, the inlet level ultrasonography measurement appears to be an appropriate method for the diagnosis of CTS.

Key Words

Ultrasound, median nerve, median neuropathy

Abbreviations

CTS: Carpal tunnel syndrome

dOR: Diagnosis odds ratio

HSROC: Hierarchical Summary Receiver Operating Characteristic

INTRODUCTION

Carpal tunnel syndrome (CTS) is a frequent condition caused by the compression of the medial nerve at the wrist, [1, 2] its prevalence ranges from 4% to 6% in the general population [1, 3, 4]. In spite of being the most common compression neuropathy in the upper extremity, the gold standard procedure for its diagnosis is controversial.

Electrodiagnosis has been widely used as the confirmatory diagnosis of CTS after clinical diagnosis, [5] and to assess the severity of the median nerve mononeuropathy [6]. However, some studies have shown that electrodiagnosis has a substantial number of false negative and false positive results [1, 7] and the confirmation of CTS is missed in 16% to 34% of patients with clinically defined CTS [8]. Additionally, the electrodiagnosis cut off point used for determining abnormality in the measurement of nerve conduction is highly variable, making comparisons between studies difficult.

Ultrasonography has been proposed as an alternative method for diagnosing CTS (2). This method seems to have important advantages including that it is readily available, inexpensive, fast and painless, but it has also proven a high capacity to detect neural and perineural alterations [9, 10]. Different studies have determined that the cross-sectional area of the median nerve measured by ultrasonography is the most predictive and reproducible measurement for the diagnosis of CTS [11, 12]. However, there is a lack of agreement on which values should be considered abnormal and on the level at which the carpal tunnel measurement should be taken [13, 14], the inlet level (usually defined as the location of the pisiform or as the proximal margin of the flexor retinaculum [15] and the outlet level (defined as the location of the level of the hook of the hamate [10] are the most commonly used measurements.

Currently, there is no consensus on which the best reference standard method for the diagnosis of CTS is. Even though electrodiagnosis has been traditionally proposed as the gold standard, ultrasonography might also be an appropriate method. However, in order for this

technique to become the standard in the diagnosis of CTS, standardization of its measurements is needed. Previous meta-analyses have been performed to determine the sensitivity and specificity of ultrasonography as compared with electrodiagnosis in the diagnosis of CTS [15-17]. Nevertheless, it has been reported that some statistical methods for meta-analyses of diagnostic accuracy might result in misleading summary estimates of sensitivity and specificity [15-17], no previous study has comprehensively reviewed and compared the accuracy of both the ultrasonography and the electrodiagnosis methods using Hierarchical Summary Receiver Operating Characteristic (HSROC), which is currently considered the most rigorous multivariate meta-analysis approach [18]. In addition, none of them have shown pooled results related to the outlet level measurement. Thus, we conducted a systematic review and meta-analysis aimed at assessing the accuracy of inlet and outlet ultrasonography measurements for the diagnosis of CTS using diagnostic odds ratio (dOR) and HSROC.

METHODS

Literature search

This study was conducted according to the PRISMA statement [19] and the recommendations of the Cochrane Collaboration Handbook [20]. This systematic review and meta-analysis was registered through PROSPERO (registration number CRD42017057722).

The following databases were used for the literature search MEDLINE (via PubMed), EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews and the Web of Science from their inception to February 2017. The following search themes were combined: “ultrasonography”, “ultrasonographic”, “ultrasound”, “sonographic”, “sonography”, “threshold”, “cutoff”, “cut off”, “cut point”, “sensitivity”, “specificity”, “diagnostic”, “diagnosis”, “differential diagnosis”, “carpal tunnel syndrome”, “median neuropathy”, “compression neuropathy”, “entrapment neuropathy” and

"median nerve neuralgia". For complementing the search, the reference lists of the retrieved articles, and of previous systematic reviews and meta-analyses were reviewed for additional studies. Two reviewers (CA and IC) independently conducted the search and inconsistencies were resolved by consensus.

Selection criteria

Original articles analyzing the relationship between ultrasonography outlet level (defined as the location of the level of the hook of the hamate) and inlet level (defined as the location of the pisiform or as the proximal margin of the flexor retinaculum) thresholds with the diagnosis of CTS, were included in this systematic review and meta-analysis. With this aim, we followed these inclusion criteria: i) study participants: individuals aged ≥18 years; ii) index tests used: ultrasonography outlet level and inlet level; iii) outcome, CTS diagnosis; and iv) study design: cross-sectional, case-control or cohort studies, with either prospective or retrospective data collection. Studies were excluded if they: i) reported insufficient data for fulfill a 2x2 table; ii) specifically reported outcomes in occupational populations, and iii) were not written in English or Spanish.

Data extraction

Two independent researchers collected the following relevant data from each included study: 1) study data as: author identification, year of publication, country of study and year of data collection, 2) wrist level at which the ultrasonography test was performed, 3) age of the participants, 4) number of participants, 5) number of wrists, 6) prevalence of CTS, and 7) area under curve (AUC) values. Disagreements were solved by consensus.

Risk of bias

The Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool [21] was used to evaluate the risk of bias of each study included. This tool assesses four domains: i) patient

selection, ii) index test, iii) reference standard, and iv) flow of patients and timing of the tests. Each domain could be evaluated as unclear, low and high risk of bias. Also, the first three domains could be evaluated in terms of the applicability of the results. Quality assessment was independently performed by two researchers (CA and IC) and inconsistencies were managed by consensus.

Statistical analysis and data synthesis

The dOR, sensitivity, specificity, positive likelihood ratio (PLR) and negative likelihood ratio (NLR), as well as their corresponding 95% confidence intervals (CIs) were calculated for ultrasonography at outlet and inlet levels in each study included. To conduct the subgroup pooled estimates at least five studies were required

To summarize overall test performance, hierarchical summary receiver operating characteristic curves (HSROC) were used. They were also used to evaluate the magnitude of heterogeneity, in such a way that wider prediction regions suggest larger heterogeneity[22].

The dOR is used as a measure of the effectiveness of a diagnostic test by combining sensitivity and specificity into a single number, which could take values from 0 to infinity. It should be understood that a value of 1 indicates null diagnostic ability of the test, while higher values represent better discriminatory test performance. Moses' constant of linear model was used to compute the dOR, considering that this approach is based on the regression line using the logit of the dOR of each study as a dependent variable and an expression of the positivity threshold of the study as an independent variable[23].

DerSimonian and Laird method was used to compute pooled estimates of dOR, sensitivity, specificity and AUC for each wrist level in the studies included. For evaluating the heterogeneity of the results across studies the I^2 statistical parameter, also its p values were considered. Following Cochrane[20] methodology, I^2 values are considered as: not be important

(0% to 40%); moderate heterogeneity (30% to 60%); substantial heterogeneity (50% to 90%) and considerable heterogeneity (75% to 100%).

Sensitivity analysis was conducted removing one by one the studies form the pooled dOR was estimated to estimate the individual influence of each study in the pooled dOR.

Random-effects meta-regression was used to evaluate separately whether dOR values were different by the median nerve cross-sectional area cut off.

Publication bias was measured by Deeks [24] test and by visually evaluating of using a funnel plot. All statistical analyses were performed using StataSE software, version 14 (StataCorp).

RESULTS

Baseline Characteristics

A total of 2011 articles were retrieved from the literature search. After removing 794 duplicates, articles were screened based on titles and abstracts. Finally, 28 studies were included in this systematic review and meta-analysis [11-14, 25-52] (Figure 1).

The studies included a total sample of 8007 wrists. Their design was always cross-sectional, and they were conducted in 15 countries: Austria, Australia, Brazil, China, Egypt, Hungary, Iran, Japan, Korea, Spain, Switzerland, Singapore, Taiwan, Turkey and the United States of America. The age of the participants ranged from 38.0 to 65.8 years. CTS prevalence varied from 38.8% to 78.8% across the studies. Only eight studies provided information regarding both inlet and outlet cut off points in the same sample [12-14, 29, 41, 42, 48] (Table 1).

Study Quality

As evaluated with QUADAS-2, all studies provided information regarding the seven quality items. Patient selection, and flow and timing were the two domains in which most of the studies had shortcomings (50% and 64% of the studies scored as low risk of bias,

153 respectively). Concerning index test, most studies assessed their results regardless of the
154 reference standard (outlet level: 100%; inlet level: 100%) (S2 Table and S1 Figure).

155 **Meta-analysis**

156 Figure 2 depicts the dOR funnel plots of outlet level and inlet level. There was substantial
157 heterogeneity across the studies in the dOR of CTS based on inlet level (I^2 = 75.0%) and
158 outlet level (I^2 = 82.4%) measurements. The pooled dOR for the diagnosis of CTS were 31.11
159 (95%CI 20.42–47.40; p < 0.001) for inlet level and 16.94 (95%CI 7.58–37.86; p < 0.001) for
160 outlet level measurements. The pooled sensitivity, specificity, positive likelihood ratio (PLR),
161 negative likelihood ratio (NLR) and dOR for outlet level and inlet level measurements are
162 shown in Table 2 (Figures S2 to S5 depict sensitivity, specificity, PLR and NLR funnel plots,
163 respectively).

164 The 95% confidence region for the point that summarized the overall test performance in the
165 area under the HSROC (Figure 3) included studies in which the test cut offs ranged from 9 to
166 12.6 mm^2 for inlet level and from 9.5 to 10.0 mm^2 for outlet level measurements.

167 When we estimated the pooled accuracy parameters using the eight studies that assessed the
168 diagnostic performance of outlet and inlet level measurements in the same sample, the pooled
169 dOR were 26.99 (95%CI 11.79–61.78; p < 0.001) for inlet level and 15.88 (95%CI 6.61–
170 38.18; p < 0.001) for outlet level measurements (S3 Table).

171 **Sensitivity analysis for the effect of individual studies**

172 When the impact of individual studies was examined by removing studies from the analysis
173 one by one, we observed that the pooled dOR was not affected after removing any study for
174 both outlet and inlet level measurements.

175 **Random-effects meta-regression model**

The random-effects meta-regression model showed that the median nerve cross-sectional area cut off was not related to the heterogeneity observed across the studies when outlet and inlet level measurements were used. Moreover, there was no relationship between accuracy, as measured by dOR, and the median nerve cross-sectional area cut off used either for inlet (p= 0.404) or for outlet (p= 0.582) level measurements (S6 Figure).

Publication bias

The asymmetry test, using Deek's method, suggested the absence of publication bias for inlet (p = 0.611) and for outlet level (p = 0.120) measurements (S7 Figure).

DISCUSSION

Clinical assessment has been routinely used as the initial step in the diagnosis of CTS and electrodiagnosis as the gold standard for confirming CTS diagnosis in clinical practice. However, because patients have complained of some discomfort with this technique and median nerve anatomy is not directly assessed [53], ultrasonography has been proposed as a good alternative. To our knowledge, this is the first meta-analysis that synthetizes evidence regarding the utility of ultrasonography as a diagnostic method of CTS in clinical settings, providing the pooled dOR and HSROC in order to assess the accuracy of ultrasonography for the diagnosis of CTS. Our data indicate that ultrasonography has a high pooled sensitivity and specificity for the diagnosis of CTS and that the measurement of the cross-sectional area at the inlet level has a better diagnostic accuracy, in terms of dOR, than the outlet level, supporting the current international recommendations [54].

Our meta-analysis confirms that ultrasonographic measurement of the cross-sectional area of the median nerve at the inlet level is a useful strategy for confirming the clinical diagnosis of CTS. This is consistent with prior findings [11, 15, 55]. In addition, several studies have reported a nerve enlargement at the outlet level [12, 29, 55], and also that the addition of outlet measurements

to inlet ones increases the sensitivity and accuracy for the diagnosis of CTS [29]. On the contrary, our data showed a better accuracy, in terms of dOR, for inlet than for outlet level measurements, and a worse diagnostic performance when using both measurements as compared with using either inlet or outlet level measurements separately. Differences in the diagnostic accuracy between both measurements may be due to swelling of the median nerve at the inlet level that has been consistently seen in the CTS wrist [15]; moreover, poor interobserver reliability in carpal tunnel outlet measurement has been reported [56].

Some variability has been shown in normal ranges for median nerve area in ultrasonography diagnostic values. Variations in equipment, measurement procedures and differences in patient characteristics, may be responsible for variability of the published cut off threshold, [57] and this has probably contributed to the lack of consensus on CTS ultrasonographic diagnostic criteria. Even though a meta-analysis of diagnostic accuracy does not allow the identification of the optimal cut off threshold, [58] a confidence region of cut off can be estimated. In this sense, our results showed that the cut offs failing in the 95% confidence region ranged from 9.0 to 12.6 mm^2 for the inlet level and 9.5 to 10.0 mm^2 for the outlet level. These cut offs are in accordance with those proposed by previous meta-analyses for inlet level measurements [15, 17]. Because of their heterogeneity, pooled data related to outlet level cut offs have not been previously provided [15].

Our pooled estimates of sensitivity [16, 17] and specificity [15] of ultrasonography for the diagnosis of CTS are similar to those of previous studies. Due to its high specificity, authors have proposed ultrasonography as an alternative procedure to electrodiagnosis as the first-line confirmatory test for the diagnosis of CTS [16, 59], since this diagnostic procedure represents a cost-effective strategy for both primary care and hospital services [60]. Furthermore, an algorithm based on an analytic literature review has been recently proposed that recommends the use of ultrasonography as a painless and faster screening test for the diagnosis of CTS,

and restricting the use of electrodiagnosis to cases of advance axonal loss or differential diagnosis [61].

Study Limitations

This review has some potential limitations that should be highlighted: i) although we did not find evidence of significant publication bias, this should not be completely excluded because some studies including small samples or written in languages other than English or Spanish may have been rejected for publication; ii) several studies were not included in this systematic review and meta-analysis because their measurements were not well defined; iii) we were not able to estimate some pooled AUCs because data were not available; iv) the number of studies reporting outlet level measurements is still scarce, thus, future studies are needed in order to determine the usefulness of this parameter in the diagnosis of CTS; v) it is known that there is substantial variability in the normal size of the patient's median nerve, and consequently providing a cut off threshold of median nerve cross sectional area as a diagnostic criterion could be rather hazardous; and vi) using electrodiagnosis as the reference standard is a limitation, since this procedure has a non-negligible rate of false negative and false positive results. However, the consistency of our findings across studies in population-based samples from multiple countries supports the generalizability of our results.

Conclusions

Ultrasonography might represent a useful tool for the diagnosis of CTS since this procedure has demonstrated a high sensitivity and specificity. Both, inlet and outlet level ultrasonography measurements show sufficient accuracy for their use in clinical settings, though the overall accuracy for the diagnosis of CTS was slightly higher for the inlet level than for the outlet one. Also, the addition of outlet measurements to inlet ones doesn't increase the accuracy for the diagnosis of CTS. Only in some cases, in which advanced axonal loss is suspected, or when differential diagnosis is required, is electrodiagnosis

recommended for assessing nerve function and quantifying nerve damage. This information could be useful to be incorporated in standard CTS clinical guidelines or diagnostic protocols including optimal site of ultrasonography measurements and consensual reference values.

REFERENCES

1. Atroshi I, Gummesson C, Johnsson R, Ornstein E, Ranstam J, Rosen I. Prevalence of carpal tunnel syndrome in a general population. Jama 1999;282(2):153-8.

2. Alfonso C, Jann S, Massa R, Torreggiani A. Diagnosis, treatment and follow-up of the carpal tunnel syndrome: a review. Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology 2010;31(3):243-52.

3. de Krom MC, Knipschild PG, Kester AD, Thijs CT, Boekkooi PF, Spaans F. Carpal tunnel syndrome: prevalence in the general population. Journal of clinical epidemiology 1992;45(4):373-6.

4. Atroshi I, Englund M, Turkiewicz A, Tagil M, Petersson IF. Incidence of physician-diagnosed carpal tunnel syndrome in the general population. Archives of internal medicine 2011;171(10):943-4.

5. Nora DB, Becker J, Ehlers JA, Gomes I. Clinical features of 1039 patients with neurophysiological diagnosis of carpal tunnel syndrome. Clinical neurology and neurosurgery 2004;107(1):64-9.

6. Mhoon JT, Juel VC, Hobson-Webb LD. Median nerve ultrasound as a screening tool in carpal tunnel syndrome: correlation of cross-sectional area measures with electrodiagnostic abnormality. Muscle & nerve 2012;46(6):871-8.

7. Koyuncuoglu HR, Kutluhan S, Yesildag A, Oyar O, Guler K, Ozden A. The value of ultrasonographic measurement in carpal tunnel syndrome in patients with negative electrodiagnostic tests. European journal of radiology 2005;56(3):365-9.

8. Jablecki CK, Andary MT, Floeter MK, Miller RG, Quartly CA, Vennix MJ et al. Practice parameter: Electrodiagnostic studies in carpal tunnel syndrome. Report of the American Association of Electrodiagnostic Medicine, American Academy of Neurology, and the American Academy of Physical Medicine and Rehabilitation. Neurology 2002;58(11):1589-92.

9. Karadag YS, Karadag O, Cicekli E, Ozturk S, Kiraz S, Ozbakir S et al. Severity of Carpal tunnel syndrome assessed with high frequency ultrasonography. Rheumatol Int 2010;30(6):761-5.

10. Roll SC, Case-Smith J, Evans KD. Diagnostic accuracy of ultrasonography vs. electromyography in carpal tunnel syndrome: a systematic review of literature. Ultrasound in medicine & biology 2011;37(10):1539-53.

11. Sarraf P, Malek M, Ghajarzadeh M, Miri S, Parhizgar E, Emami-Razavi SZ. The best cutoff point for median nerve cross sectional area at the level of carpal tunnel inlet. Acta medica Iranica 2014;52(8):613-8.

12. Nakamichi K, Tachibana S. Ultrasonographic measurement of median nerve cross-sectional area in idiopathic carpal tunnel syndrome: Diagnostic accuracy. Muscle & nerve 2002;26(6):798-803.

13. Wong SM, Griffith JF, Hui AC, Tang A, Wong KS. Discriminatory sonographic criteria for the diagnosis of carpal tunnel syndrome. Arthritis and rheumatism 2002;46(7):1914-21.

14. Sarria L, Cabada T, Cozcolluela R, Martinez-Berganza T, Garcia S. Carpal tunnel syndrome: usefulness of sonography. European radiology 2000;10(12):1920-5.

15. Tai TW, Wu CY, Su FC, Chern TC, Jou IM. Ultrasonography for diagnosing carpal tunnel syndrome: a meta-analysis of diagnostic test accuracy. Ultrasound in medicine & biology 2012;38(7):1121-8.

16. Fowler JR, Gaughan JP, Ilyas AM. The sensitivity and specificity of ultrasound for the diagnosis of carpal tunnel syndrome: a meta-analysis. Clinical orthopaedics and related research 2011;469(4):1089-94.

17. Descatha A, Huard L, Aubert F, Barbato B, Gorand O, Chastang JF. Meta-analysis on the performance of sonography for the diagnosis of carpal tunnel syndrome. Seminars in arthritis and rheumatism 2012;41(6):914-22.

18. Harbord RM, Whiting P, Sterne JA, Egger M, Deeks JJ, Shang A et al. An empirical comparison of methods for meta-analysis of diagnostic accuracy showed hierarchical models are necessary. Journal of clinical epidemiology 2008;61(11):1095-103.

19. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International journal of surgery 2010;8(5):336-41.

20. MacAskill P GC, Deeks J, Harbord R, Takwoingi Y. Cochrane handbook for systematic reviews of diagnostic test accuracy. Version 09 0 London: The Cochrane Collaboration;. 2010.

21. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Annals of internal medicine 2011;155(8):529-36.

22. Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. Statistics in medicine 2002;21(11):1525-37.

23. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. Journal of clinical epidemiology 2005;58(10):982-90.

24. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. Journal of clinical epidemiology 2005;58(9):882-93.

25. Akcar N, Ozkan S, Mehmetoglu O, Calisir C, Adapinar B. Value of power Doppler and gray-scale US in the diagnosis of carpal tunnel syndrome: contribution of cross-sectional area just before the tunnel inlet as compared with the cross-sectional area at the tunnel. Korean journal of radiology 2010;11(6):632-9.

26. Ashraf AR, Jali R, Moghtaderi AR, Yazdani AH. The diagnostic value of ultrasonography in patients with electrophysiologicaly confirmed carpal tunnel syndrome. Electromyography and clinical neurophysiology 2009;49(1):3-8.

27. Azami A, Maleki N, Anari H, Iranparvar Alamdari M, Kalantarhormozi M, Tavosi Z. The diagnostic value of ultrasound compared with nerve conduction velocity in carpal tunnel syndrome. International journal of rheumatic diseases 2014;17(6):612-20.

28. Bueno-Gracia E, Haddad-Garay M, Tricas-Moreno JM, Fanlo-Mazas P, Malo-Urries M, Estebanez-de-Miguel E et al. [Diagnostic validity of ultrasonography in carpal tunnel syndrome]. Revista de neurologia 2015;61(1):1-6.

29. Csillik A, Bereczki D, Bora L, Aranyi Z. The significance of ultrasonographic carpal tunnel outlet measurements in the diagnosis of carpal tunnel syndrome. Clinical neurophysiology : official journal of the International Federation of Clinical Neurophysiology 2016;127(12):3516-23.

30. Dejaco C, Stradner M, Zauner D, Seel W, Simmet NE, Klammer A et al. Ultrasound for diagnosis of carpal tunnel syndrome: comparison of different methods to determine

346 median nerve volume and value of power Doppler sonography. Annals of the rheumatic
347 diseases 2013;72(12):1934-9.
348 31. Duncan I, Sullivan P, Lomas F. Sonography in the diagnosis of carpal tunnel
349 syndrome. AJR American journal of roentgenology 1999;173(3):681-4.
350 32. Ghajarzadeh M, Dadgostar M, Sarraf P, Emami-Razavi SZ, Miri S, Malek M.
351 Application of ultrasound elastography for determining carpal tunnel syndrome severity.
352 Japanese journal of radiology 2015;33(5):273-8.
353 33. Ghanei ME, Karami M, Zarezadeh A, Sarrami AH. Usefulness of combination of
354 grey-scale and color Doppler ultrasound findings in the diagnosis of ulnar nerve entrapment
355 syndrome. Journal of research in medical sciences : the official journal of Isfahan University
356 of Medical Sciences 2015;20(4):342-5.
357 34. Ghasemi-Esfe AR, Khalilzadeh O, Vaziri-Bozorg SM, Jajroudi M, Shakiba M,
358 Mazloumi M et al. Color and power Doppler US for diagnosing carpal tunnel syndrome and
359 determining its severity: a quantitative image processing method. Radiology
360 2011;261(2):499-506.
361 35. Hunderfund AN, Boon AJ, Mandrekar JN, Sorenson EJ. Sonography in carpal tunnel
362 syndrome. Muscle & nerve 2011;44(4):485-91.
363 36. Kang S, Kwon HK, Kim KH, Yun HS. Ultrasonography of median nerve and
364 electrophysiologic severity in carpal tunnel syndrome. Annals of rehabilitation medicine
365 2012;36(1):72-9.
366 37. Kantarci F, Ustabasioglu FE, Delil S, Olgun DC, Korkmazer B, Dikici AS et al.
367 Median nerve stiffness measurement by shear wave elastography: a potential sonographic
368 method in the diagnosis of carpal tunnel syndrome. European radiology 2014;24(2):434-40.

38. Keles I, Karagulle Kendi AT, Aydin G, Zog SG, Orkun S. Diagnostic precision of ultrasonography in patients with carpal tunnel syndrome. American journal of physical medicine & rehabilitation 2005;84(6):443-50.

39. Klauser AS, Halpern EJ, De Zordo T, Feuchtner GM, Arora R, Gruber J et al. Carpal tunnel syndrome assessment with US: value of additional cross-sectional area measurements of the median nerve in patients versus healthy volunteers. Radiology 2009;250(1):171-7.

40. Lu Y, Meng Z, Pan X, Qin L, Wang G. Value of high-frequency ultrasound in diagnosing carpal tunnel syndrome. International journal of clinical and experimental medicine 2015;8(12):22418-24.

41. Moghtaderi A, Sanei-Sistani S, Sadoughi N, Hamed-Azimi H. Ultrasound evaluation of patients with moderate and severe carpal tunnel syndrome. Prague medical report 2012;113(1):23-32.

42. Ooi CC, Wong SK, Tan AB, Chin AY, Abu Bakar R, Goh SY et al. Diagnostic criteria of carpal tunnel syndrome using high-resolution ultrasonography: correlation with nerve conduction studies. Skeletal radiology 2014;43(10):1387-94.

43. Paliwal PR, Therimadasamy AK, Chan YC, Wilder-Smith EP. Does measuring the median nerve at the carpal tunnel outlet improve ultrasound CTS diagnosis? Journal of the neurological sciences 2014;339(1-2):47-51.

44. Pinilla I, Martin-Hervas C, Sordo G, Santiago S. The usefulness of ultrasonography in the diagnosis of carpal tunnel syndrome. The Journal of hand surgery, European volume 2008;33(4):435-9.

45. Roll SC, Evans KD, Li X, Freimer M, Sommerich CM. Screening for carpal tunnel syndrome using sonography. Journal of ultrasound in medicine : official journal of the American Institute of Ultrasound in Medicine 2011;30(12):1657-67.

393 46. Sernik RA, Abicalaf CA, Pimentel BF, Braga-Baiak A, Braga L, Cerri GG.
394 Ultrasound features of carpal tunnel syndrome: a prospective case-control study. Skeletal
395 radiology 2008;37(1):49-53.
396 47. Wang LY, Leong CP, Huang YC, Hung JW, Cheung SM, Pong YP. Best diagnostic
397 criterion in high-resolution ultrasonography for carpal tunnel syndrome. Chang Gung medical
398 journal 2008;31(5):469-76.
399 48. Yu G, Chen Q, Wang D, Wang X, Li Z, Zhao J et al. Diagnosis of carpal tunnel
400 syndrome assessed using high-frequency ultrasonography: cross-section areas of 8-site
401 median nerve. Clinical rheumatology 2016;35(10):2557-64.
402 49. Ziswiler HR, Reichenbach S, Vogelin E, Bachmann LM, Villiger PM, Juni P.
403 Diagnostic value of sonography in patients with suspected carpal tunnel syndrome: a
404 prospective study. Arthritis and rheumatism 2005;52(1):304-11.
405 50. Yesildag A, Kutluhan S, Sengul N, Koyuncuoglu HR, Oyar O, Guler K et al. The role
406 of ultrasonographic measurements of the median nerve in the diagnosis of carpal tunnel
407 syndrome. Clinical radiology 2004;59(10):910-5.
408 51. Shaheen HA, Yossef AT. Ultrasound has supplementary diagnostic value to clinical
409 and neurophysiological studies in carpal tunnel syndrome. The Egyptian journal of neurology,
410 psychiatry and neurosurgery 2011;48:207-14.
411 52. Shim JH, Doh JW, Lee KS, Shim JJ, Yoon SM, Bae HG. The diagnostic value of
412 ultrasonography in Korean carpal tunnel syndrome patients. Korean journal of neurotrauma
413 2013;9(1):1-5.
414 53. Beekman R, Visser LH. Sonography in the diagnosis of carpal tunnel syndrome: a
415 critical review of the literature. Muscle & nerve 2003;27(1):26-33.

54. Cartwright MS, Hobson-Webb LD, Boon AJ, Alter KE, Hunt CH, Flores VH et al. Evidence-based guideline: neuromuscular ultrasound for the diagnosis of carpal tunnel syndrome. Muscle & nerve 2012;46(2):287-93.

55. Wiesler ER, Chloros GD, Cartwright MS, Smith BP, Rushing J, Walker FO. The use of diagnostic ultrasound in carpal tunnel syndrome. J Hand Surg Am 2006;31(5):726-32.

56. Moran L, Perez M, Esteban A, Bellon J, Arranz B, del Cerro M. Sonographic measurement of cross-sectional area of the median nerve in the diagnosis of carpal tunnel syndrome: correlation with nerve conduction studies. Journal of clinical ultrasound : JCU 2009;37(3):125-31.

57. Ibrahim I, Khan WS, Goddard N, Smitham P. Carpal tunnel syndrome: a review of the recent literature. The open orthopaedics journal 2012;6:69-76.

58. Charoensawat S, Bohning W, Bohning D, Holling H. Meta-analysis and meta-modelling for diagnostic problems. BMC medical research methodology 2014;14:56.

59. McDonagh C, Alexander M, Kane D. The role of ultrasound in the diagnosis and management of carpal tunnel syndrome: a new paradigm. Rheumatology 2015;54(1):9-19.

60. Fowler JR, Maltenfort MG, Ilyas AM. Ultrasound as a first-line test in the diagnosis of carpal tunnel syndrome: a cost-effectiveness analysis. Clinical orthopaedics and related research 2013;471(3):932-7.

61. Goldberg G, Zeckser JM, Mummaneni R, Tucker JD. Electrosonodiagnosis in Carpal Tunnel Syndrome: A Proposed Diagnostic Algorithm Based on an Analytic Literature Review. PM & R : the journal of injury, function, and rehabilitation 2016;8(5):463-74.

Figure Legend

Figure 1. Literature search PRISMA consort diagram.

Figure 2. Forest plot of the diagnostic odds ratio (dOR) of each index test in the reviewed studies.

Figure 3. Hierarchical summary receiver operating characteristic (HSROC) curves summarizing the ability of outlet level and inlet level to identify carpal tunnel syndrome.

A. Inlet level

B. Outlet level

Table 1. Characteristics of studies included in the meta-analysis.

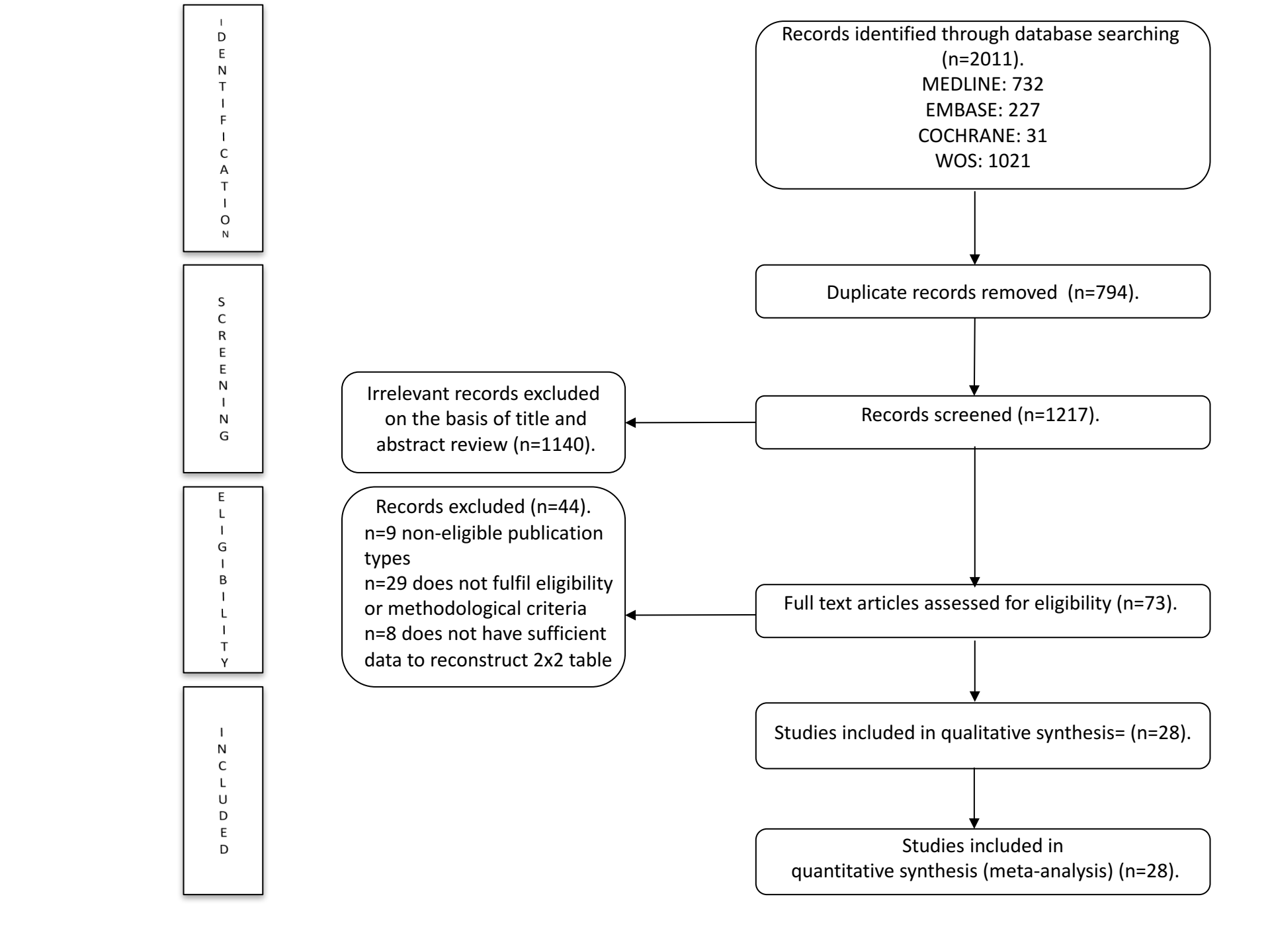
Author	Country	US test level	N (women)		N wrists		Age		Prevalence %	AUC
			Case	Control	Case	Control	Case	Control		
Akcar et al (2010)	Turkey	Inlet level	42 (26)	33 (22)	62	33	45.7±9.7	42.3±10.7	56.0	-
Azami et al (2014)	Iran	Inlet/Outlet level	60 (55)	30 (28)	120	60	56.8±10.6	54.8±7.8	66.6	0.783 (Inlet) 0.739 (Outlet)
Bueno-García et al (2015)	Spain	Inlet level	59 (42)	35 (25)	97	70	59.2±14.2	46.2±13.2	51.6	0.830
Csillik et al (2016)	Hungary	Inlet/Outlet level	87 (59)	23 (15)	118	44	65.8±15.5	60.0±15.5	72.8	0.910 (Inlet) 0.920 (Outlet)
Dejaco et al (2014)	Austria	Inlet level	135 (99)	45 (NA)	111	40	51.9±14.5	NA	73.5	0.850
Duncan et al (1999)	Australia	Inlet level	68 (50)	36 (23)	102	68	54.0±NA	44.0±NA	60.0	-
Ghasemi-Esfe et al (2010)	Iran	Inlet level	85 (70)	49 (39)	85	49	50.36±1.0	46.39±1.6	63.4	-
Hunderfund et al (2011)	USA	Inlet level	55 (22)	49 (26)	55	49	59.0±15.0	56.0±16.0	52.9	0.890
Kang et al (2012)	Korea	Inlet level	55 (50)	19 (18)	110	38	53.2±6.2	53.2±6.2	74.3	0.988
Kantarci et al (2013)	Turkey	Inlet level	37 (30)	18 (14)	60	36	51.6±11.9	51.7±14.0	63.5	0.844
Keleç et al (2005)	Turkey	Inlet level	40 (40)	40 (40)	35	40	45.2±10.4	41.5±6.7	46.7	0.833
Lu et al (2015)	China	Inlet level	45 (26)	40 (NA)	63	43	45.0±NA (20.0-68.0)	42.0±NA (27.0-56.0)	59.4	-
Moghtaderi et al (2012)	Iran	Inlet/Outlet level	43 (34)	36 (32)	43	36	45.0±6.1	39.7±6.9	54.4	0.801 (Inlet) 0.659 (Outlet)
Nakamichi et al (2002)	Japan	Inlet/Outlet level	275 (235)	408 (408)	414	408	55.0±NA	57.0±NA	50.4	-
Ooi et al (2014)	Singapore	Inlet/Outlet level	51 (42)	15 (12)	75	30	55.0±NA	53.0±NA	71.4	0.950 (Inlet) 0.870 (Outlet)
Paliwal et al (2014)	Singapore	Inlet level	77 (55)	35 (21)	130	35	53.7±11.8	NA	78.8	0.933 (Inlet) 0.925 (Outlet)
Pinilla et al (2008)	Spain	Inlet level	27 (26)	15 (11)	40	30	53.0±NA	44.0±NA	57.1	-
Roll et al (2011)	USA	Inlet level	47 (37)	44 (30)	83	83	45.6±10.6	40.0±12.1	50.0	0.899
Sarraf et al (2013)	Iran	Inlet level	38 (NA)	22 (NA)	71	44	47.1±10.9	NA	56.8	0.870
Sarria et al (2000)	Spain	Inlet/Outlet level	40 (34)	24 (14)	64	42	50.9±11.5	50.6±14.6	59.2	-
Sernik et al (2006)	Brazil	Inlet level	31 (31)	37 (37)	40	63	49.1±NA	45.1±NA	38.8	-
Shaheen et al (2011)	Egypt	Inlet level	50 (46)	25 (23)	50	25	38.9±11.8	38.0±11.0	50.0	-
Shim et al (2013)	Korea	Inlet level	48 (43)	18 (10)	60	36	58.5±12.1	54.3±12.9	62.5	0.935
Wang et al (2008)	Taiwan	Inlet level	37 (34)	20 (15)	61	40	44.0±9.4	43.7±12.9	60.4	0.901
Wong et al (2002)	China	Inlet/Outlet level	35 (NA)	35 (NA)	54	70	44.4±NA	44.0±NA	43.5	-
Yesildag et al (2004)	Turkey	Inlet level	86 (76)	45 (39)	48	76	49.8±NA	42.7±NA	66.1	-
Yu et al (2016)	China	Inlet/Outlet level	26 (NA)	23	36	34	57.1±9.0	51.8±10.8	51.4	0.770 (Inlet) 0.874 (Outlet)
Ziswiler et al (2005)	Swtizerland	Outlet level	NA	NA	78	23	51.0±16.0	NA	77.2	0.890

NA: Not available; AUC: Area under curve; US: Ultrasonography

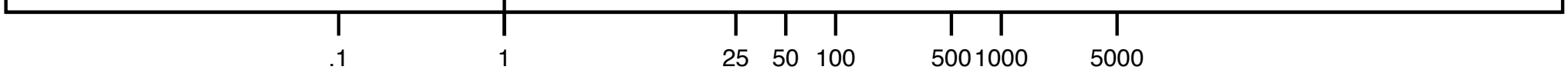
Table 2. Pooled accuracy parameters in the diagnosis of carpal tunnel syndrome, by index test.

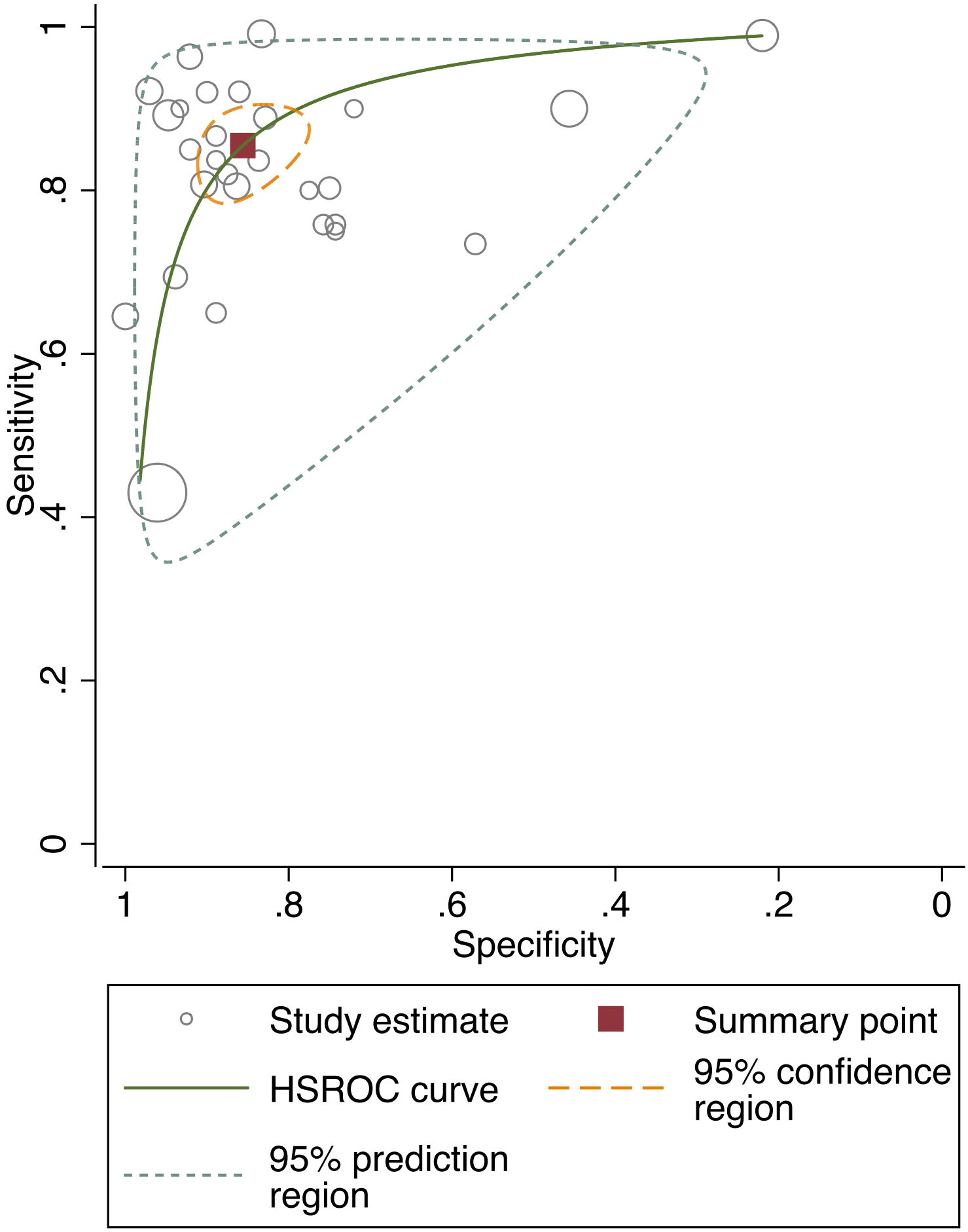
	Sensitivity (%)	**Specificity (%)**	**PLR**	**NLR**	**dOR**
Inlet level	81.00 (74.00–88.00)	84.00 (78.00–90.00)	6.22 (3.99–9.71)	0.16 (0.11–0.26)	31.11 (20.42–47.40)
Outlet level	74.00 (62.00–87.00)	76.00 (63.00–92.00)	4.63 (2.02–10.59)	0.25 (0.11–0.57)	16.94 (7.58–37.86)

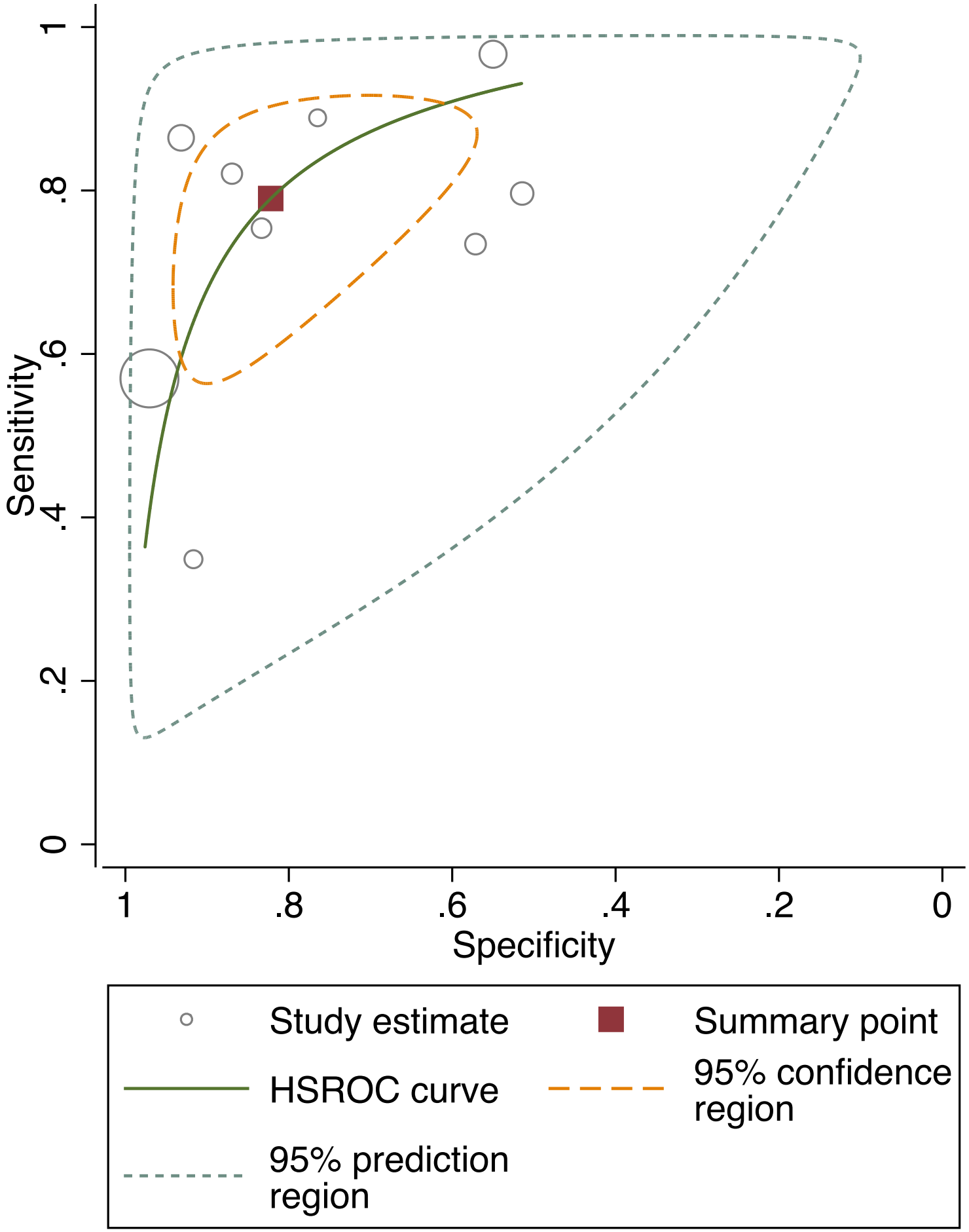
Values in parentheses are 95%confidence intervals. PLR: positive likelihood ratio, NLR: negative likelihood ratio, dOR: diagnostic odds ratio


IDENTIFICATION
SCREENING
ELIGIBILITY
INCLUDED
Records identified through database searching (n=2011).
MEDLINE: 732
EMBASE: 227
COCHRANE: 31
WOS: 1021
Duplicate records removed (n=794).
Records screened (n=1217).
Irrelevant records excluded on the basis of title and abstract review (n=1140).
Full text articles assessed for eligibility (n=73).
Records excluded (n=44).
n=9 non-eligible publication types
n=29 does not fulfil eligibility or methodological criteria
n=8 does not have sufficient data to reconstruct 2x2 table
Studies included in qualitative synthesis= (n=28).
Studies included in quantitative synthesis (meta-analysis) (n=28).

References	dOR (95% CI)	% Weight
INLET LEVEL		
Akcar et al (2010)	9.79 (3.65, 26.24)	4.06
Azami et al (2014)	595.00 (74.19, 4772.18)	2.30
Bueno-García et al (2015)	9.05 (3.48, 23.53)	4.12
CsilliK et al (2016)	26.16 (9.88, 69.29)	4.09
Dejaco et al (2014)	7.56 (3.74, 15.27)	4.56
Duncan et al (1999)	387.75 (79.78, 1884.64)	3.01
Ghasemi-Esfe et al (2010)	34.79 (9.91, 122.14)	3.57
Hunderfund et al (2011)	26.19 (9.25, 74.20)	3.96
Kang et al (2012)	309.17 (65.95, 1449.28)	3.07
Kantarci et al (2013)	14.86 (4.63, 47.73)	3.73
Keleç et al (2005)	13.78 (4.53, 41.89)	3.83
Lu et al (2015)	71.53 (20.36, 251.28)	3.57
Mhoon et al (2012)	26.79 (5.71, 125.68)	3.07
Moghtaderi et al (2012)	41.14 (11.02, 153.64)	3.46
Nakamichi et al (2002)	18.48 (10.81, 31.60)	4.82
Ooi et al (2014)	103.50 (24.14, 443.70)	3.22
Pinilla et al (2008)	126.00 (21.51, 738.08)	2.72
Roll et al (2011)	39.26 (15.80, 97.57)	4.20
Sarraf et al (2013)	12.21 (4.97, 30.00)	4.22
Sarria et al (2000)	3.69 (1.61, 8.41)	4.35
Sernik et al (2006)	65.73 (18.64, 231.75)	3.56
Shahenn et al (2011)	23.14 (6.49, 82.50)	3.54
Shim et al (2011)	52.00 (14.48, 186.74)	3.53
Wang et al (2008)	31.82 (10.16, 99.68)	3.78
Wong et al (2002)	38.67 (13.50, 110.71)	3.94
Yesildag et al (2004)	148.50 (47.84, 460.93)	3.79
Yu et al (2016)	8.67 (2.97, 25.25)	3.91
Subtotal (I-squared = 75.0%, p = 0.000)	31.11 (20.42, 47.40)	100.00
.		
OUTLET LEVEL		
Azami et al (2014)	35.44 (11.58, 108.52)	11.00
CsilliK et al (2016)	87.12 (24.10, 315.01)	10.30
Moghtaderi et al (2012)	5.89 (1.55, 22.46)	10.08
Nakamichi et al (2002)	43.75 (23.86, 80.23)	12.94
Ooi et al (2014)	15.31 (5.03, 46.64)	11.02
Sarria et al (2000)	3.69 (1.61, 8.41)	12.18
Wong et al (2002)	4.14 (1.84, 9.32)	12.23
Yu et al (2016)	26.00 (7.04, 96.08)	10.21
Ziswiler et al (2005)	30.48 (7.95, 116.88)	10.05
Subtotal (I-squared = 82.4%, p = 0.000)	16.94 (7.58, 37.86)	100.00
.		




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


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

Supporting information

S1 Table PRISMA Guidelines Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
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.	2-3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
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.	N/A
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.	5-6
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.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
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).	6

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.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
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.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	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.	7-8
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).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
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
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.	9-10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10

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).	11-13
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).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13-14
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.	N/A

S2 Table QUADAS-2 risk of bias assessment

	Akcar 2010	Azami 2014	Bueno-García 2015	Csillik 2016	Dejaco 2014	Duncan 1999	Ghasemi-Esfe 2010	Hunderfund 2011	Kang 2009
DOMAIN 1: PATIENT SELECTION									
Was a consecutive or random sample of patients enrolled?	**N**	**Y**	**N**	**N**	**Y**	**Y**	**N**	**N**	**N**
Was a case-control design avoided?	**U**	**Y**	**U**	**N**	**Y**	**U**	**Y**	**U**	**U**
Did the study avoid inappropriate exclusions?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**N**	**Y**	**Y**
Risk of Bias	**U**	**L**	**U**	**H**	**L**	**L**	**H**	**U**	**U**
Concerns regarding applicability	**U**	**L**	**U**	**U**	**L**	**L**	**U**	**U**	**U**
DOMAIN 2: INDEX TEST(S)	**Inlet level**	**Inlet level**	**Inlet level**	**Inlet/Outlet levels**	**Inlet level**	**Inlet level**	**Inlet level**	**Inlet level**	
Were the index test results interpreted without knowledge of the results of the reference standard?	**Y/Y**	**Y**	**Y**	**Y/ Y**	**Y**	**Y**	**Y**	**Y**	**Inlet level**
If a threshold was used, was it pre-specified?	**N/N**	**N**	**N**	**N/N**	**N**	**N**	**N**	**N**	**Y**
Risk of Bias	**L/L**	**L**	**L**	**L/ L**	**L**	**L**	**L**	**L**	**N**
Concerns regarding applicability	**U/U**	**U**	**U**	**U/U**	**U**	**U**	**U**	**U**	**L**
									U
DOMAIN 3: REFERENCE STANDARD									
Is the reference standard likely to correctly classify the target condition?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	
Were the reference standard results interpreted without knowledge of the results of the index test?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Risk of Bias	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**Y**
Concerns regarding applicability	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**

									L
DOMAIN 4: FLOW AND TIMING									
Was there an appropriate interval between index test(s) and reference standard?	**Y**	**U**	**U**	**U**	**U**	**U**	**Y**	**U**	**U**
Did all patients receive a reference standard?	**Y**	**N**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Did patients receive the same reference standard?	**Y**	**Y**	**Y**	**U**	**Y**	**U**	**Y**	**Y**	**Y**
Were all patients included in the analysis?	**Y**	**N**	**N**	**Y**	**N**	**U**	**Y**	**U**	**N**
Risk of Bias	**L**	**H**	**L**	**L**	**L**	**U**	**L**	**L**	**L**

U: unclear; Y: yes; N: no; L: low; H: high

	Kantarci 2013	Keleç 2003	Lu 2015	Moghtaderi 2012	Nakamichi 2002	Ooi 2014	Paliwal 2014	Pinilla 2008	Roll 2011	Sarraf 2009
DOMAIN 1: PATIENT SELECTION										
Was a consecutive or random sample of patients enrolled?	**Y**	**Y**	**N**	**Y**	**N**	**Y**	**N**	**N**	**N**	**N**
Was a case-control design avoided?	**Y**	**Y**	**U**	**U**	**Y**	**U**	**N**	**U**	**U**	**U**
Did the study avoid inappropriate exclusions?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Risk of Bias	**L**	**L**	**U**	**L**	**L**	**L**	**H**	**U**	**U**	**U**
Concerns regarding applicability	**L**	**L**	**U**	**L**	**U**	**L**	**U**	**U**	**U**	**U**
DOMAIN 2: INDEX TEST(S)	**Inlet level**	**Inlet level**	**Inlet level**	**Inlet/Outlet levels**	**Inlet/Outlet levels**	**Inlet/Outlet levels**	**Inlet/Outlet levels**	**Inlet level**	**Inlet level**	**Inlet level**
Were the index test results interpreted without knowledge of the results of the reference standard?	**Y**	**Y**	**Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y/Y**	**Y**	**Y**	**Y**
If a threshold was used, was it pre-specified?	**N**	**N**	**N**	**N/N**	**N/N**	**N/N**	**Y/Y**	**N**	**N**	**N**
Risk of Bias	**L**	**L**	**L**	**L/L**	**L/L**	**L/L**	**L/L**	**L**	**L**	**L**
Concerns regarding applicability	**U**	**U**	**U**	**U/U**	**U/U**	**U/U**	**L/L**	**U**	**U**	**U**
DOMAIN 3: REFERENCE STANDARD										
Is the reference standard likely to correctly classify the target condition?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Were the reference standard results interpreted without knowledge of the results of the index test?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Risk of Bias	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Concerns regarding applicability	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**

DOMAIN 4: FLOW AND TIMING										
Was there an appropriate interval between index test(s) and reference standard?	**U**	**U**	**U**	**U**	**U**	**U**	**U**	**U**	**Y**	**Y**
Did all patients receive a reference standard?	**U**	**Y**	**U**	**Y**	**Y**	**N**	**Y**	**Y**	**N**	**U**
Did patients receive the same reference standard?	**U**	**Y**	**U**	**Y**	**Y**	**U**	**Y**	**Y**	**Y**	**Y**
Were all patients included in the analysis?	**Y**	**N**	**Y**	**Y**	**Y**	**N**	**U**	**Y**	**N**	**Y**
Risk of Bias	**U**	**L**	**U**	**L**	**L**	**U**	**L**	**L**	**U**	**L**

U: unclear; Y: yes; N: no; L: low; H: high

	Sarria 2000	Sernik 2006	Shahenn 2011	Shim 2013	Wang 2008	Wong 2002	Yesildag 2004	Yu 2016	Ziswiler 2005
DOMAIN 1: PATIENT SELECTION									
Was a consecutive or random sample of patients enrolled?	**Y**	**N**	**N**	**N**	**N**	**Y**	**Y**	**Y**	**Y**
Was a case-control design avoided?	**U**	**N**	**U**	**Y**	**U**	**N**	**U**	**U**	**Y**
Did the study avoid inappropriate exclusions?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Risk of Bias	**L**	**H**	**U**	**L**	**U**	**L**	**L**	**L**	**L**
Concerns regarding applicability	**L**	**U**	**U**	**U**	**U**	**U**	**L**	**L**	**L**
DOMAIN 2: INDEX TEST(S)	**Inlet/Outlet levels**	**Inlet level**	**Inlet level**	**Inlet level**	**Inlet level**	**Inlet/Outlet levels**	**Inlet level**	**Inlet/Outlet levels**	**Outlet level**
Were the index test results interpreted without knowledge of the results of the reference standard?	**Y/Y**	**Y**	**Y**	**Y**	**Y**	**Y/N**	**Y**	**Y/Y**	**Y**
If a threshold was used, was it pre-specified?	**N/N**	**N**	**Y**	**N**	**N**	**Y/N**	**N**	**N/N**	**N**
Risk of Bias	**L/L**	**L**	**L**	**L**	**L**	**L/L**	**L**	**L/L**	**L**
Concerns regarding applicability	**U/U**	**U**	**L**	**U**	**U**	**U/U**	**U**	**U/U**	**U**
DOMAIN 3: REFERENCE STANDARD									
Is the reference standard likely to correctly classify the target condition?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Were the reference standard results interpreted without knowledge of the results of the index test?	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Risk of Bias	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
Concerns regarding applicability	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**	**L**
DOMAIN 4: FLOW AND TIMING									

Was there an appropriate interval between index test(s) and reference standard?	**Y**	**U**	**U**	**U**	**U**	**Y**	**Y**	**Y**	**U**
Did all patients receive a reference standard?	**Y**	**U**	**U**	**Y**	**U**	**N**	**Y**	**U**	**U**
Did patients receive the same reference standard?	**Y**	**U**	**Y**	**Y**	**Y**	**Y**	**U**	**Y**	**Y**
Were all patients included in the analysis?	**Y**	**Y**	**U**	**Y**	**Y**	**N**	**Y**	**U**	**N**
Risk of Bias	**L**	**U**	**U**	**L**	**L**	**U**	**L**	**L**	**U**

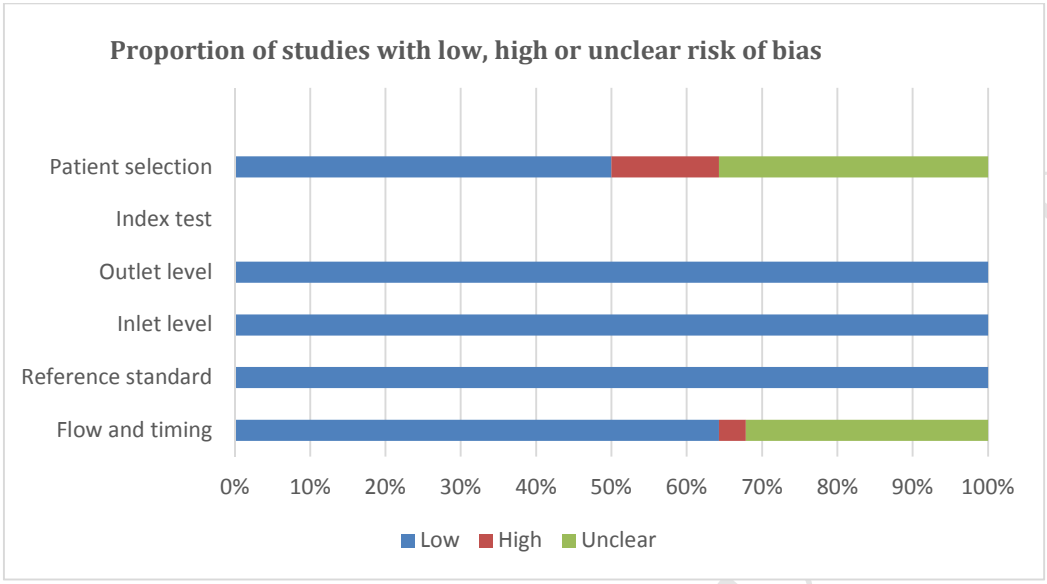
U: unclear; Y: yes; N: no; L: low; H: high.

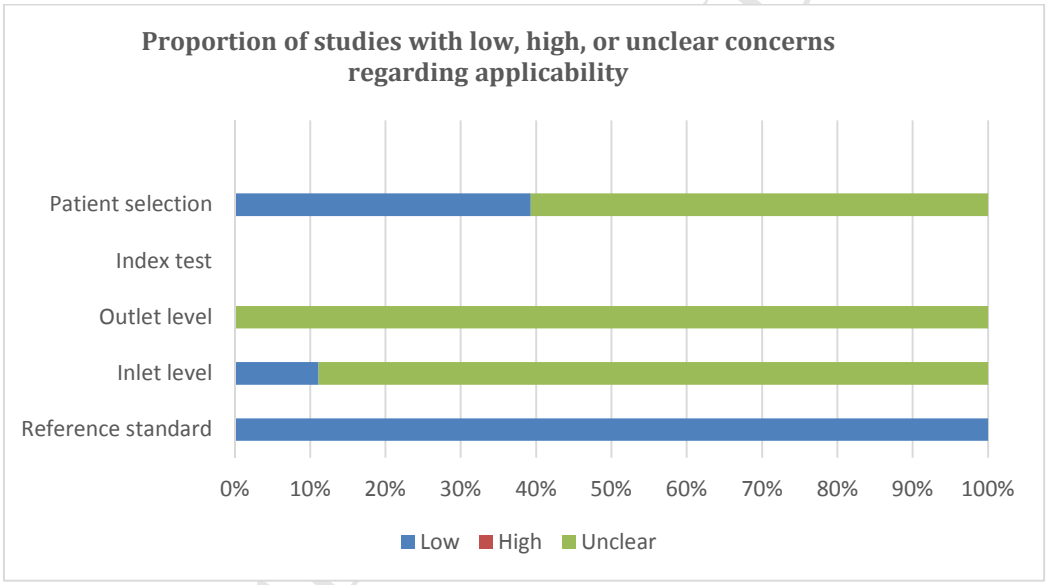
S3 Table Subgroup analysis of the seven studies that included measurements of inlet and outlet levels.

	Sensitivity (%)	Specificity (%)	PLR	NLR	dOR
Inlet level	77.00 (59.70–99.40)	87.90 (79.90–96.60)	5.65 (2.46–12.96)	0.14 (0.06–0.36)	26.99 (11.79–61.78)
Outlet level	72.50 (59.80–87.90)	75.00 (61.30–91.80)	4.41 (1.82–10.73)	0.26 (0.11–0.63)	15.88 (6.61–38.18)

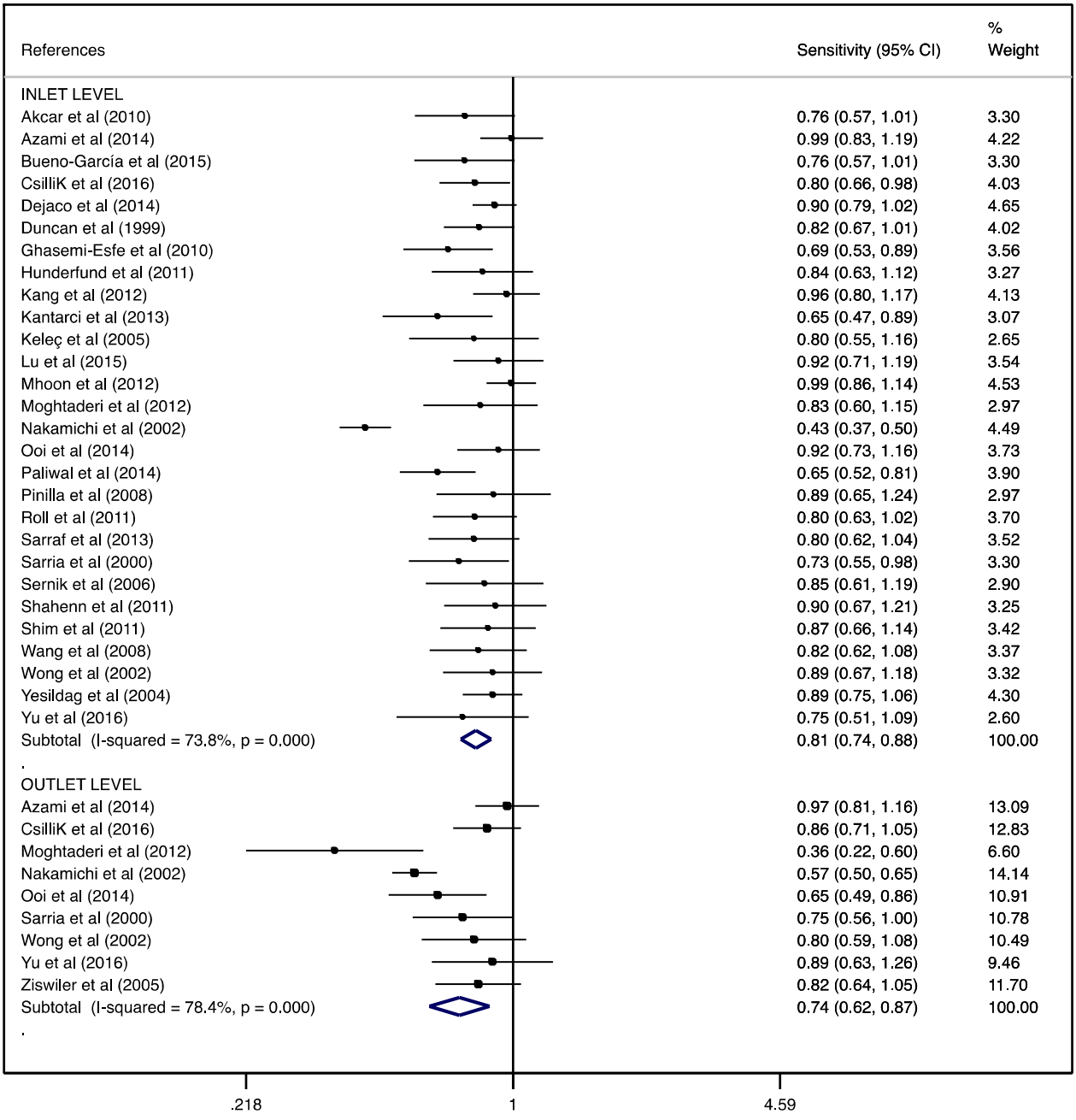
Values in parentheses are 95% confidence intervals. FPG: fasting plasma glucose, PLR: positive likelihood ratio, NLR: negative likelihood ratio, dOR: diagnostic odds ratio.

S1 Figure Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria, for the reviewed studies.



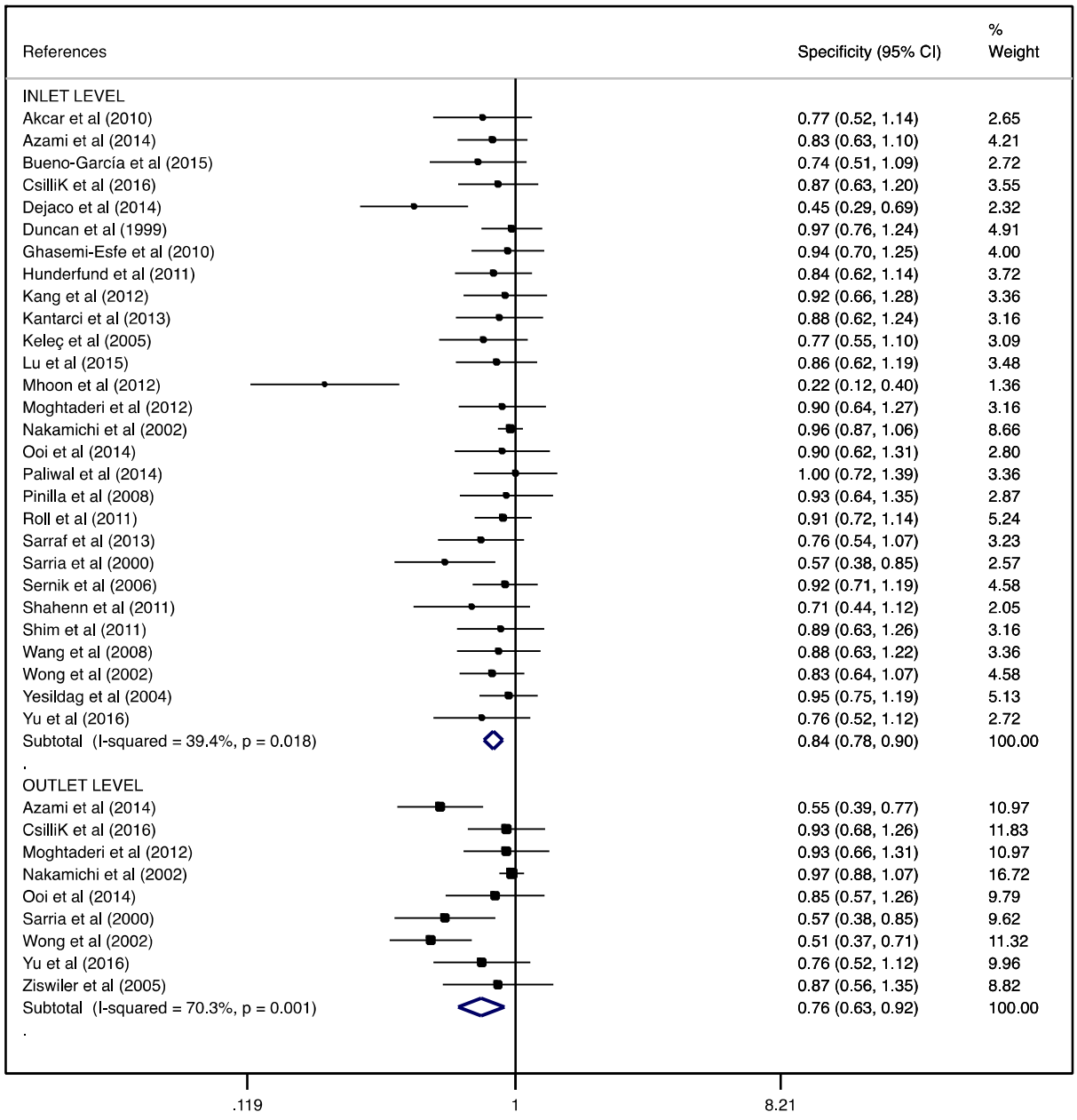


S2 Figure Forest plot of the sensitivity of each index test for diagnosing carpal tunnel syndrome in the studies included.



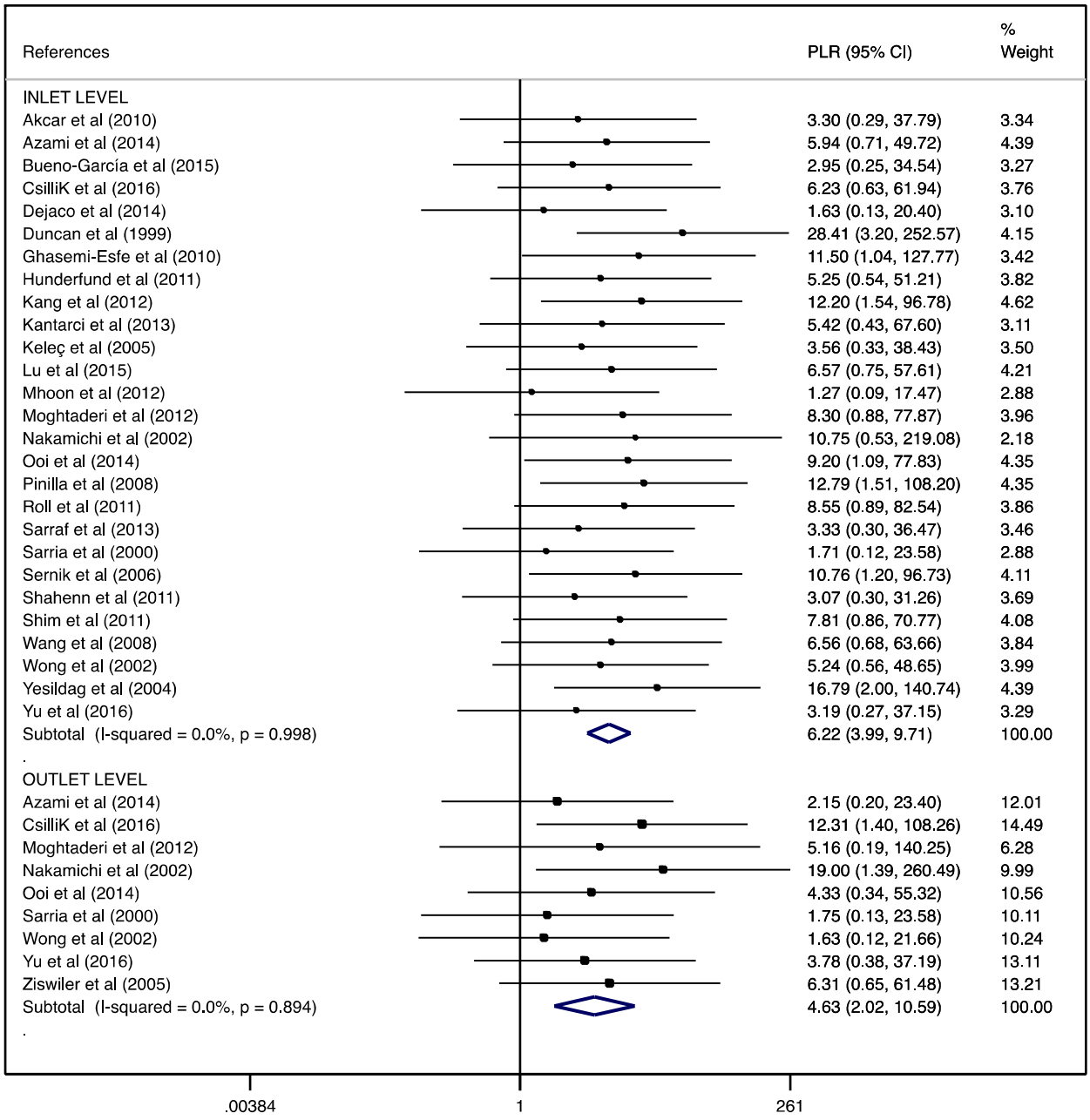
CI: confidence interval

S3 Figure Forest plot of the specificity of each index test for diagnosing carpel tunnel syndrome in the studies included.



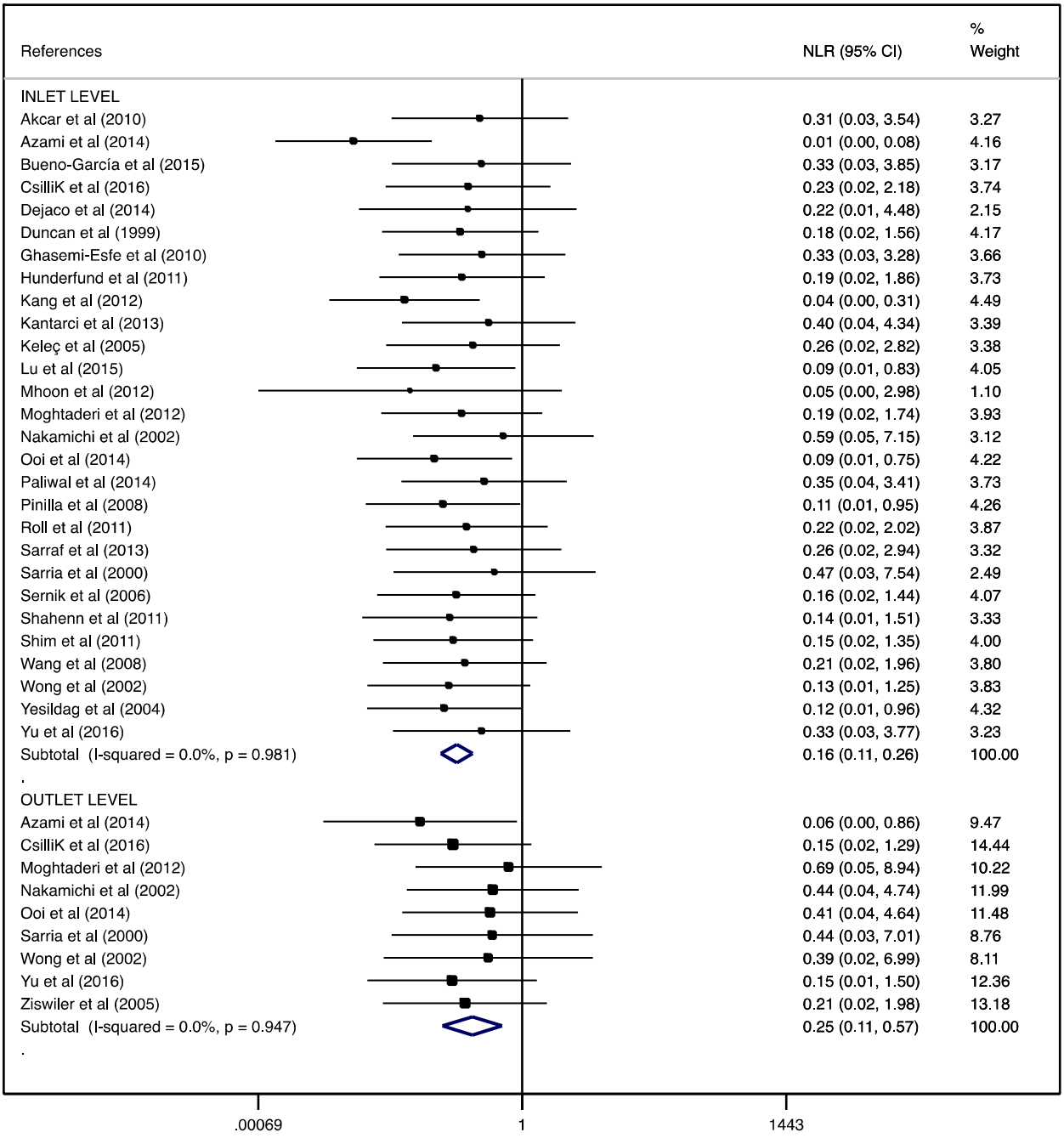
CI: confidence interval

S4 Figure Forest plot of the positive likelihood ratio (PLR) of each index test for diagnosing carpel tunnel syndrome in the studies included.



CI: confidence interval

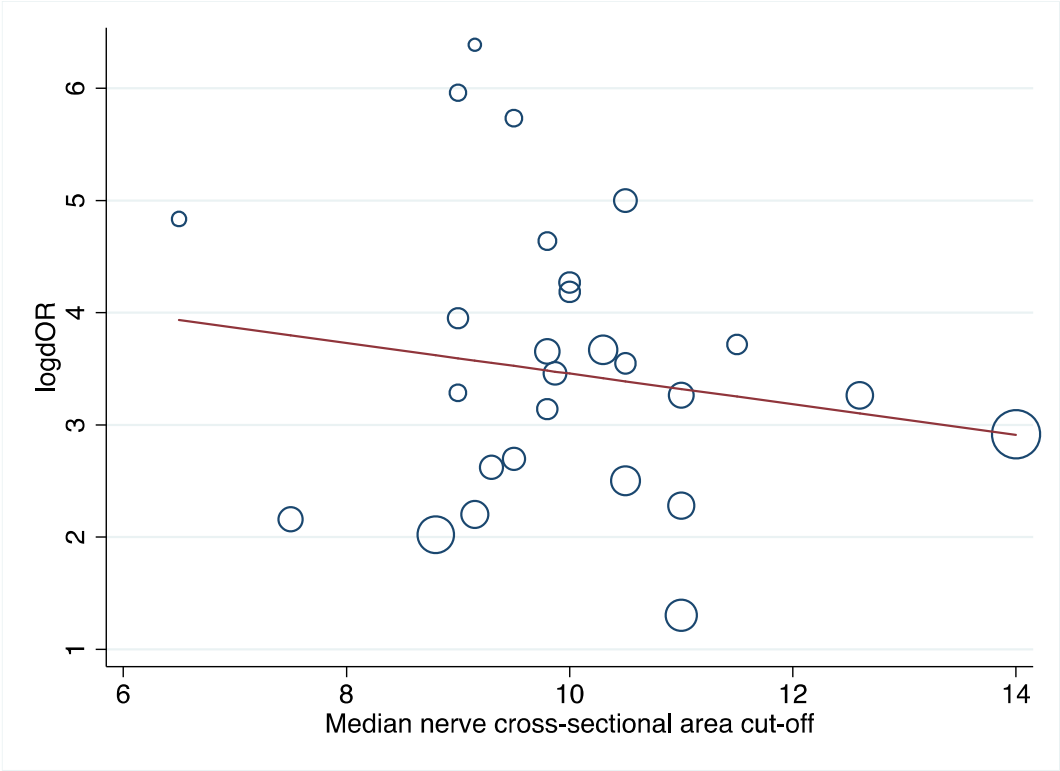
S5 Figure Forest plot of the negative likelihood ratio (NLR) of each index test for diagnosing carpel tunnel syndrome in the studies included.



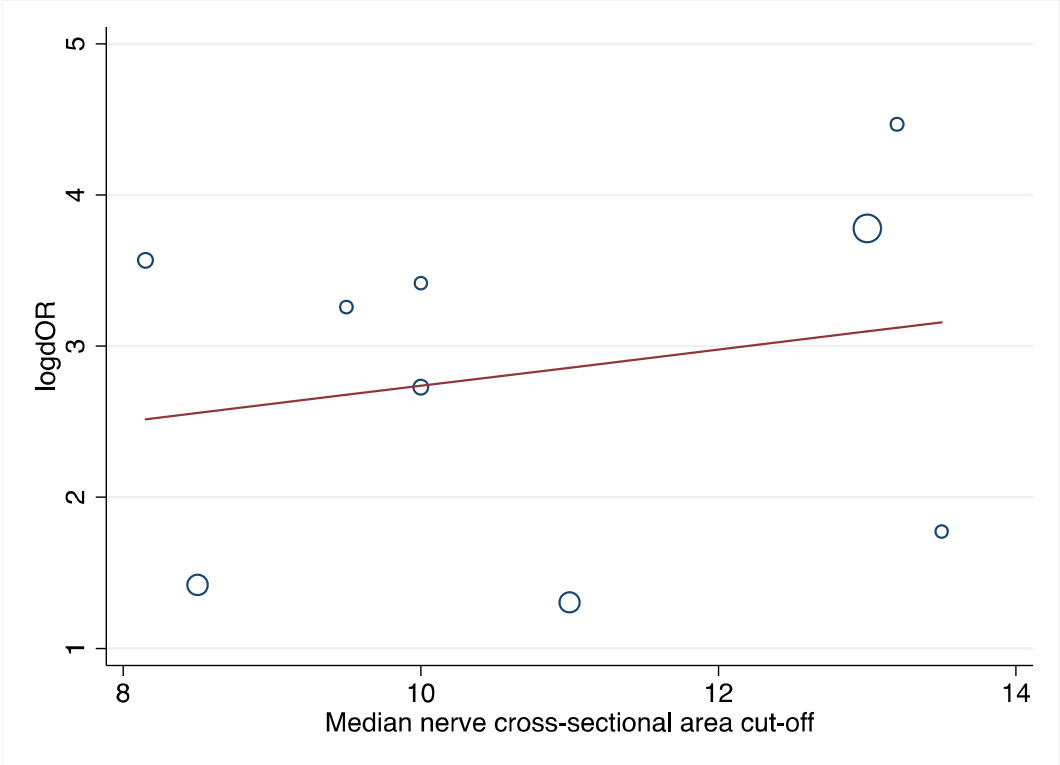
CI: confidence interval

S6 Figure Random-effects meta regresion model.

A. Inlet level

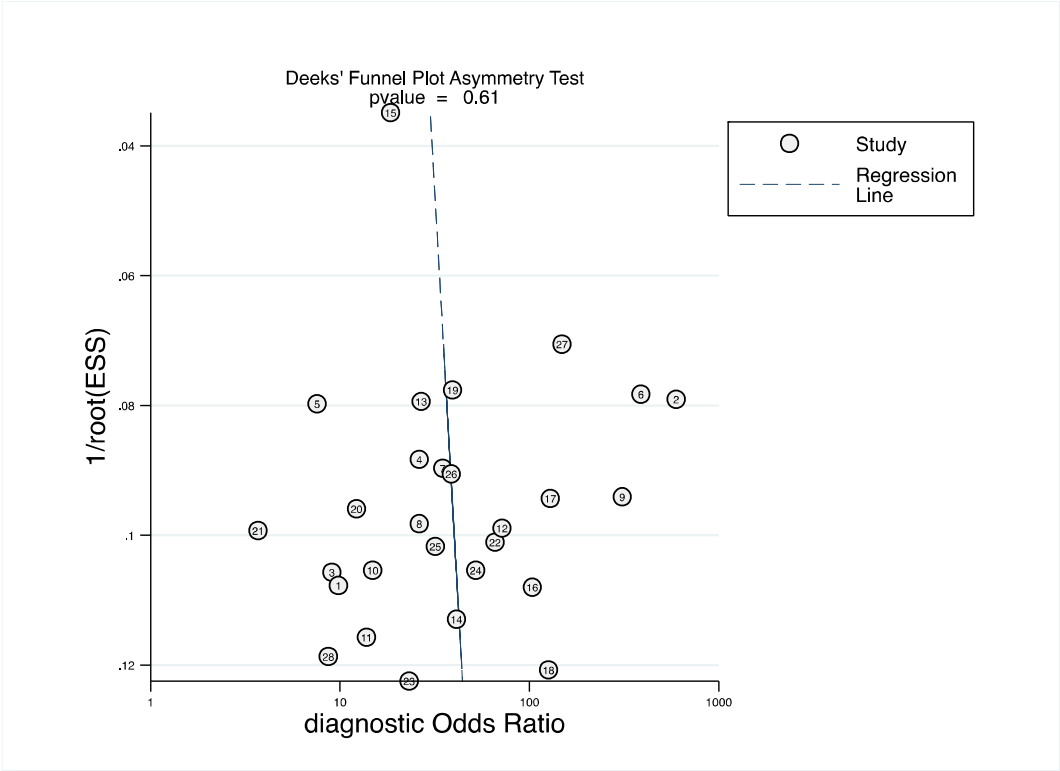


B. Outlet level



S7 Figure Funnel plot for the assessment of potential publication bias. ESS: Effective sample size.

A. Inlet level



B. Outlet level