ELECTRONIC SUPPLEMENTARY MATERIAL

Optic nerve sheath diameter measured sonographically as non-invasive estimator of intracranial pressure: a systematic review and meta-analysis

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ESM Table 1A PRISMA-DTA checklist

Section and Topic	Item No.	Description	Reported on Page #(*) or Section
Title			
Title	1	Identify the report as a systematic review (meta-analysis) of DTA studies.	1
Abstract			
Abstract	2	Abstract checklist for PRISMA-DTA (ESM Table 1B)	Abstract.
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	Introduction.
Clinical role of index test	D1	State the scientific and clinical background, including the intended use and clinical role of the index test, and if applicable, the rationale for minimally acceptable test accuracy (or minimum difference in accuracy for a comparative design).	Introduction.
Objectives	4	Provide an explicit statement of question being addressed in terms of participants, index test, and target conditions.	Introduction.
Methods			
Protocol and registration	5	Indicate where the review protocol can be accessed (e.g., web address) and provide trial registration number if available.	Methods and Footnote 1.
Eligibility criteria	6	Specify study characteristics (participants, setting, index test, reference standards, target conditions, and study design) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility and providing rationale.	Methods ("Data sources and search strategy" and "Study screening and selection").**
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 the date last searched.	Methods ("Data sources and search strategy"), ESM Table 2.
Search	8	Present full search strategies for all electronic databases and other sources searched, including any limits used so that they can be repeated.	Methods ("Data sources and search strategy"), ESM Table 2.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, whether included in systematic review, and, if applicable, included in the meta-analysis).	Methods ("Study screening and selection").**
Data collection process	10	Describe the methods of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from the investigators.	Methods ("Study screening and selection").
Definitions for data extraction	11	Provide definitions used in data extraction and classifications of target conditions, index tests, reference standards, and other characteristics (e.g., study design, clinical setting).	Methods (Study screening and selection")**, ESM Table 3.
Risk of bias and applicability	12	Describe methods used for assessing risk of bias in individual studies and concerns regarding the applicability to the review question.	Methods ("Appraisal of study quality").**
Diagnostic accuracy measures	13	State the principal diagnostic accuracy measures reported (e.g., sensitivity, specificity) and state the unit of assessment (e.g., per patient vs per lesion).	Methods ("Statistical Analysis"), ESM Table 5.

(*) The page number is referred to the ".doc" file of the final version. ** Partially overlapped with information provided in the Results and related ESM.

Section and Topic	Item No.	Description	Reported on Page # or Section
Methods			
Synthesis of results	14	Describe the methods of handling the data, combining the results of the studies and describing the variability between studies. This could include, but is not limited to (1) handling of multiple definitions of the target condition, (2) handling of multiple thresholds of test positivity, (3) handling multiple index test readers, (4) handling of indeterminate test results, (5) grouping and comparing tests, and (6) handling of different reference standards.	Methods ("Statistical Analysis").* Further elements are reported in ESM Table 2-4, 6-7.
Meta-analysis	D2	Report the statistical methods used for meta-analyses if performed.	Methods ("Statistical Analysis").
Additional analyses	16	Describe the methods of the additional analyses (eg, sensitivity or subgroup analyses, meta-regression) if done, indicating which were prespecified.	Methods ("Statistical Analysis"), ESM Sec. 1.
Results			
Study Selection	17	Provide the numbers of studies screened, assessed for eligibility, included in the review, and included in the meta-analysis if applicable, with reasons for exclusions at each stage, ideally with a flow diagram.	Results ("Study selection"), Fig. 1, ESM Table 4.
Study characteristics	18	For each included study, provide citations and present key characteristics including (1) participant characteristics (presentation, prior testing), (2) clinical setting, (3) study design, (4) target condition definition, (5) index test, (6) reference standard, (7) sample size, and (8) funding sources.**	Results ("Study characteristics"), Table 1, Table 2.
Risk of bias and applicability	19	Present evaluation of risk of bias and concerns regarding applicability for each study.	Results ("Quality of evidence and risk of bias", "Publication bias and heterogeneity of the included studies"), Fig. 2, ESM Table 7.
Results of individual studies	20	For each analysis in each study (e.g., unique combination of index test, reference standard, and positivity threshold), report 2 × 2 data (TP, FP, FN, TN) with estimates of diagnostic accuracy and confidence intervals, ideally with a forest plot or a receiver operating characteristic curve.	ESM Table 5, Fig. 3, ESM Fig. 2.
Synthesis of results	21	Describe test accuracy, including variability; if meta-analysis was done, include results and confidence intervals.	Results ("Publication bias and heterogeneity of the included studies", "Diagnostic meta-analysis for the included studies"), Fig. 4.
Additional analyses	23	Give results of additional analyses if done (e.g., sensitivity or subgroup analyses, meta-regression, analysis of index test, failure rates, proportion of inconclusive results, and adverse events).	Results ("Diagnostic meta-analysis for the included studies", "Publication bias and heterogeneity in a subset of included studies", "Diagnostic meta-analysis for a subset of included studies"), ESM Fig. 1-3, ESM Sec. 1, ESM Fig. 4-5.

* Partially overlapped with information provided in the Results. ** No funding sources were reported in the included studies.

Section and Topic	Item No.	Description	Reported on Page # or Section
Discussion			
Summary	24	Summarize the main findings including the strength of the evidence.	Discussion
Limitations	25	Discuss limitations from included studies (e.g., risk of bias and concerns regarding applicability) and from the review process (e.g., incomplete retrieval of identified research).	Discussion and "Strengths and limitations" subsection.
Conclusions	26	Provide a general interpretation of the results in the context of other evidence. Discuss implications for future research and clinical practice (e.g., the intended use and clinical role of the index test).	Discussion and "Conclusions" subsection.
Other			
Funding	27	For the systematic review, describe the sources of funding and other support and the role of the funders.	Not applicable (no public or private funding for this study).

ESM Table 1B Abstract checklist for PRISMA-DTA

Section and Topic	Item No.	Description	Reported on the Abstract Section
Title and Purpose			
Title	1	Identify the report as a systematic review (meta-analysis) of DTA studies.	Purpose
Objectives	2	Indicate the research question, including components such as participants, index test, and target conditions.	Purpose / Methods
Methods			
Eligibility criteria	3	Include study characteristics used as criteria for eligibility	Methods
Information sources	4	List the key databases searched and the search dates	Methods
Risk of bias and applicability	5	Indicate the methods of assessing risk of bias and applicability.	Methods
Synthesis of results	A1	Indicate the methods for the data synthesis.	Methods
Results			
Included studies	6	Indicate the number and type of included studies and the participants, and relevant characteristics of the studies (including the reference standard).	Results / Methods
Synthesis of results	7	Include the results for the analysis of diagnostic accuracy, preferably indicating the number of studies and participants. Describe test accuracy including variability; if meta-analysis was done, include summary results and confidence intervals.	Results
Discussion			
Strengths and limitations	9	Provide a brief summary of the strengths and limitations of the evidence	Conclusions
Interpretation	10	Provide a general interpretation of the results and the important implications.	Conclusions
Other			
Funding	11	Indicate the primary source of funding for the review.	Not applicable
Registration	12	Provide the registration number and the registry name.	Conclusions

ESM Table 2 Full search strategy

Database	Query	Time-point	Records
MEDLINE/PubMed®	(("optical" [All Fields] AND "nerve" [All Fields] AND "sheath"[All Fields] AND "diameter" [All Fields]) OR "ONSD"[All Fields]) AND ("1980/01/01"[PDAT] : "2018/05/31"[PDAT] {or "2017/12/31"[PDAT]}) AND English[lang])	01/01/1980-31/12/2017 01/01/1980-31/05/2018	228 250
	("intracranial pressure"[All Fields] OR "intracranial hypertension"[All Fields]) AND ("1980/01/01"[PDAT] : "2018/05/31"[PDAT] {or "2017/12/31"[PDAT]}) AND English[lang])	01/01/1980-31/12/2017 01/01/1980-31/05/2018	19,474 19,878
	("intracranial pressure"[All Fields] OR "intracranial hypertension"[All Fields]) AND ("brain injuries"[All Fields] OR "swelling"[All Fields] OR "papilledema"[All Fields]) AND ("1980/01/01"[PDAT] : "2018/05/31"[PDAT] {or "2017/12/31"[PDAT]}) AND English[lang])	01/01/1980-31/12/2017 01/01/1980-31/05/2018	4,753 4,801
	("optical" [All Fields] AND "nerve" [All Fields] AND "sheath"[All Fields]) AND "diameter" [All Fields]) OR "ONSD"[All Fields]) AND ("optic nerve"[All Fields] OR "nervus opticus"[All Fields]) AND "ultrasonography"[All Fields] AND ("intracranial pressure"[All Fields] OR "intracranial hypertension"[All Fields]) AND ("brain injuries"[All Fields] OR "swelling"[All Fields] OR "papilledema"[All Fields]) AND ("1980/01/01"[PDAT] : "2018/05/31"[PDAT] {or "2017/12/31"[PDAT]}) AND English[lang])	01/01/1980-31/12/2017 01/01/1980-31/05/2018	15 16
	("optical" [All Fields] AND "nerve" [All Fields] AND "sheath"[All Fields] AND "diameter" [All Fields]) OR "ONSD"[All Fields]) AND ("1980/01/01"[PDAT] : "2018/05/31"[PDAT] {or "2017/12/31"[PDAT]})	01/01/1980-31/12/2017 01/01/1980-31/05/2018	237 259
	("intracranial pressure"[All Fields] OR "intracranial hypertension"[All Fields]) AND ("1980/01/01"[PDAT] : "2018/05/31"[PDAT] {or "2017/12/31"[PDAT]})	01/01/1980-31/12/2017 01/01/1980-31/05/2018	23,230 23,651
	("intracranial pressure"[All Fields] OR "intracranial hypertension"[All Fields]) AND ("brain injuries"[All Fields] OR "swelling"[All Fields] OR "papilledema"[All Fields]) AND ("1980/01/01"[PDAT] : "2018/05/31"[PDAT] {or "2017/12/31"[PDAT]})	01/01/1980-31/12/2017 01/01/1980-31/05/2018	5,514 5,562
	(("optical" [All Fields] AND "nerve" [All Fields] AND "sheath"[All Fields]) AND "diameter" [All Fields]) OR "ONSD"[All Fields]) AND ("optic nerve"[All Fields] OR "nervus opticus"[All Fields]) AND "ultrasonography"[All Fields] AND ("intracranial pressure"[All Fields] OR "intracranial hypertension"[All Fields]) AND ("brain injuries"[All Fields] OR "swelling"[All Fields] OR "papilledema"[All Fields]) AND ("1980/01/01"[PDAT] : "2018/05/31"[PDAT] {or "2017/12/31"[PDAT]})	01/01/1980-31/12/2017 01/01/1980-31/05/2018	16 17

Database	Query	Time-point	Records
Scopus®	ALL (("optical nerve sheath diameter" OR "ONSD") AND ("optic nerve" OR "nervus opticus") AND ("ultrasonography")) AND (LIMIT-TO (LANGUAGE, "English")) AND PUBYEAR > 1979 {AND PUBYEAR < 2018}	01/01/1980-31/12/2017 01/01/1980-31/05/2018	193 212
	ALL (("intracranial pressure" OR "intracranial hypertension")) AND (LIMIT-TO (LANGUAGE, "English")) AND PUBYEAR > 1979 {AND PUBYEAR < 2018}	01/01/1980-31/12/2017 01/01/1980-31/05/2018	57,438 58,967
	ALL (("intracranial pressure" OR "intracranial hypertension") AND ("brain injuries" OR "swelling" OR "papilledema"))) AND (LIMIT-TO (LANGUAGE, "English")) AND PUBYEAR > 1979 {AND PUBYEAR < 2018}	01/01/1980-31/12/2017 01/01/1980-31/05/2018	23,336 24,112
	ALL (("optical nerve sheath diameter" OR "ONSD") AND ("optic nerve" OR "nervus opticus") AND ("ultrasonography") AND ("intracranial pressure" OR "intracranial hypertension") AND AND (LIMIT-TO (LANGUAGE, "English")) AND PUBYEAR > 1979 {AND PUBYEAR < 2018}	01/01/1980-31/12/2017 01/01/1980-31/05/2018	160 176
	ALL (("optical nerve sheath diameter" OR "ONSD") AND ("optic nerve" OR "nervus opticus") AND ("ultrasonography")) AND PUBYEAR > 1979 {AND PUBYEAR < 2018}	01/01/1980-31/12/2017 01/01/1980-31/05/2018	200 220
	ALL (("intracranial pressure" OR "intracranial hypertension")) AND PUBYEAR > 1979 {AND PUBYEAR < 2018}	01/01/1980-31/12/2017 01/01/1980-31/05/2018	65,353 66,940
	ALL (("intracranial pressure" OR "intracranial hypertension") AND ("brain injuries" OR "swelling" OR "papilledema")) AND PUBYEAR > 1979 {AND PUBYEAR < 2018}	01/01/1980-31/12/2017 01/01/1980-31/05/2018	25,851 26,647
	ALL (("optical nerve sheath diameter" OR "ONSD") AND ("optic nerve" OR "nervus opticus") AND ("ultrasonography") AND ("intracranial pressure" OR "intracranial hypertension") AND ("brain injuries" OR "swelling" OR "papilledema")) AND PUBYEAR > 1979 {AND PUBYEAR < 2018}	01/01/1980-31/12/2017 01/01/1980-31/05/2018	164 181
Science Citation Index® Expanded from Web of Science®	(TS=(optical nerve sheath diameter OR ONSD) AND TS=(optic nerve OR nervus opticus) AND TS=(ultrasonography)) AND LANGUAGE: (English)	01/01/1985*-31/05/2017 01/01/1985-31/05/2018	107 118
	(TS=("intracranial pressure" OR "intracranial hypertension")) AND LANGUAGE: (English)	01/01/1985-31/05/2017 01/01/1985-31/05/2018	17,784 18,196
	(TS=("intracranial pressure" OR "intracranial hypertension") AND TS=("brain injuries" OR "swelling" OR "papilledema")) AND LANGUAGE: (English)	01/01/1985-31/05/2017 01/01/1985-31/05/2018	1,823 1,873
	(TS=("optical nerve sheath diameter" OR "ONSD") AND TS=("optic nerve" OR "nervus opticus") AND TS=("ultrasonography") AND TS=("intracranial pressure" OR "intracranial hypertension") AND TS=("brain injuries" OR "swelling" OR "papilledema")) AND LANGUAGE: (English)	01/01/1985-31/05/2017 01/01/1985-31/05/2018	3 5
	TS=(optical nerve sheath diameter OR ONSD) AND TS=(optic nerve OR nervus opticus) AND TS=(ultrasonography)	01/01/1985-31/05/2017 01/01/1985-31/05/2018	109 120
	TS=("intracranial pressure" OR "intracranial hypertension")	01/01/1985-31/05/2017 01/01/1985-31/05/2018	19,276 19,698
	TS=("intracranial pressure" OR "intracranial hypertension") AND TS=("brain injuries" OR "swelling" OR "papilledema")	01/01/1985-31/05/2017 01/01/1985-31/05/2018	1,973 2,024
	TS=("optical nerve sheath diameter" OR "ONSD") AND TS=("optic nerve" OR "nervus opticus") AND TS=("ultrasonography") AND TS=("intracranial pressure" OR "intracranial hypertension") AND TS=("brain injuries" OR "swelling" OR "papilledema")	01/01/1985-31/05/2017 01/01/1985-31/05/2018	3 5

* The queries within the Science Citation Index® Expanded from Web of Science database must start from 01/01/1985.

Database	Query	Time-point	Records
ScienceDirect® (*)	(“optical nerve sheath diameter” OR "ONSD") AND (“optic nerve” OR “nervus opticus”) AND (“ultrasonography”)	01/01/1980-31/12/2017 01/01/1980-31/05/2018	82 92
	(“intracranial pressure” OR “intracranial hypertension”)	01/01/1980-31/12/2017 01/01/1980-31/05/2018	41,498 43,297
	("intracranial pressure" OR "intracranial hypertension") AND (“brain injuries” OR “swelling” OR “papilledema”)	01/01/1980-31/12/2017 01/01/1980-31/05/2018	17,821 18,518
	(“optical nerve sheath diameter” OR "ONSD") AND (“optic nerve” OR “nervus opticus”) AND (“ultrasonography”) AND (“intracranial pressure” OR “intracranial hypertension”) AND (“brain injuries” OR “swelling” OR “papilledema”)	01/01/1980-31/12/2017 01/01/1980-31/05/2018	49 53
Cochrane Library® via Wiley Online Library (*)	(“optical nerve sheath diameter” OR "ONSD") AND (“optic nerve” OR “nervus opticus”) AND (“ultrasonography”)	01/01/1980-31/12/2017 01/01/1980-31/05/2018	8 9
	(“intracranial pressure” OR “intracranial hypertension”)	01/01/1980-31/12/2017 01/01/1980-31/05/2018	194 197
	("intracranial pressure" OR "intracranial hypertension") AND (“brain injuries” OR “swelling” OR “papilledema”)	01/01/1980-31/12/2017 01/01/1980-31/05/2018	86 89
	(“optical nerve sheath diameter” OR "ONSD") AND (“optic nerve” OR “nervus opticus”) AND (“ultrasonography”) AND (“intracranial pressure” OR “intracranial hypertension”) AND (“brain injuries” OR “swelling” OR “papilledema”)	01/01/1980-31/12/2017 01/01/1980-31/05/2018	2 2

(*) The English-only search was refined screening manually each record.

A systematic literature search was performed in the following databases: MEDLINE/PubMed® (https://www.ncbi.nlm.nih.gov/pubmed), Scopus® (https://www.scopus.com/search/form.uri?display=basic), Science Citation Index® Expanded from Web of Science® (http://apps.webofknowledge.com/), ScienceDirect® (https://www.sciencedirect.com/), and Cochrane Library® (http://cochranelibrary-wiley.com/cochranelibrary/search). The search was carried out using the following terms: “optical nerve sheath diameter”, “optic nerve”, “nervus opticus”, “ultrasonography”, “brain injuries”, “swelling”, “papilledema”, “intracranial pressure”, and “intracranial hypertension”. The search was primarily set by including only original studies published in English in peer-review sources, followed by a search without language limitations. Additionally, reference lists of the pre-screened studies were manually checked, using an iterative approach.

ESM Table 3 Extracted data in each study assessed for eligibility

Extracted Data	Details
Study Reference	Names and surnames of authors, year of publication.
Country	Country/countries in which the study was carried out.
Study design	Type of recruitment.
Gender	Percentage of male patients.
Age	Patient age reported in the study (as mean ± sd or median).
Patient number	Number of eligible patients, number of patients with and without intracranial hypertension, number of excluded patients.
Pathology	Diseases reported in the included studies (healthy volunteers and animal models were excluded).
ICP	Intracranial pressure, with intracranial hypertension assumed for ICP >20 mmHg or >25 cm H_2O.
Cut-off	Threshold values of optic nerve sheath diameter with reference to gold standard.
Correlation coefficient (*r*)	Correlation coefficient between mean ONSD and opening ICP measurement.
Sensitivity	Sensitivity calculated from the ROC curve.
Specificity	Specificity calculated from the ROC curve.

ICP: intracranial pressure; ONSD: optic nerve sheath diameter.

ESM Table 4 Full text articles excluded, not fitting eligibility criteria

Excluded Studies	Main reason for exclusion
Aduayi et al. 2015	No comparison with gold standard as reference.
Amini et al. 2013	Cut-off for ICP <25 cmH_2O.
Anas 2014	Study conducted in healthy volunteers.
Bekerman et al. 2016	No comparison with gold standard as reference.
Bolesch et al. 2015	No comparison with gold standard as reference.
Caffery et al. 2014	Cut-off for ICP <25 cmH_2O.
Chelly et al. 2016	No comparison with gold standard as reference.
Chen et al. 2015	Study conducted in healthy volunteers.
Chin et al. 2015	No comparison with gold standard as reference.
Cimilli et al. 2015	No comparison with gold standard as reference.
Cooley et al. 2015	Study conducted in animal models.
Dalal 2016	Review article.
Dip et al. 2016	No comparison with gold standard as reference.
Di Pasquale et al. 2016	No comparison with gold standard as reference.
Dubourg et al. 2011	Review article.
Ebraheim et al. 2018	No comparison with gold standard as reference; some patients with only probable intracranial hypertension (not defined).
Geeraerts et al. 2008	Not specified patients in each ICP subgroup.
Goeres et al. 2016	Study conducted in healthy volunteers.
Hansen et al. 2016	No comparison with gold standard as reference.
Heckmann et al. 1998	Review article.
Hylkema et al. 2016	Review article.
Kaffery et al. 2014	Cut-off for ICP <25 cmH_2O.
Karami et al. 2015	Study conducted in healthy volunteers.
Kim et al. 2015	No comparison with gold standard as reference.
Kim et al. 2014	No comparison with gold standard as reference.
Komut et al. 2016	No comparison with gold standard as reference.
Lee et al. 2016	No comparison with gold standard as reference.
Liu et al. 2017	Cut-off for ICP <25 cmH_2O.
Lochner et al. 2016	No comparison with gold standard as reference.
Lochner et al. 2015	Review article.
Lochner et al. 2014	No comparison with gold standard as reference.
Luberda et al. 2013	Review article.
Masquère et al. 2013	No comparison with gold standard as reference.
Mehrpour et al. 2015	No information regarding correlation coefficient.
Messerer et al. 2013	Review article.
Min et al. 2015	No comparison with gold standard as reference.
Moretti and Pizzi 2011	Review article.
Moretti et al. 2009	Potential patients overlapping with another study.
Robba et al. 2016	No comparison with gold standard as reference.
Robba et al. 2015a	No comparison with gold standard as reference.
Robba et al. 2015b	Review article.
Sekhon et al. 2014	No comparison with gold standard as reference.
Shah et al. 2015	No comparison with gold standard as reference.

Excluded Studies	Main reason for exclusion
Shofty et al. 2012	No comparison with gold standard as reference.
Singh et al. 2012	Review article.
Soldatos et al. 2008	No comparison with gold standard as reference; study design.
Soliman et al. 2018	Different and not validated sonographic ONSD quality criteria.
Steinborn et al. 2016	No comparison with gold standard as reference.
Strumwasser et al. 2011	Not specified patients in each ICP subgroup.
Tarzamni et al. 2016	No comparison with gold standard as reference.
Terkawi et al. 2013	Review article.
Topcuoglu et al. 2015	No comparison with gold standard as reference.
Ueda et al. 2015	No comparison with gold standard as reference.
Vaiman et al. 2016	No comparison with gold standard as reference.
Vaiman et al. 2015	No comparison with gold standard as reference.
Verdonck et al. 2014	No comparison with gold standard as reference.
Wang et al. 2015	Cut-off for ICP <25 cmH_2O.
Wang et al. 2018	Study design (ONSD before the lumbar puncture in 60 patients on admission, with cut-off for ICP <25 cmH_2O; subsequent grouping of the 25 enrolled patients for ICP ≤300/>300 mmH_2O).

ESM Table 5 Diagnostic accuracy parameters estimated for each included study

Jeon et al. 2017
TP: 30. FP: 4. FN: 2. TN: 26. Sensitivity: 0.938 (95% CI 0.799–0.983). Specificity: 0.867 (95% CI 0.703–0.947). OFC: 0.903 (95% CI 0.786–0.955). MCR: 0.097 (95% CI 0.045–0.214). PPV: 0.882 (95% CI 0.775–0.930). NPV: 0.929 (95% CI 0.799–0.986). J: 0.804 (95% CI 0.569–0.908). DOR: 97.5 (95% CI 16.496–576.293). PLR: 7.031 (95% CI 2.811–17.585). NLR: 0.072 (95% CI 0.019–0.278).

Robba et al. 2017
TP: 16. FP: 8. FN: 2. TN: 38. Sensitivity: 0.889 (95% CI 0.672–0.969). Specificity: 0.826 (95% CI 0.693–0.909). OFC: 0.844 (95% CI 0.728–0.895). MCR: 0.156 (95% CI 0.105–0.272). PPV: 0.667 (95% CI 0.512–0.735). NPV: 0.950 (95% CI 0.857–0.991). J: 0.715 (95% CI 0.428–0.841). DOR: 38 (95% CI 7.255–199-041). PLR: 5.111 (95% CI 2.666–9.797). NLR: 0.135: (95% CI 0.036–0.5).

del Saz-Saucedo et al. 2016
TP: 18. FP: 1. FN: 1. TN: 10. Sensitivity: 0.947 (95% CI 0.754–0.991). Specificity: 0.909 (95% CI 0.623–0.984). OFC: 0.933 (95% CI 0.747–0.994). MCR: 0.067 (95% CI 0.006–0.253). PPV: 0.947 (95% CI 0.8–0.995). NPV: 0.909 (95% CI 0.655–0.992). J: 0.856 (95% CI 0.456–0.987). DOR: 180 (95% CI 10.129–3198.825). PLR: 10.421 (95% CI 1.603–67.734). NLR: 0.058 (95% CI 0.009–0.394).

Rajajee et al. 2011
TP: 37. FP: 1. FN: 2. TN: 25. Sensitivity: 0.949 (95% CI 0.831–0.986). Specificity: 0.962 (95% CI 0.811–0.993). OFC: 0.954 (95% CI 0.853–0.983). MCR: 0.046 (95% CI 0.017–0.147). PPV: 0.974 (95% CI 0.888–0.999). NPV: 0.926 (95% CI 0.805–0.961). J: 0.910 (95% CI 0.7–0.971). DOR: 462.5 (95% CI 39.771–5378.41). PLR: 24.667 (95% CI 3.604–168.804). NLR: 0.053 (95% CI 0.014–0.206).

Moretti and Pizzi 2009
TP: 18. FP: 9. FN: 1. TN: 25. Sensitivity: 0.947: (95% CI 0.754–0.991). Specificity: 0.735 (95% CI 0.569–0.854). OFC: 0.811 (95% CI 0.678–0.847). MCR: 0.189 (95% CI 0.153–0.322). PPV: 0.667 (95% CI 0.536–0.702). NPV: 0.962 (95% CI 0.825–0.998). J: 0.683 (95% CI 0.392–0.760). DOR: 50 (95% CI 5.807–430.528). PLR: 3.579 (95% CI 2.024–6.330). NLR: 0.072 (95% CI 0.011–0.487).

Kimberly et al. 2008
TP: 7. FP: 1. FN: 1. TN: 6. Sensitivity: 0.875 (95% CI 0.529–0.978). Specificity: 0.857 (95% CI 0.487–0.974). OFC: 0.867 (95% CI 0.549–0.988). MCR: 0.133 (95% CI 0.012–0.451). PPV: 0.875 (95% CI 0.577–0.989). NPV: 0.857 (95% CI 0.517–0.987). J: 0.732 (95% CI 0.094–0.976). DOR: 42 (95% CI 2.136–825.715). PLR: 6.125 (95% CI 0.979–38.312). NLR: 0.146 (95% CI 0.023–0.35).

Geeraerts et al. 2007
TP: 15. FP: 3. FN: 1. TN: 12. Sensitivity: 0.938 (95% CI 0.717–0.989). Specificity: 0.8 (95% CI 0.548–0.930). OFC: 0.871 (95% CI 0.677–0.932). MCR: 0.129 (95% CI 0.068–0.323). PPV: 0.938 (95% CI 0.761–0.994). NPV: 0.923 (95% CI 0.706–0.993). J: 0.738 (95% CI 0.349–0.86). DOR: 60 (95% CI 5.514–652.902). PLR: 4.688 (95% CI 1.69–12.999). NLR: 0.078 (95% CI 0.012–0.53).

TP: True Positives (Sensitivity * Prevalence). FP: False Positives [(1－Specificity) * (1－Prevalence)]. FN: False Negatives [(1－Sensitivity) * Prevalence]. TN: True Negatives [(Specificity * (1－Prevalence)]. CI: Confidence interval. OFC: Overall Fraction Correct, also referred as Accuracy [(TP + TN) / (TP + FP + FN + TN)]. MCR: Mis-Classification Rate (1－OFC). PPV: Positive Predictive Value [TP / (TP + FP]. NPV: Negative Predictive Value [TN / (FN + TN)]. J: Youden's J (Sensitivity ＋ Specificity－1). DOR: Diagnostic Odds Ratio [Sensitivity/(1－Sensitivity)] / [(1－Specificity) / Specificity]. PLR: Positive Likelihood Ratio [Sensitivity / (1－Specificity)]. NLR: Negative Likelihood Ratio [(1－Sensitivity) / Specificity].
All calculations were performed by using the R statistical environment (version 3.4.2. R Foundation for Statistical Computing), with "`mada`" package (version 0.5.8. Doebler P. *"mada: Meta-Analysis of Diagnostic Accuracy*") and "`madad`" function. For more details, see: https://cran.r-project.org/web/packages/mada/mada.pdf.

ESM Table 6 Overall quality assessment of the diagnostic accuracy studies enrolled in the meta-analysis, following the GRADE system

Quality assessment							Summary of findings				
							No. of patients		Effect		
No. of studies	Design	Limitations	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Intracranial hypertension[1]	Absence of intracranial hypertension[2]	Relative (95% CI)	Absolute (95% CI)[3]	Quality
7 studies (320 adult patients)	6 prospective observational studies, 1 diagnostic phase I-II study	Some limitations exist[4]	Serious[5]	Serious[6]	Serious[7]	The QUADAS-2 outcome suggested a high risk of bias for 3 studies[8]	151	169	-	From 34.058 to 177.034	⊕○○○ VERY LOW

[1] Patients with intracranial hypertension [True Positives (patients with intracranial hypertension) and False Negatives (patients incorrectly classified has not having intracranial hypertension)]. [2] Patients with absence of intracranial hypertension [True Negatives (patients without intracranial hypertension) and False Positives (patients incorrectly classified has having intracranial hypertension). [3] 95% Confidence interval (CI) of the conventional pooled diagnostc odds ratio (DOR) calculated with the "`madad`" function of the R "`mada`" package (version 0.5.8. Doebler P. *"mada: Meta-Analysis of Diagnostic Accuracy*"). [4] Enrollment of patient based on investigator availability (2 studies). [5] Prevalence of males (3 studies), prevalence of females (2 studies), adult patients (7 studies), absence of traumatic brain injury (TBI) (1 study); absence of invasive ICP monitoring in patients with severe TBI (1 study), different cut-off values for intracranial hypertension definition (>20 mmHg in 5 studies, >25 cmH_2O in 2 studies). [6] Wide variation in the DOR estimates, wide 95% CIs. [7] Small (4 studies) or very small (3 studies) samples size; failure to adequately control confounding [not simultaneous measurement of intracranial pressure (ICP) between invasive methods and optic nerve sheath diameter (ONSD)] (3 studies); measurements obtained in patients with relatively well-controlled ICP (1 study); differences in scans; majority of scans for ONSD measurements were performed by a single experienced operator, while some were performed by a second investigator with a limited experience (1 study). [8] For more details, see ESM Table 7.

Each domain was evaluated according to Ryan R, Hill S (2016) How to GRADE the quality of the evidence. Cochrane Consumers and Communication Group. Version 3.0 December 2016. Available on: http://cccrg.cochrane.org/author-resources (last access: June 15, 2018). The table structure and quality of evidence were showed according to Schünemann H, Brożek J, Guyatt G, Oxman A (2013) GRADE handbook for grading quality of evidence and strength of recommendations. The GRADE Working Group. Available on: https://gdt.gradepro.org/app/handbook/handbook.html (last access: May 19, 2018), and Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, Brozek J, Norris S, Meerpohl J, Djulbegovic B, Alonso-Coello P, Post PN, Busse JW, Glasziou P, Christensen R, Schünemann HJ (2013) GRADE guidelines: 12. Preparing Summary of Findings tables - binary outcomes. J Clin Epidemiol 66:158-172 (doi: 10.1016/j.jclinepi.2012.01.012).

ESM Table 7 Application of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 for each included study

Study	Risk of Bias				Applicability Concerns		
	Patient Selection	Index Test	Reference Standard	Flow and Timing	Patient Selection	Index Text	Reference Standard
Jeon et al. 2017	○	?	○	●	○	?	○
Robba et al. 2017	○	○	○	○	○	○	○
del Saz-Saucedo et al. 2016	○	○	○	●	○	○	○
Rajajee et al. 2011	○	○	○	○	○	○	○
Moretti and Pizzi 2009	○	○	○	○	○	○	○
Kimberly et al. 2008	?	○	○	○	?	○	○
Geeraerts et al. 2007	●	○	○	●	?	○	○

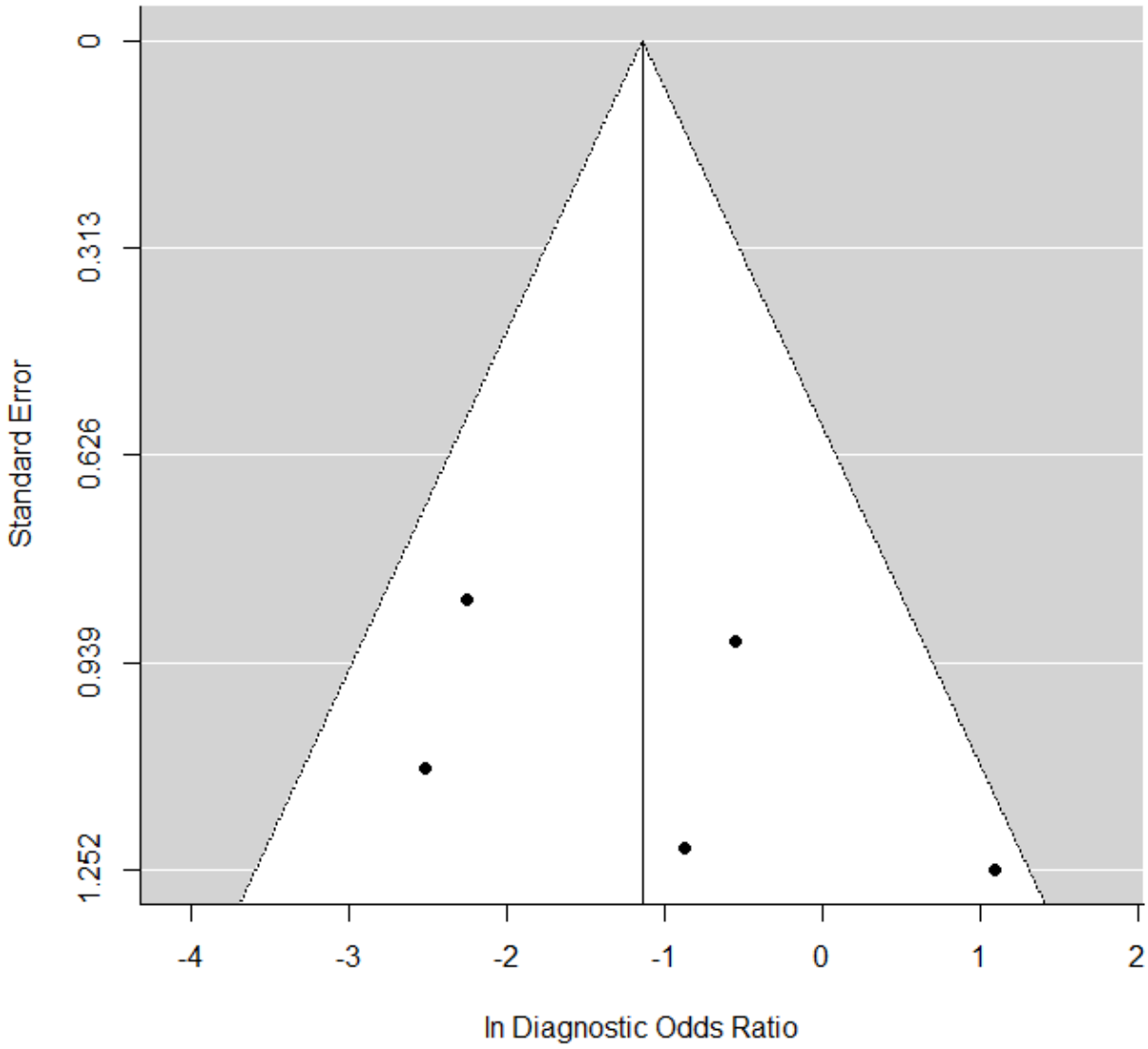
○ = low risk; ● = high risk; ? = unclear risk.

Domain 1: Patient Selection
Risk of Bias (RB): Could the selection of patients have introduced bias? [Signaling question (SQ)1: *Was a consecutive or random sample of patients enrolled?* SQ2: *Was a case-control design avoided?* SQ3: *Did the study avoid inappropriate exclusions?*].

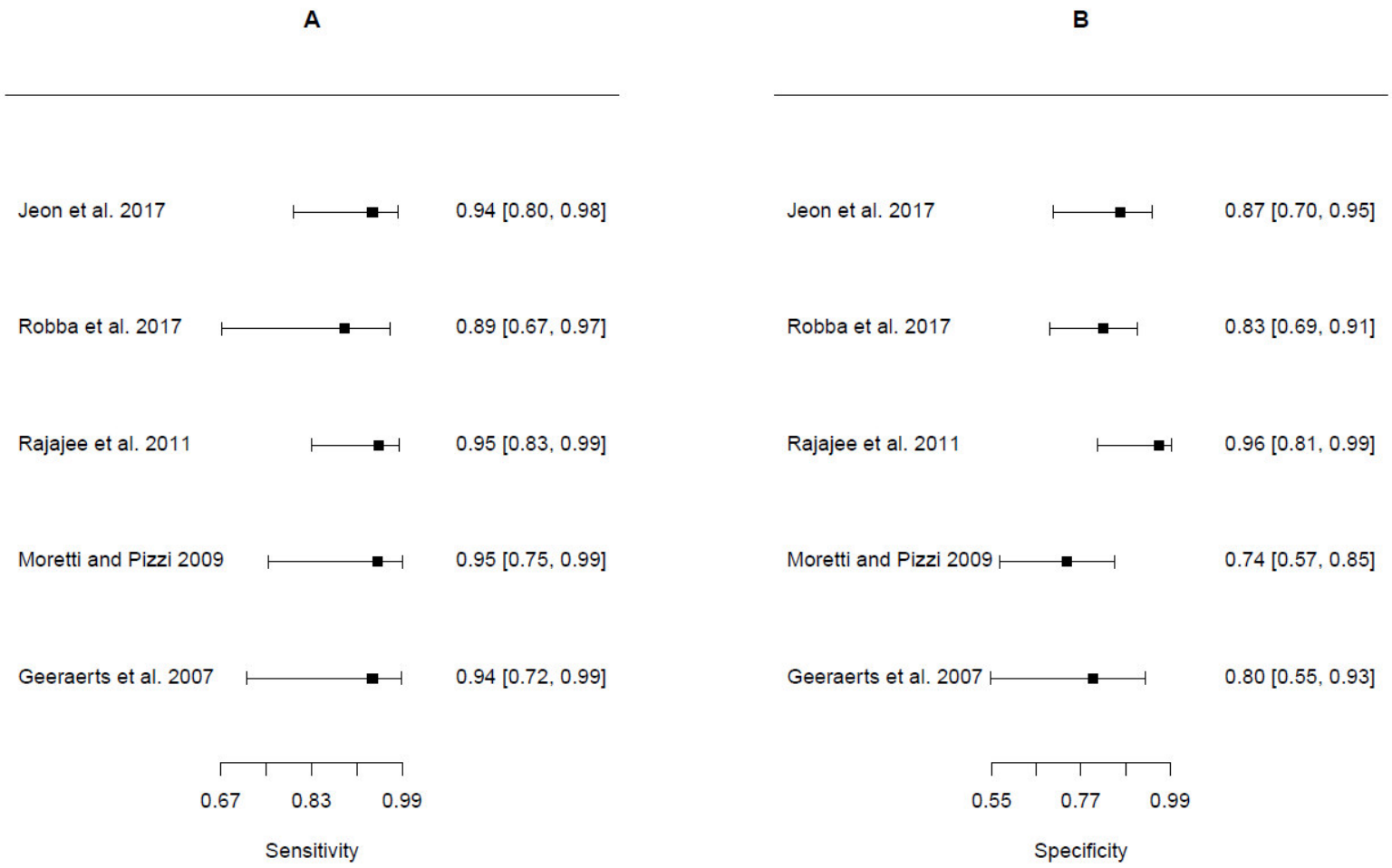
Domain 2: Index Test
RB: Could the conduct or interpretation of the index test have introduced bias? (SQ1: *Were the index test results interpreted without knowledge of the results of the reference standard?* SQ2: *If a threshold was used, was it prespecified?*).

Domain 3: Reference Standard
RB: Could the reference standard, its conduct, or its interpretation have introduced bias? (SQ1: *Is the reference standard likely to correctly classify the target condition?* SQ2: *Were the reference standard results interpreted without knowledge of the results of the index test?*).

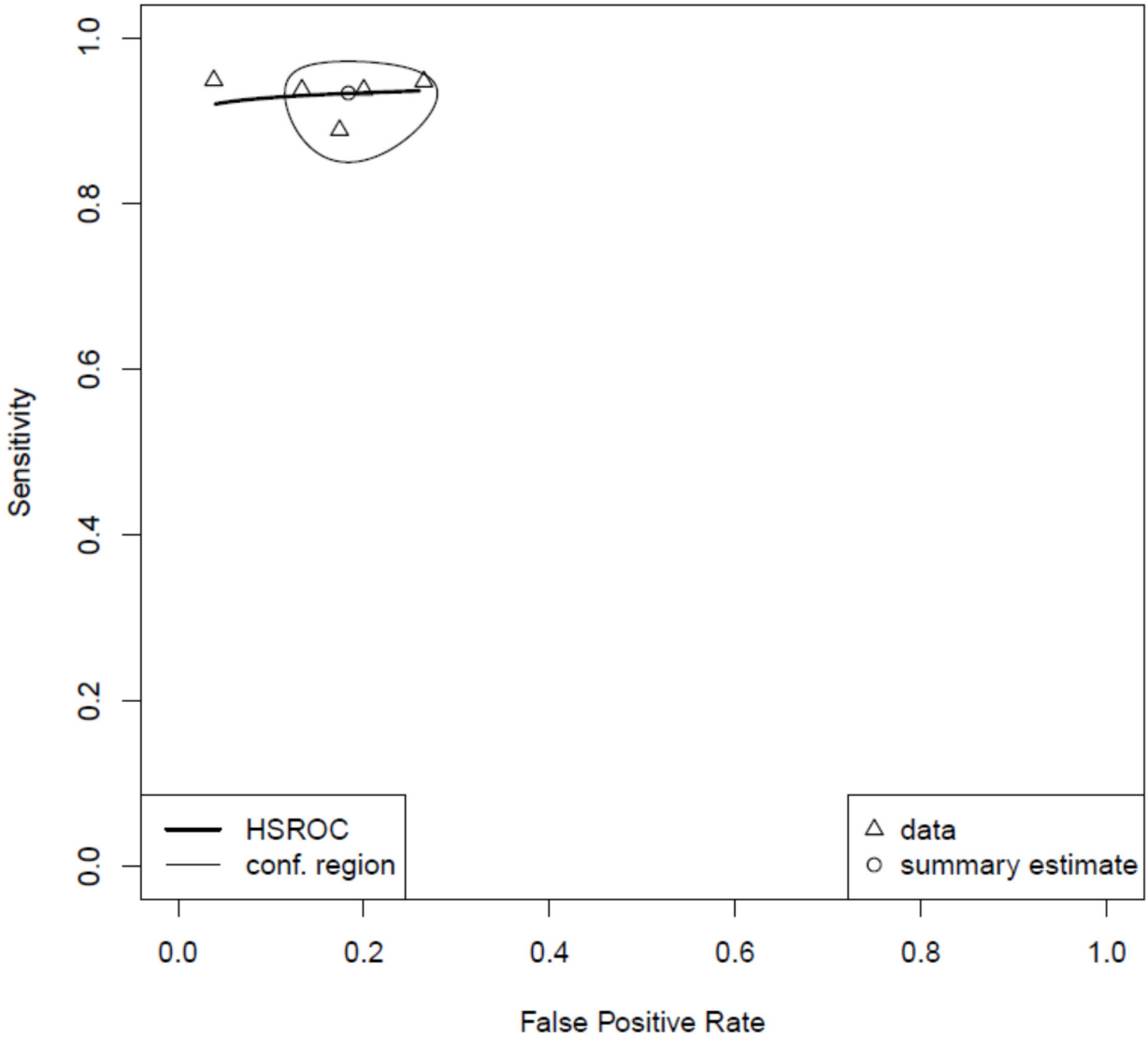
Domain 4: Flow and Timing
RB: Could the patient flow have introduced bias? (SQ1: *Was there an appropriate interval between the index test and reference standard?* SQ2: *Did all patients receive the same reference standard?* SQ3: *Were all patients included in the analysis?*).



ESM Fig. 1 Evaluation of publication bias in a subset of included study (intracranial hypertension assumed for ICP >20 mmHg): Funnel plot for the trim and fill method.



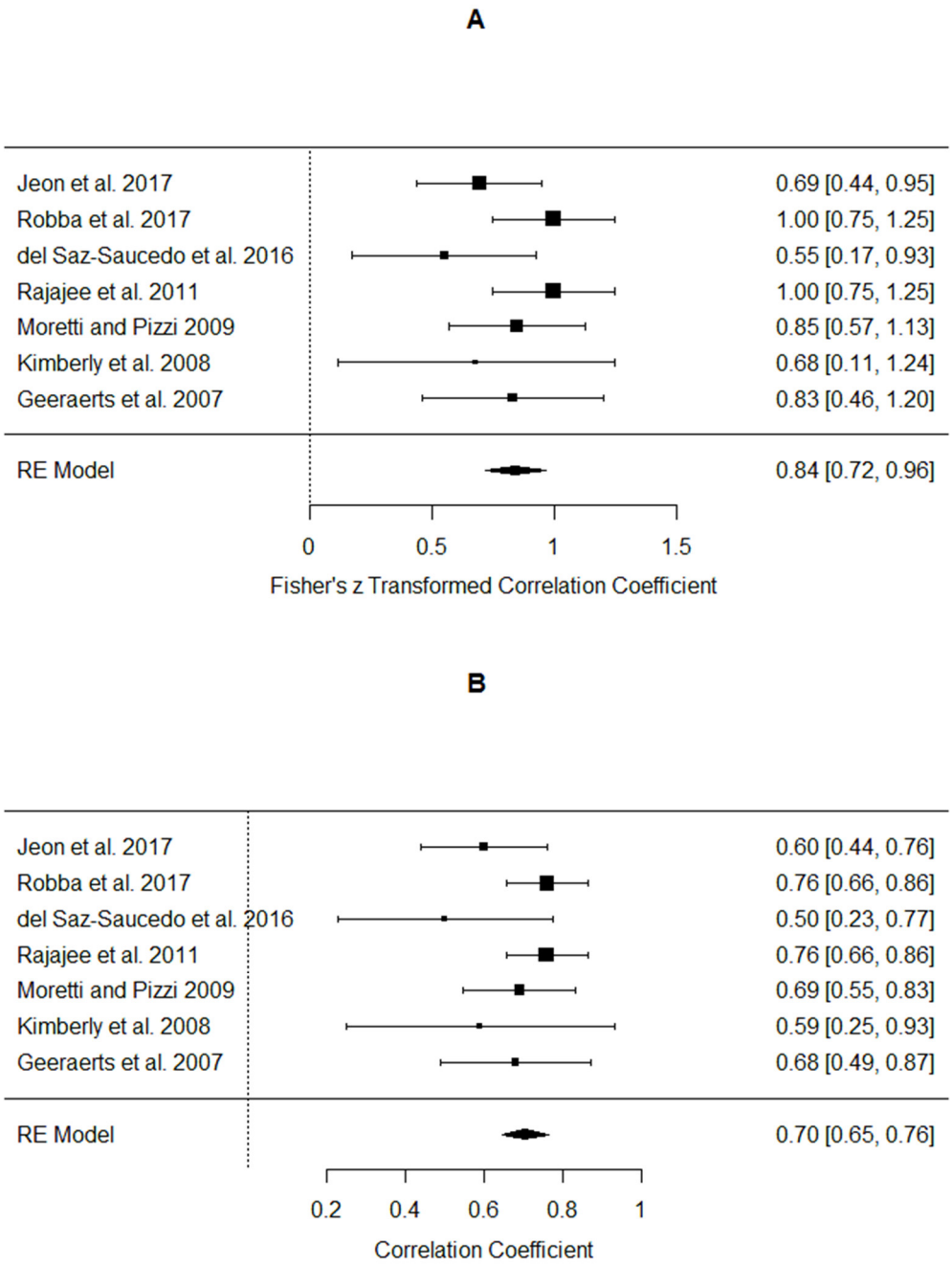
ESM Fig. 2 Sensitivity (A) and specificity (B) of sonographic ONSD compared with invasive ICP measurement in a subset of included study (intracranial hypertension assumed for ICP >20 mmHg).



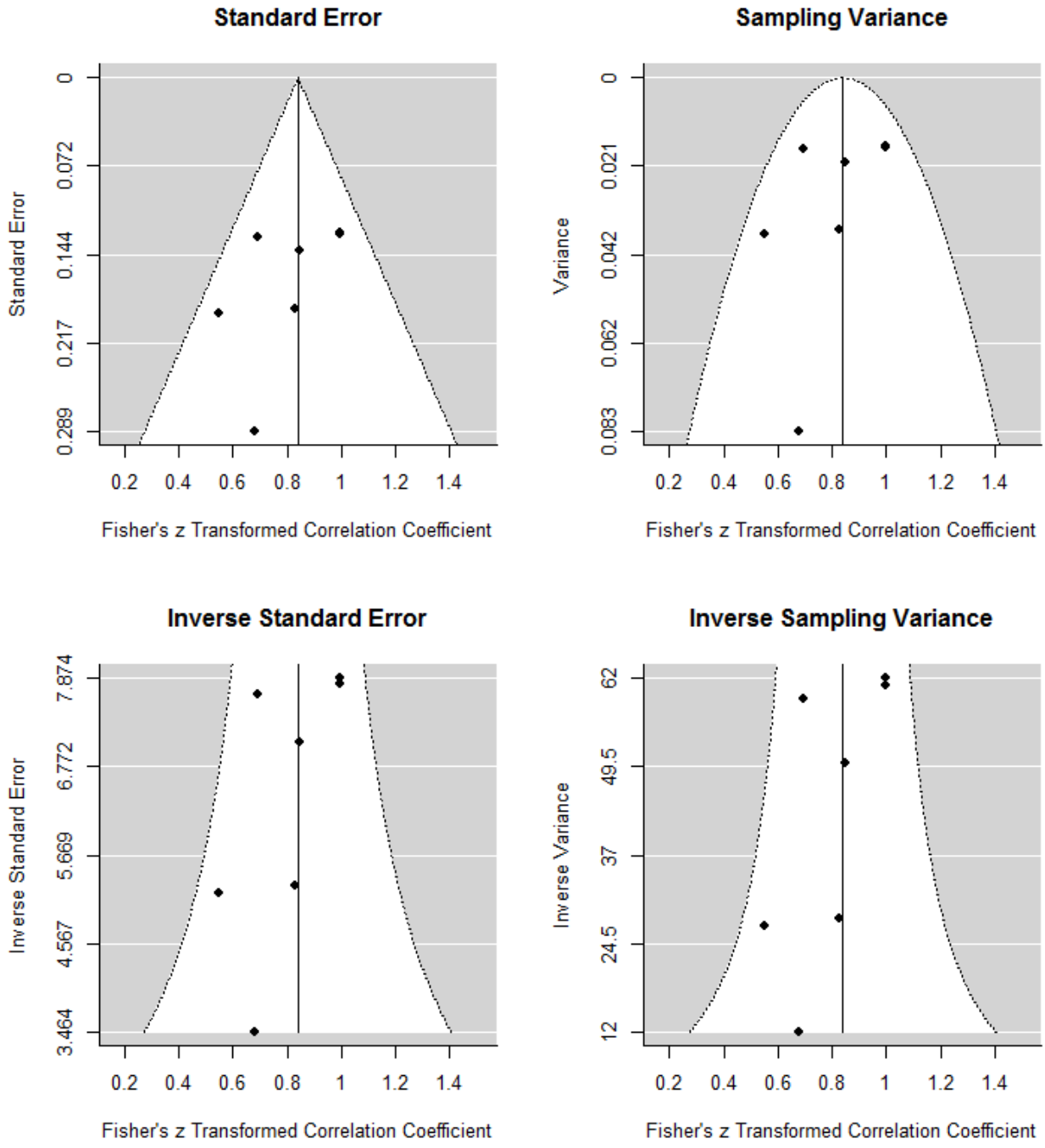
ESM Fig. 3 HSROC curve of sonographic ONSD compared with invasive ICP measurement for diagnosis of intracranial hypertension, in a subset of included studies (intracranial hypertension assumed for ICP >20 mmHg). The HSROC curve was not extrapolated beyond the range of the original data.

ESM Sec. 1 Further analyses by assuming correlation coefficient as effect size

We performed additional analyses in the same studies selected for diagnostic meta-analysis, assuming the correlation coefficient (*r*) between the means of sonographic ONSD and invasive ICP measurements as effect size. The pooled *r* was 0.701 (95% CI 0.650–0.760), whereas the pooled *r*-to-*z* transformed correlation coefficients was 0.842 (95% CI 0.722–0.960). The DerSimonian-Laird random-effects (RE) model was applied to the Fisher's *r*-to-*z* transformed correlation coefficients. The forest plots of the Fisher's *r*-to-*z* transformed correlation coefficients and the *z*-values back-transformed to *r*-space are presented in ESM Fig. 4. The RE model was statistical significant (p <0.001), without heterogeneity (Q = 6.876, p = 0.332; I^2 = 12.74%). An extensive panel of funnel plots found as all included studies fell within the pseudo-confidence region (ESM Fig. 5). By entering ONSD threshold values as moderator in the RE model, no statistical significance for this covariate was found (p = 0.248), without addition of heterogeneity (Q = 5.428, p = 0.366; I^2 = 7.89%). Finally, the same RE model was evaluated in the subset of five studies that assumed intracranial hypertension for ICP >20 mmHg, reaching statistical significance (p <0.001) without heterogeneity (Q = 3.844, p = 0.427; I^2 = 0.00%).



ESM Fig. 4 Forest plots of the Fisher's *r*-to-*z* transformed correlation coefficients (A) and the *z*-values back-transformed to *r*-space (B).



ESM Fig. 5 Funnel plots of the DerSimonian-Laird random-effects model applied to the Fisher's *r*-to-*z* transformed correlation coefficients.