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Optic nerve sheath diameter sonography for the diagnosis of increased intracranial pressure: a systematic review and meta-analysis protocol

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ABSTRACT

Introduction: Increased intracranial pressure (ICP) is a significant neurological issue that may lead to permanent neurological sequelae. When evaluating patients with traumatic brain injury, it is crucial to identify those with high ICP in order to expedite ICP lowering measures and maintain adequate cerebral perfusion. Several measures are used to recognize patients with increased ICP including computed tomography (CT) scan, magnetic resonance imaging (MRI), ICP monitor, and lumbar puncture (LP). However, these tests can be invasive, associated with radiation exposure, contraindicated, or not readily available. Ultrasonography measurement of the optic nerve sheath diameter (ONSD) is proposed as a non-invasive and quick measure to identify high ICP. The aim of this systematic review and meta-analysis will be to examine the accuracy of ONSD sonography for increased ICP diagnosis.

Methods and analyses: We will include published and unpublished randomised controlled trials, observational studies, and abstracts, with no publication type or language restrictions. Search strategies will be designed to peruse the MEDLINE, Embase, Web of Science, WHO Clinical Trials, ClinicalTrials.gov, CINAHL, and the Cochrane Library databases. We will also implement strategies to search grey literature. Two reviewers will independently complete data abstraction and conduct quality assessment. Included studies will be assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. We will construct the hierarchical summary receiver operating characteristic curve for included studies and pool sensitivity and specificity using the bivariate model. We also plan to conduct prespecified subgroup analyses to explore heterogeneity. The overall quality of evidence will be rated using Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

Ethics and dissemination: Research ethics board approval is not required for this study as it draws from published data and raises no concerns related to patient privacy. This review will provide a comprehensive assessment of the evidence on ONSD sonography diagnostic accuracy and is directed to a wide audience. Results from the review will be disseminated extensively through conferences and submitted to a peer-reviewed journal for publication.

PROSPERO registration number: CRD42017055485.

ARTICLE SUMMARY

Strengths and limitations of this study

- This study will investigate the diagnostic accuracy of optic nerve sheath diameter (ONSD) sonography for increased ICP across all available patient populations, reference standards, and covariates without publication type restriction.
- A comprehensive literature search, developed in consultation with a librarian with experience in systematic review search strategies, will be performed to include studies from multiple databases without language type restriction.
- Heterogeneity may exist due to potential multiple covariates; however, we plan to explore this using prespecified subgroup analyses.
- The current study protocol does not plan to evaluate cost-effectiveness and economic analysis when using ONSD sonography.

INTRODUCTION

Increased intracranial pressure (ICP) is a significant neurological issue that may lead to permanent neurological sequelae.¹ It can arise from head injury, intracranial mass lesion, disturbance of cerebrospinal fluid (CSF) circulation, obstruction to major venous sinuses, or occasionally be idiopathic.² When evaluating patients with traumatic brain injury, it is crucial to identify those with high ICP in order to expedite ICP lowering measures and maintain adequate cerebral perfusion.³ Several measures are used to recognise patients with increased ICP including computed tomography (CT) scan, magnetic resonance imaging (MRI), ICP monitor, and lumbar puncture (LP). However, these tests can be invasive, associated with radiation exposure, contraindicated, or not readily available.⁴ Ultrasonography measurement of the optic nerve sheath diameter (ONSD) is proposed as a non-invasive and quick measure to identify high ICP. The optic nerve is wrapped by a sheath derived from the meninges and extends towards the orbit.⁵ This communication allows CSF to transfer and therefore have similar pressure changes between the intracranial and intraorbital subarachnoid spaces. This method has been proposed in the setting of trauma, neurosurgery, and emergency medicine.^{6,7}

The aim of this systematic review and meta-analysis protocol will be to examine the accuracy of ONSD sonography for the diagnosis of increased ICP. This systematic review and meta-analysis protocol is designed in accordance to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P)⁸ and is registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42017055485).

METHODS

We will conduct a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)^{8,9} and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.¹⁰ This protocol will be amended and updated in conjunction with the PRISMA-P guidelines. Updated versions will be made available on PROSPERO with record of version history.

Literature search

A detailed librarian-assisted search will be conducted of the MEDLINE, Embase, Web of Science, WHO, ClinicalTrials.gov, and the Cochrane Library databases through March 5, 2017.

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3 We will include published and unpublished reports on the diagnostic accuracy of ONSD in
4 detecting increased ICP without language or publication type restrictions. This search will be
5 developed in collaboration with a librarian who has experience in conducting searches for
6 systematic reviews and meta-analyses.¹¹ Keywords and medical subject heading (MeSH) terms
7 related to optic nerve, sonography, and ICP will be used. The search strategy utilised for
8 MEDLINE is provided in Table 1. This search will be supplemented by manually reviewing the
9 references of included articles. We will search for grey literature, which may include
10 dissertations, reports, and conference abstracts. Experts will be contacted for potential eligible
11 studies.
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21 **Study selection**

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23 Obtained studies from the literature search will be independently evaluated by two
24 investigators (AK, FK) for eligibility. Disagreements between reviewers regarding whether to
25 include or exclude a study will be resolved by consensus and a third reviewer (SAA) will be
26 consulted, if necessary. Inclusion criteria for this study will include:
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- 30 • Study design: Randomised controlled trials (RCTs; including pilot studies), controlled
31 (non-randomised) clinical trials, prospective and retrospective cohort studies, and
32 abstracts. There will be no restriction to publication type or language.
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- 34 • Population: Patients of any age group and demographic with suspected increased ICP.
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- 36 • Index test: ONSD sonography.
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- 38 • Reference standard: CT scan, MRI, ICP monitor, or LP.
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41 For studies that were published more than once, only the most recent and comprehensive
42 report will be included. Studies that did not include a reference standard, studies without clinical
43 outcomes including *in vitro* studies, review articles, letters, and correspondences or comments
44 will be excluded (Figure 1).
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49 **Monitoring of ocular nerve sheath in traumatic increased ICP (MOONSTRIP) study** 50 **(NCT00783809)**

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53 In addition, we will present and then include the MOONSTRIP unpublished prospective
54 blinded study conducted at a level 1 tertiary care trauma centre. Investigators of this study were
55 given visual materials and readings prior to attending didactic and hands-on supervised
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3 ultrasound training sessions. During these sessions, quality assurance data were collected to
4 ensure all investigators met acceptable standards.
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7 In this study, all patients referred to the trauma centre will undergo assessment in
8 accordance with advanced trauma life support protocol. If assessment warrants investigation for
9 increased ICP, a CT scan will be performed. An investigator blinded to the CT scan will assess
10 the patient based on the following inclusion criteria: age \geq 16 years, following trauma, and
11 ONSD sonography required to be performed within 1 hour of the CT scan. All patients will be
12 consented prior to enrolment. Exclusion criteria includes: penetrating trauma to the head or
13 significant ocular trauma; patient not expected to survive transfer out of emergency room
14 department; patient too unstable to undergo CT of head or ONSD sonography.
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21 ONSD sonography of the eye will be conducted by an investigator blinded to CT scan
22 findings. The investigator will use an ultrasound machine with a linear transducer. A layer of
23 sterile coupling gel will be applied to the closed eyelid with the patient in supine position. ONSD
24 sonography will be conducted 3 mm posterior to the globe for each eye. Transverse and sagittal
25 ONSD measurements of each eye will be averaged and recorded for subsequent inter-observer
26 variability analysis.
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32 The reference test for this study is CT scan, which will be reviewed by a neuroradiologist
33 blinded to the ONSD sonography findings. The presence of elevated ICP will be based on the
34 following criteria: midline shift from mass effect of 3 mm or greater, collapse of third ventricle,
35 hydrocephalus, effacement of sulci with evidence of significant oedema, collapse of
36 mesencephalic cisterns, or evidence of herniation.¹² The patient will be followed up by the
37 research coordinator who is blinded to sonography and CT findings for a duration of 48 hours
38 after ONSD sonography. During this period if the patient needs a repeat CT of the head or any
39 intervention that would require the insertion of an ICP monitor, repeat measurements of the
40 ONSD will be performed. Patients demographics will be evaluated including age, Glasgow
41 Coma Scale (GCS), mechanism of injury, Injury Severity Score (ISS), whether patient is
42 intubated, time from presentation to CT scan, CT findings, haemodynamic parameters,
43 monocular and binocular ONSD. This patient information will be stored in a confidential
44 encrypted database. The inter-observer variability will be calculated using the kappa statistic for
45 the left eye, right eye, and binocular average of ONSD measurements. In addition, the ONSD
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3 sonography accuracy will be calculated using sensitivity, specificity, positive and negative
4 predictive value, and positive and negative likelihood ratio.
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8 9 **Data management and collection**

10 Literature search results will be downloaded from databases as .ris files or .ciw files
11 which will contain the complete reference and loaded into EndNote X7 for reference
12 management. Reviewers will develop and pilot screening questions and forms based on the
13 eligibility criteria. Full text articles will be retrieved before data extraction. For studies not
14 published in English, the full text will be translated and a medical expert fluent in the original
15 language of the article will be contacted to assist with data abstraction. We will retrieve the full
16 text of each article that meets eligibility criteria or that contains ambiguity. If necessary, the
17 authors of potentially relevant studies will be contacted for missing data or to resolve questions
18 about eligibility. Discrepancies will be resolved by consensus. A third author will be consulted in
19 the event of a disagreement. Reasons for article exclusion will be recorded.
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28 Two reviewers will independently extract data from eligible articles, which will be
29 verified by a third reviewer. Data collection forms will contain fields for variables, such as: study
30 design; study first author; year of publication; journal of publication; language; countries and
31 years of patient recruitment; sample size; number of males and females; sample mean age;
32 patient population with high ICP (e.g., trauma or brain pathology); patient diagnosis; index and
33 reference test specifications; number of trained sonographers in a study; medical specialty of
34 sonographer; GCS; number of ONSD measurements; monocular versus binocular ONSD
35 measurement; timing of ONSD measurement; reference test findings; ONSD cutoff for high ICP
36 and whether this cutoff was determined *a priori* or calculated as *post hoc*; time interval between
37 conducting ONSD sonography and reference standard; number of true and false positives, true
38 and false negatives; sensitivity and specificity; positive and negative predictive value; positive
39 and negative likelihood ratio; area under receiver operating characteristic (ROC) curve.
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51 **Risk of bias in individual studies**

52 Two reviewers will independently perform quality assessment. Risk of bias will be
53 assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool¹³ to
54 evaluate the risk of bias and applicability of studies across four domains: patient selection, index
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3 test, reference standard, and flow and timing. Each domain is evaluated for risk of bias with the
4 first three domains evaluated based on applicability. In the instance of unresolved disagreement,
5 a third reviewer will be consulted.
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10 **Index test**

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12 The optic nerve sheath is contiguous with the dura mater, and the CSF contained within it
13 is contiguous with the subarachnoid space surrounding the brain and spinal cord. As such, raised
14 ICP can be visualised sonographically by increased ONSD.¹⁴ Ultrasound examinations are
15 typically conducted with a linear array ultrasound transducer with a layer of sterile coupling gel
16 applied to the closed eyelid while the patient is positioned supine. The ONSD is measured 3 mm
17 posterior to the globe for each eye¹⁴⁻¹⁶. The cut-off of ONSD measurement to diagnose high ICP
18 used in individual studies is either determined *a priori* or *post-hoc* analysis after calculating the
19 area under the ROC curve.
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28 **Reference standard**

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30 Several reference tests are used for the diagnosis of increased ICP which may include CT
31 scan, MRI, invasive ICP monitoring, or LP. CT scan can diagnose increased ICP and determine
32 its cause by identifying mass lesion, cerebral oedema, midline structural shift, ventricular
33 collapse or enlargement, and cistern compression.¹² Due to cost concerns and relatively minimal
34 added value of MRI in detecting high ICP beyond CT scan findings,¹⁷ MRI is not used as
35 common as CT to diagnose patients with high ICP. Invasive ICP monitoring may include
36 intraventricular or intraparenchymal catheters, and subdural or subarachnoid bolts. A raised ICP
37 is generally defined as pressure greater than 22 mm Hg that warrants treatment.¹⁸ These devices
38 involve creating a burr-hole and insertion of the ICP monitor either in the ventricular system,
39 brain parenchyma, subdural, or subarachnoid space. LP can also be used for the diagnosis of
40 increased ICP by measuring the opening pressure.
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51 **Statistical analysis and data synthesis**

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53 Sensitivity and specificity estimates will be used to produce a forest plot with
54 corresponding 95% confidence intervals (CI) and a summary ROC (SROC) curve to explore
55 between-study variation for the accuracy of ONSD sonography.
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The sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratios will be extracted from eligible studies with associated 95% CIs. If required, these measures will be calculated using 2 x 2 contingency table consisting of true and false positives and true and false negatives that will be reconstructed for each study. We will pool the summary sensitivity and specificity stratified according to reference standard using the bivariate model¹⁹ with random-effects weighting.¹⁰ This model for diagnostic meta-analysis accounts for between-study variability when pooling sensitivity and specificity.

We will also perform meta-analysis using the hierarchical summary receiver operating characteristic (HSROC) model²⁰ with random-effects weighting to obtain the SROC curve.¹⁰ The HSROC model includes two parameters that account for between-study variation regarding accuracy and threshold level, and a shape parameter that allows for non-symmetrical underlying summary ROC curve. For this model, we will combine all eligible studies regardless of thresholds and reference standards used. We shall use this model to explore heterogeneity by examining how the curve's position and shape may alter with study level covariates.^{10,21} The magnitude of heterogeneity will be depicted by approximating the degree of proximity of observed study results to the SROC curve. We will also indicate how much greater the 95% prediction regions of the SROC curve are compared to the 95% confidence regions.²² High heterogeneity will be noted when the 95% prediction regions are much larger graphically relative to the 95% confidence regions.²² Meta-analyses will be performed using the NLMIXED procedure in the Statistical Analysis System (SAS) software package (version 9.3; SAS Institute Inc., Cary, North Carolina, USA).

Methods for evaluating publication bias in diagnostic accuracy studies are limited, and hence, results will be interpreted with caution. Potential publication bias will be investigated by funnel plot asymmetry inspection which will be constructed using Deeks model.²³ Diagnostic odds ratio (DOR) will be calculated to evaluate potential publication bias using the following equation¹⁰:

$$DOR = \frac{TP/FP}{FN/TN}$$

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3 We will use likelihood ratios to determine post-test probabilities, which will be computed
4 using these pre-test probabilities and the summary positive and negative likelihood ratios.
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7 Covariates that may affect study heterogeneity and contribute to variance in index test
8 diagnostic accuracy parameters will be explored. We plan to conduct prespecified subgroup
9 analyses stratified by: quality of included study; patient population; reference standard; trained
10 versus untrained sonographer; whether the sonographer was blinded or not from reference
11 standard results; timing of ONSD sonography; whether this cutoff was determined *a priori* or
12 calculated as *post hoc*. In addition, we will conduct sensitivity analysis by performing a meta-
13 analysis including and excluding the MOONSTRIP study. Quality of evidence from the meta-
14 analysis will be rated using the Grading of Recommendations Assessment Development and
15 Evaluation (GRADE) methodology.²⁴
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24 **ETHICS AND DISSEMINATION**

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26 Approval from the research ethics board is not required for this study as it examines data
27 from conducted studies. Therefore, there are no concerns regarding patient privacy or participant
28 ethics. Results from this study are expected to significantly change clinical practice. The
29 examination of the literature investigating the diagnostic accuracy of ONSD sonography for
30 increased ICP is expected to inform clinicians in different fields of medicine, such as trauma,
31 neurosurgery, and emergency medicine. The results from this review will be submitted to a peer-
32 reviewed journal for publication and will be widely presented at conferences and seminars.
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40 **AUTHORS' CONTRIBUTIONS**

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42 AK, NS, and SAA conceived and designed the protocol. AK, LB, and SAA designed the
43 search strategy and piloted it across all relevant databases. AK, NS, FK, and SAA developed the
44 review protocol, selection criteria, and risk of bias assessment. AK and SAA designed the data
45 management and synthesis methodology. AK, NS, FK, WA, SN, JHB, TR, PE, FS, AH, KK, LB,
46 SS, KR, GWJH, AWK, and SAA critically reviewed and collaborated in the discussion of the
47 intellectual content of the manuscript.
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3 This research received no specific grant from any funding agency in the public,
4 commercial, or not-for-profit sectors.
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8 9 **COMPETING INTERESTS STATEMENT**

10 The authors have no competing interests to declare.
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13 14 **REFERENCES**

- 15 1. Zanier ER, Ortolano F, Ghisoni L, et al. Intracranial pressure monitoring in intensive care:
16 clinical advantages of a computerized system over manual recording. *Crit Care*
17 2007;**11**(1):R7.
18
- 19 2. Dunn L. Raised Intracranial Pressure. *Journal of Neurol Neurosurg Psychiatry*.
20 2002;**73**(suppl 1):i23-7.
21
- 22 3. Joseph B, Haider AA, Pandit V, et al. Changing Paradigms in the Management of 2184
23 Patients With Traumatic Brain Injury. *Ann Surg* 2015;**262**(3):440-8.
24
- 25 4. Mayhall CG, Archer NH, Lamb VA, et al. Ventriculostomy-Related Infections. *N Engl J*
26 *Med* 1984;**310**(9):553-9.
27
- 28 5. Wang L, Feng L, Yao Y, et al. Optimal Optic Nerve Sheath Diameter Threshold for the
29 Identification of Elevated Opening Pressure on Lumbar Puncture in a Chinese Population.
30 *PLoS One* 2015;**10**(2):e0117939.
31
- 32 6. Amin D, McCormick T, Mailhot T. Elevated Intracranial Pressure Diagnosis with
33 Emergency Department Bedside Ocular Ultrasound. *Case Rep Emerg Med* 2015;**2015**:1-3.
34
- 35 7. Tayal VS, Neulander M, Norton HJ, et al. Emergency Department Sonographic Measurement
36 of Optic Nerve Sheath Diameter to Detect Findings of Increased Intracranial Pressure in
37 Adult Head Injury Patients. *Ann Emerg Med* 2007;**49**(4):508-14.
38
- 39 8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic
40 reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and
41 elaboration. *BMJ* 2009;**339**:b2700.
42
- 43 9. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and
44 meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.
45
- 46 10. Macaskill P, Gatsonis C, Deeks JJ, et al. Chapter 10: Analysing and Presenting Results. In:
47 Deeks JJ, Bossuyt PM, Gatsonis C, eds. *Cochrane Handbook for Systematic Reviews of*
48
49
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- 1
2
3 Diagnostic Test Accuracy Version 1.0. The Cochrane Collaboration, 2010. Available from:
4 <http://srdta.cochrane.org/>
5
6
- 7 11. Sollenberger JF, Holloway RG, Jr. The evolving role and value of libraries and librarians in
8 health care. *JAMA* 2013;**310**(12):1231-2.
9
 - 10 12. Golshani K, Ebrahim Zadeh M, Farajzadegan Z, et al. Diagnostic Accuracy of Optic Nerve
11 Ultrasonography and Ophthalmoscopy in Prediction of Elevated Intracranial Pressure. *Emerg*
12 *(Tehran)* 2015; **3**(2):54-8.
13
 - 14 13. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality
15 Assessment of Diagnostic Accuracy Studies. *Ann Intern Med* 2011;**155**(8):529-36.
16
 - 17 14. Hansen HC, Helmke K. The subarachnoid space surrounding the optic nerves: an ultrasound
18 study of the optic nerve sheath. *Surg Radiol Anat* 1996; **18**(4):323-8.
19
 - 20 15. Hansen HC, Helmke K, Kunze K. Optic nerve sheath enlargement in acute intracranial
21 hypertension. *Neuro-ophthalmology* 1994; **14**(6):345-54.
22
 - 23 16. Helmke K, Hansen HC. Fundamentals of transorbital sonographic evaluation of optic nerve
24 sheath expansion under intracranial hypertension, I: experimental study. *Pediatr Radiol*
25 1996; **26**(10):701-5.
26
 - 27 17. Said RR, Rosman NP. A Negative Cranial Computed Tomographic Scan Is Not Adequate to
28 Support a Diagnosis of Pseudotumor Cerebri. *J Child Neurol* 2004;**19**(8):609-13.
29
 - 30 18. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe
31 Traumatic Brain Injury, Fourth Edition. *Neurosurgery* Published Online First: 20 September
32 2016. Doi: 10.1227/NEU.0000000000001432
33
 - 34 19. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity
35 produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*
36 2005;**58**(10):982-90
37
 - 38 20. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic
39 test accuracy evaluations. *Stat Med* 2001;**20**(19):2865-84.
40
 - 41 21. Lee J, Kim KW, Choi SH, et al. Systematic Review and Meta-Analysis of Studies Evaluating
42 Diagnostic Test Accuracy: A Practical Review for Clinical Researchers-Part II. Statistical
43 Methods of Meta-Analysis. *Korean J Radiol* 2015;**16**(6):1188-96.
44
 - 45 22. B Bossuyt P, Davenport C, Deeks J, et al. Chapter 11: Interpreting results and drawing
46 conclusions. In: Deeks JJ, Bossuyt PM, Gatsonis C (editors), *Cochrane Handbook for*
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3 Systematic Reviews of Diagnostic Test Accuracy Version 0.9. The Cochrane Collaboration,
4 2013. Available from: <http://srdta.cochrane.org/>.
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- 7 23. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other
8 sample size effects in systematic reviews of diagnostic test accuracy was assessed. *J Clin*
9 *Epidemiol* 2005;**58**(9):882–93.
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11 24. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of
12 recommendations for diagnostic tests and strategies. *BMJ* 2008;**336**(7653):1106-10.
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FIGURE LEGENDS

Figure 1: PRISMA flow diagram

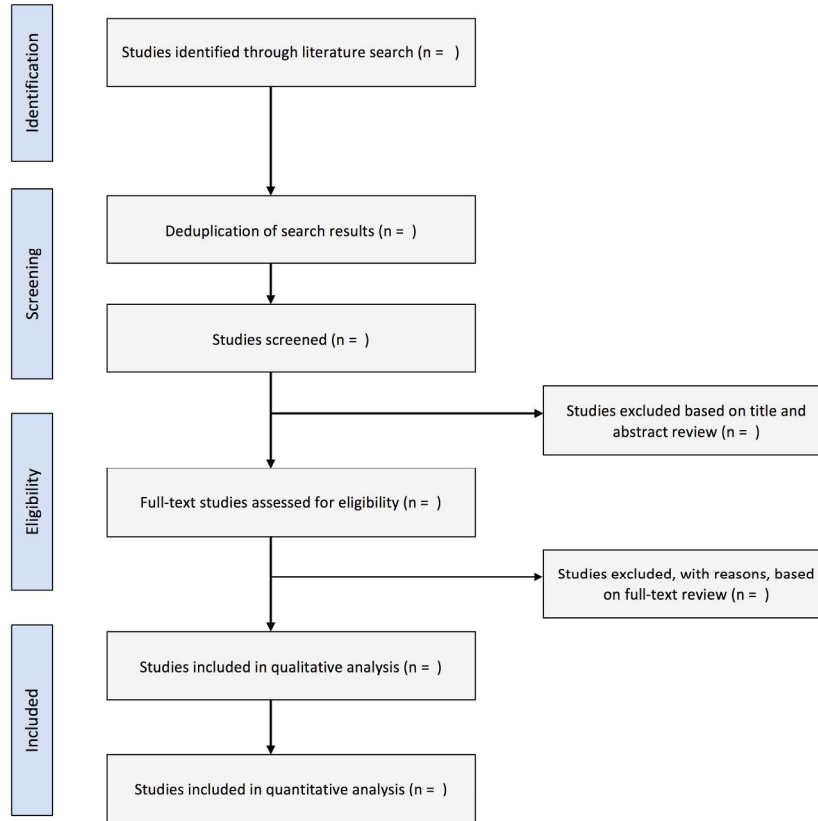
For peer review only

Table 1: Search strategy for the MEDLINE electronic database using the Ovid interface

Database	Search Terms
MEDLINE 1946 - present	1. optic nerve/
	2. optic nerve*.ti,ab,kf.
	3. nervus opticus.ti,ab,kf.
	4. second cranial nerve*.ti,ab,kf.
	5. cranial nerve ii.ti,ab,kf.
	6. cranial nerve 2.ti,ab,kf.
	7. or/1-6
	8. oligodendroglia/ or myelin sheath/
	9. sheath.ti,ab,kf.
	10. oligodendroglia.ti,ab,kf.
	11. oligodendrocyte*.ti,ab,kf.
	12. myelin.ti,ab,kf.
	13. or/8-12
	14. diameter*.ti/ab/kf.
	15. diametre*.ti,ab,kf.
	16. dilat*.ti/ab/kf.
	17. thick*.ti,ab,kf.
	18. volume.ti,ab,kf.
	19. (swelling or swollen).ti,ab,kf.
	20. edema.ti,ab,kf.
	21. or/14-20
	22. intracranial pressure/
	23. ((intracranial or subarachnoid*) adj2 pressure).ti,ab,kf.
	24. intracranial hypertension/
	25. intracranial hypertension.ti,ab,kf.
	26. icp.ti,ab,kf.
	27. papilledema/
	28. papilledema*.ti,ab,kf.
	29. or/22-28
	30. (7 or 13) and 21 and 29

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Figure 1: PRISMA flow diagram



PRISMA flow diagram

215x279mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Corresponding Page Number in Manuscript
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3,5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1,2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2,11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11,12
Sponsor	5b	Provide name for the review funder and/or sponsor	11,12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11,12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5,6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5,6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5,6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned	16, Table 1

		limits, such that it could be repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6, 8, Figure 1
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8,9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	9-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10,11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647

BMJ Open

Optic nerve sheath diameter sonography for the diagnosis of increased intracranial pressure: a systematic review and meta-analysis protocol

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2017-016194.R1
Article Type:	Protocol
Date Submitted by the Author:	02-May-2017
Complete List of Authors:	<p>Koziarz, Alex; McMaster University, Division of Neurosurgery Sne, Niv; McMaster University, Division of General Surgery and Trauma Kegel, Fraser; McMaster University, Division of General Surgery and Trauma Alhazzani, Waleed; McMaster University, Department of Medicine Nath, Siddharth; McMaster University, Department of Biochemistry and Biomedical Sciences and Division of Neurosurgery Badhiwala, Jetan; University of Toronto, Division of Neurosurgery Rice, Timothy; McMaster University, Division of General Surgery Engels, Paul; McMaster University, Division of General Surgery, Trauma, and Critical Care Samir, Faidi; McMaster University, Division of General Surgery and Trauma Healey, Andrew; McMaster University, Division of Emergency Medicine Kahnamoui, Kamyar; McMaster University, Division of General Surgery and Critical Care Banfield, Laura; McMaster University, Health Sciences Library Sharma, Sunjay; McMaster University, Division of Neurosurgery Reddy, Kesava; McMaster University, Division of Neurosurgery Hawryluk, Gregory; University of Utah, Department of Neurosurgery and Neurology Kirkpatrick, Andrew; University of Calgary, Department of Surgery and Critical Care Almenawer, Saleh; McMaster University, Division of Neurosurgery</p>
Primary Subject Heading:	Diagnostics
Secondary Subject Heading:	Emergency medicine, Intensive care, Surgery, Neurology
Keywords:	optic nerve sheath diameter sonography, increased intracranial pressure, severe head injury, Ultrasound < RADIOLOGY & IMAGING

SCHOLARONE™
Manuscripts

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3 **Optic nerve sheath diameter sonography for the diagnosis of increased intracranial**
4 **pressure: a systematic review and meta-analysis protocol**
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ABSTRACT

Introduction: Increased intracranial pressure (ICP) is a significant neurological issue that may lead to permanent neurological sequelae. When evaluating patients with traumatic brain injury, it is crucial to identify those with high ICP in order to expedite ICP lowering measures and maintain adequate cerebral perfusion. Several measures are used to recognize patients with increased ICP including computed tomography (CT) scan, magnetic resonance imaging (MRI), ICP monitor, and lumbar puncture (LP). However, these tests can be invasive, associated with radiation exposure, contraindicated, or not readily available. Ultrasonography measurement of the optic nerve sheath diameter (ONSD) is proposed as a non-invasive and quick measure to identify high ICP. The aim of this systematic review and meta-analysis will be to examine the accuracy of ONSD sonography for increased ICP diagnosis.

Methods and analyses: We will include published and unpublished randomised controlled trials, observational studies, and abstracts, with no publication type or language restrictions. Search strategies will be designed to peruse the MEDLINE, Embase, Web of Science, WHO Clinical Trials, ClinicalTrials.gov, CINAHL, and the Cochrane Library databases. We will also implement strategies to search grey literature. Two reviewers will independently complete data abstraction and conduct quality assessment. Included studies will be assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool. We will construct the hierarchical summary receiver operating characteristic curve for included studies and pool sensitivity and specificity using the bivariate model. We also plan to conduct prespecified subgroup analyses to explore heterogeneity. The overall quality of evidence will be rated using Grading of Recommendations, Assessment, Development and Evaluations (GRADE).

Ethics and dissemination: Research ethics board approval is not required for this study as it draws from published data and raises no concerns related to patient privacy. This review will provide a comprehensive assessment of the evidence on ONSD sonography diagnostic accuracy and is directed to a wide audience. Results from the review will be disseminated extensively through conferences and submitted to a peer-reviewed journal for publication.

PROSPERO registration number: CRD42017055485.

ARTICLE SUMMARY

Strengths and limitations of this study

- This study will investigate the diagnostic accuracy of optic nerve sheath diameter (ONSD) sonography for increased ICP across all available patient populations, reference standards, and covariates without publication type restriction.
- A comprehensive literature search, developed in consultation with a librarian with experience in systematic review search strategies, will be performed to include studies from multiple databases without language type restriction.
- Heterogeneity may exist due to potential multiple covariates; however, we plan to explore this using prespecified subgroup analyses.
- The current study protocol does not plan to evaluate cost-effectiveness and economic analysis when using ONSD sonography.

INTRODUCTION

Increased intracranial pressure (ICP) is a significant neurological issue that may lead to permanent neurological sequelae.¹ It can arise from head injury, intracranial mass lesion, disturbance of cerebrospinal fluid (CSF) circulation, obstruction to major venous sinuses, or occasionally be idiopathic.² When evaluating patients with traumatic brain injury, it is crucial to identify those with high ICP in order to expedite ICP lowering measures and maintain adequate cerebral perfusion.³ Several measures are used to recognise patients with increased ICP including computed tomography (CT) scan, magnetic resonance imaging (MRI), ICP monitor, and lumbar puncture (LP). However, these tests can be invasive, associated with radiation exposure, contraindicated, or not readily available.⁴ Ultrasonography measurement of the optic nerve sheath diameter (ONSD) is proposed as a non-invasive and quick measure to identify high ICP. The optic nerve is wrapped by a sheath derived from the meninges and extends towards the orbit.⁵ This communication allows CSF to transfer and therefore have similar pressure changes between the intracranial and intraorbital subarachnoid spaces. This method has been proposed in the setting of trauma, neurosurgery, and emergency medicine.^{6,7}

The aim of this systematic review and meta-analysis protocol will be to examine the accuracy of ONSD sonography for the diagnosis of increased ICP. This systematic review and meta-analysis protocol is designed in accordance to the Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols (PRISMA-P)⁸ and is registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42017055485).

METHODS

We will conduct a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)^{8,9} and the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.¹⁰ This protocol will be amended and updated in conjunction with the PRISMA-P guidelines. Updated versions will be made available on PROSPERO with record of version history.

Literature search

A detailed librarian-assisted search will be conducted of the MEDLINE, Embase, Web of Science, WHO Clinical Trials, ClinicalTrials.gov, and the Cochrane Library databases from

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inception to an update on June 5, 2017 to ensure all recent relevant studies are captured. We will include published and unpublished reports on the diagnostic accuracy of ONSD in detecting increased ICP without language or publication type restrictions. This search will be developed in collaboration with a librarian who has experience in conducting searches for systematic reviews and meta-analyses.¹¹ Keywords and medical subject heading (MeSH) terms related to optic nerve, sonography, and ICP will be used. The search strategy utilised for MEDLINE is provided in Table 1. This search will be supplemented by manually reviewing the references of included articles. We will search for grey literature, which may include dissertations, reports, and conference abstracts. Experts will be contacted for potential eligible studies.

Study selection

Obtained studies from the literature search will be independently evaluated by two investigators (AK, FK) for eligibility. Disagreements between reviewers regarding whether to include or exclude a study will be resolved by consensus and a third reviewer (SAA) will be consulted, if necessary. Inclusion criteria for this study will include:

- Study design: Randomised controlled trials (RCTs; including pilot studies), controlled (non-randomised) clinical trials, prospective and retrospective cohort studies, and abstracts. There will be no restriction to publication type or language.
- Population: Patients of any age group and demographic with suspected increased ICP.
- Index test: ONSD sonography.
- Reference standard: CT scan, MRI, ICP monitor, or LP.

For studies that were published more than once, only the most recent and comprehensive report will be included. Studies that did not include a reference standard, studies without clinical outcomes including *in vitro* studies, review articles, letters, and correspondences or comments will be excluded (Figure 1).

Monitoring of ocular nerve sheath in traumatic increased ICP (MOONSTRIP) study (NCT00783809)

In addition, we will present and then include the MOONSTRIP unpublished prospective blinded study conducted at a level 1 tertiary care trauma centre. Investigators of this study were given visual materials and readings prior to attending didactic and hands-on supervised

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3 ultrasound training sessions. During these sessions, quality assurance data were collected to
4 ensure all investigators met acceptable standards.
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7 In this study, all patients referred to the trauma centre will undergo assessment in
8 accordance with advanced trauma life support protocol. If assessment warrants investigation for
9 increased ICP, a CT scan will be performed. An investigator blinded to the CT scan will assess
10 the patient based on the following inclusion criteria: age ≥ 16 years, following trauma, and
11 ONSD sonography required to be performed within 1 hour of the CT scan. All patients will be
12 consented prior to enrolment. Exclusion criteria includes: penetrating trauma to the head or
13 significant ocular trauma; patient not expected to survive transfer out of emergency room
14 department; patient too unstable to undergo CT of head or ONSD sonography.
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21 ONSD sonography of the eye will be conducted by an investigator blinded to CT scan
22 findings. The investigator will use an ultrasound machine with a linear transducer. A layer of
23 sterile coupling gel will be applied to the closed eyelid with the patient in supine position. ONSD
24 sonography will be conducted 3 mm posterior to the globe for each eye. Transverse and sagittal
25 ONSD measurements of each eye will be averaged and recorded for subsequent inter-observer
26 variability analysis.
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32 The reference test for this study is CT scan, which will be reviewed by a neuroradiologist
33 blinded to the ONSD sonography findings. The presence of elevated ICP will be based on the
34 following criteria: midline shift from mass effect of 3 mm or greater, collapse of third ventricle,
35 hydrocephalus, effacement of sulci with evidence of significant oedema, collapse of
36 mesencephalic cisterns, or evidence of herniation.¹² The patient will be followed up by the
37 research coordinator who is blinded to sonography and CT findings for a duration of 48 hours
38 after ONSD sonography. During this period if the patient needs a repeat CT of the head or any
39 intervention that would require the insertion of an ICP monitor, repeat measurements of the
40 ONSD will be performed. Patients demographics will be evaluated including age, Glasgow
41 Coma Scale (GCS), mechanism of injury, Injury Severity Score (ISS), whether patient is
42 intubated, time from presentation to CT scan, CT findings, haemodynamic parameters,
43 monocular and binocular ONSD. This patient information will be stored in a confidential
44 encrypted database. The inter-observer variability will be calculated using the kappa statistic for
45 the left eye, right eye, and binocular average of ONSD measurements. In addition, the ONSD
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3 sonography accuracy will be calculated using sensitivity, specificity, positive and negative
4 predictive value, and positive and negative likelihood ratio.
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8 9 **Data management and collection**

10 Literature search results will be downloaded from databases as .ris files or .ciw files
11 which will contain the complete reference and loaded into EndNote X7 for reference
12 management. Reviewers will develop and pilot screening questions and forms based on the
13 eligibility criteria. Full text articles will be retrieved before data extraction. For studies not
14 published in English, the full text will be translated and a medical expert fluent in the original
15 language of the article will be contacted to assist with data abstraction. We will retrieve the full
16 text of each article that meets eligibility criteria or that contains ambiguity. If necessary, the
17 authors of potentially relevant studies will be contacted for missing data or to resolve questions
18 about eligibility. Discrepancies will be resolved by consensus. A third author will be consulted in
19 the event of a disagreement. Reasons for article exclusion will be recorded.
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28 Two reviewers will independently extract data from eligible articles, which will be
29 verified by a third reviewer. Data collection forms will contain fields for variables, such as: study
30 design; study first author; year of publication; journal of publication; language; countries and
31 years of patient recruitment; sample size; number of males and females; sample mean age;
32 sample age cutoff for inclusion; patient population with high ICP (e.g., trauma or brain
33 pathology) and units of measurement for high ICP (mm Hg or cm H₂O); patient diagnosis; index
34 and reference test specifications; number of trained sonographers in a study; medical specialty of
35 sonographer; GCS; number of ONSD measurements; monocular versus binocular ONSD
36 measurement; timing of ONSD measurement; reference test findings; ONSD cutoff for high ICP
37 and whether this cutoff was determined *a priori* or calculated as *post hoc*; time interval between
38 conducting ONSD sonography and reference standard; number of true and false positives, true
39 and false negatives; sensitivity and specificity; positive and negative predictive value; positive
40 and negative likelihood ratio; area under receiver operating characteristic (ROC) curve.
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53 **Risk of bias in individual studies**

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55 Two reviewers will independently perform quality assessment. Risk of bias will be
56 assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool¹³ to
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3 evaluate the risk of bias and applicability of studies across four domains: patient selection, index
4 test, reference standard, and flow and timing. Each domain is evaluated for risk of bias with the
5 first three domains evaluated based on applicability. In the instance of unresolved disagreement,
6 a third reviewer will be consulted.
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10 11 12 **Index test**

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14 The optic nerve sheath is contiguous with the dura mater, and the CSF contained within it
15 is contiguous with the subarachnoid space surrounding the brain and spinal cord. As such, raised
16 ICP can be visualised sonographically by increased ONSD.¹⁴ Ultrasound examinations are
17 typically conducted with a linear array ultrasound transducer with a layer of sterile coupling gel
18 applied to the closed eyelid while the patient is positioned supine. The ONSD is measured 3 mm
19 posterior to the globe for each eye¹⁴⁻¹⁶. The cut-off of ONSD measurement to diagnose high ICP
20 used in individual studies is either determined *a priori* or *post-hoc* analysis after calculating the
21 area under the ROC curve.
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30 31 **Reference standard**

32 Several reference tests are used for the diagnosis of increased ICP which may include CT
33 scan, MRI, invasive ICP monitoring, or LP. CT scan can diagnose increased ICP and determine
34 its cause by identifying mass lesion, cerebral oedema, midline structural shift, ventricular
35 collapse or enlargement, and cistern compression.¹² Due to cost concerns and relatively minimal
36 added value of MRI in detecting high ICP beyond CT scan findings,¹⁷ MRI is not used as
37 common as CT to diagnose patients with high ICP. Invasive ICP monitoring may include
38 intraventricular or intraparenchymal catheters, and subdural or subarachnoid bolts. A raised ICP
39 is generally defined as pressure greater than 22 mm Hg that warrants treatment.¹⁸ These devices
40 involve creating a burr-hole and insertion of the ICP monitor either in the ventricular system,
41 brain parenchyma, subdural, or subarachnoid space. LP can also be used for the diagnosis of
42 increased ICP by measuring the opening pressure.
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52 53 **Statistical analysis and data synthesis**

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3 Sensitivity and specificity estimates will be used to produce a forest plot with
4 corresponding 95% confidence intervals (CI) and a summary ROC (SROC) curve to explore
5 between-study variation for the accuracy of ONSD sonography.
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9 The sensitivity, specificity, positive and negative predictive value, and positive and
10 negative likelihood ratios will be extracted from eligible studies with associated 95% CIs. If
11 required, these measures will be calculated using 2 x 2 contingency table consisting of true and
12 false positives and true and false negatives that will be reconstructed for each study. We will
13 pool the summary sensitivity and specificity stratified according to reference standard using the
14 bivariate model¹⁹ with random-effects weighting.¹⁰ This model for diagnostic meta-analysis
15 accounts for between-study variability when pooling sensitivity and specificity.
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19 We will also perform meta-analysis using the hierarchical summary receiver operating
20 characteristic (HSROC) model²⁰ with random-effects weighting to obtain the SROC curve and
21 determine if the summary point is an accurate predictors of raised ICP.¹⁰ The HSROC model
22 includes two parameters that account for between-study variation regarding accuracy and
23 threshold level, and a shape parameter that allows for non-symmetrical underlying summary
24 ROC curve. For this model, we will combine all eligible studies regardless of thresholds and
25 reference standards used. We shall use this model to explore heterogeneity by examining how
26 the curve's position and shape may alter with study level covariates.^{10,21} The magnitude of
27 heterogeneity will be depicted by approximating the degree of proximity of observed study
28 results to the SROC curve. We will also indicate how much greater the 95% prediction regions
29 of the SROC curve are compared to the 95% confidence regions.²² High heterogeneity will be
30 noted when the 95% prediction regions are much larger graphically relative to the 95%
31 confidence regions.²² Meta-analyses will be performed using the NLMIXED procedure in the
32 Statistical Analysis System (SAS) software package (version 9.3; SAS Institute Inc., Cary, North
33 Carolina, USA).
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37 Methods for evaluating publication bias in diagnostic accuracy studies are limited, and
38 hence, results will be interpreted with caution. Potential publication bias will be investigated by
39 funnel plot asymmetry inspection which will be constructed using Deeks model.²³ Diagnostic
40 odds ratio (DOR) will be calculated to evaluate potential publication bias using the following
41 equation¹⁰:
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$$DOR = \frac{TP/FP}{FN/TN}$$

We will use likelihood ratios to determine post-test probabilities, which will be computed using these pre-test probabilities and the summary positive and negative likelihood ratios.

Covariates that may affect study heterogeneity and contribute to variance in index test diagnostic accuracy parameters will be explored. We plan to conduct prespecified subgroup analyses stratified by: quality of included study; patient population; reference standard; trained versus untrained sonographer; whether the sonographer was blinded or not from reference standard results; timing of ONSD sonography; whether this cutoff was determined *a priori* or calculated as *post hoc*. In addition, we will conduct sensitivity analysis by performing a meta-analysis including and excluding the MOONSTRIP study. Quality of evidence from the meta-analysis will be rated using the Grading of Recommendations Assessment Development and Evaluation (GRADE) methodology.²⁴

ETHICS AND DISSEMINATION

Approval from the research ethics board is not required for this study as it examines data from conducted studies. Therefore, there are no concerns regarding patient privacy or participant ethics. Results from this study are expected to significantly change clinical practice. The examination of the literature investigating the diagnostic accuracy of ONSD sonography for increased ICP is expected to inform clinicians in different fields of medicine, such as trauma, neurosurgery, and emergency medicine. The results from this review will be submitted to a peer-reviewed journal for publication and will be widely presented at conferences and seminars.

AUTHORS' CONTRIBUTIONS

AK, NS, and SAA conceived and designed the protocol. AK, LB, and SAA designed the search strategy and piloted it across all relevant databases. AK, NS, FK, and SAA developed the review protocol, selection criteria, and risk of bias assessment. AK and SAA designed the data management and synthesis methodology. AK, NS, FK, WA, SN, JHB, TR, PE, FS, AH, KK, LB, SS, KR, GWJH, AWK, and SAA critically reviewed and collaborated in the discussion of the intellectual content of the manuscript.

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COMPETING INTERESTS STATEMENT

The authors have no competing interests to declare.

REFERENCES

1. Zanier ER, Ortolano F, Ghisoni L, et al. Intracranial pressure monitoring in intensive care: clinical advantages of a computerized system over manual recording. *Crit Care* 2007;**11**(1):R7.
2. Dunn L. Raised Intracranial Pressure. *Journal of Neurol Neurosurg Psychiatry*. 2002;**73**(suppl 1):i23-7.
3. Joseph B, Haider AA, Pandit V, et al. Changing Paradigms in the Management of 2184 Patients With Traumatic Brain Injury. *Ann Surg* 2015;**262**(3):440-8.
4. Mayhall CG, Archer NH, Lamb VA, et al. Ventriculostomy-Related Infections. *N Engl J Med* 1984;**310**(9):553-9.
5. Wang L, Feng L, Yao Y, et al. Optimal Optic Nerve Sheath Diameter Threshold for the Identification of Elevated Opening Pressure on Lumbar Puncture in a Chinese Population. *PLoS One* 2015;**10**(2):e0117939.
6. Amin D, McCormick T, Mailhot T. Elevated Intracranial Pressure Diagnosis with Emergency Department Bedside Ocular Ultrasound. *Case Rep Emerg Med* 2015;**2015**:1-3.
7. Tayal VS, Neulander M, Norton HJ, et al. Emergency Department Sonographic Measurement of Optic Nerve Sheath Diameter to Detect Findings of Increased Intracranial Pressure in Adult Head Injury Patients. *Ann Emerg Med* 2007;**49**(4):508-14.
8. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009;**339**:b2700.
9. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009;**339**:b2535.

10. Macaskill P, Gatsonis C, Deeks JJ, et al. Chapter 10: Analysing and Presenting Results. In: Deeks JJ, Bossuyt PM, Gatsonis C, eds. *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 1.0*. The Cochrane Collaboration, 2010. Available from: <http://srdta.cochrane.org/>
11. Sollenberger JF, Holloway RG, Jr. The evolving role and value of libraries and librarians in health care. *JAMA* 2013;**310**(12):1231-2.
12. Golshani K, Ebrahim Zadeh M, Farajzadegan Z, et al. Diagnostic Accuracy of Optic Nerve Ultrasonography and Ophthalmoscopy in Prediction of Elevated Intracranial Pressure. *Emerg (Tehran)* 2015; **3**(2):54-8.
13. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: A Revised Tool for the Quality Assessment of Diagnostic Accuracy Studies. *Ann Intern Med* 2011;**155**(8):529-36.
14. Hansen HC, Helmke K. The subarachnoid space surrounding the optic nerves: an ultrasound study of the optic nerve sheath. *Surg Radiol Anat* 1996; **18**(4):323-8.
15. Hansen HC, Helmke K, Kunze K. Optic nerve sheath enlargement in acute intracranial hypertension. *Neuro-ophthalmology* 1994; **14**(6):345-54.
16. Helmke K, Hansen HC. Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension, I: experimental study. *Pediatr Radiol* 1996; **26**(10):701-5.
17. Said RR, Rosman NP. A Negative Cranial Computed Tomographic Scan Is Not Adequate to Support a Diagnosis of Pseudotumor Cerebri. *J Child Neurol* 2004;**19**(8):609-13.
18. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. *Neurosurgery* Published Online First: 20 September 2016. Doi: 10.1227/NEU.0000000000001432
19. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;**58**(10):982-90
20. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* 2001;**20**(19):2865-84.
21. Lee J, Kim KW, Choi SH, et al. Systematic Review and Meta-Analysis of Studies Evaluating Diagnostic Test Accuracy: A Practical Review for Clinical Researchers-Part II. Statistical Methods of Meta-Analysis. *Korean J Radiol* 2015;**16**(6):1188-96.

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22. B Bossuyt P, Davenport C, Deeks J, et al. Chapter 11: Interpreting results and drawing conclusions. In: Deeks JJ, Bossuyt PM, Gatsonis C (editors), *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy Version 0.9*. The Cochrane Collaboration, 2013. Available from: <http://srdta.cochrane.org/>.
23. 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. *J Clin Epidemiol* 2005;**58**(9):882–93.
24. Schünemann HJ, Oxman AD, Brozek J, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008;**336**(7653):1106-10.

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FIGURE LEGENDS

Figure 1: Flowchart of study selection

For peer review only

Table 1: Search strategy for the MEDLINE electronic database using the Ovid interface

Database	Search Terms
MEDLINE 1946 - present	1. optic nerve/
	2. optic nerve*.ti,ab,kf.
	3. nervus opticus.ti,ab,kf.
	4. second cranial nerve*.ti,ab,kf.
	5. cranial nerve ii.ti,ab,kf.
	6. cranial nerve 2.ti,ab,kf.
	7. or/1-6
	8. oligodendroglia/ or myelin sheath/
	9. sheath.ti,ab,kf.
	10. oligodendroglia.ti,ab,kf.
	11. oligodendrocyte*.ti,ab,kf.
	12. myelin.ti,ab,kf.
	13. or/8-12
	14. diameter*.ti/ab/kf.
	15. diametre*.ti,ab,kf.
	16. dilat*.ti/ab/kf.
	17. thick*.ti,ab,kf.
	18. volume.ti,ab,kf.
	19. (swelling or swollen).ti,ab,kf.
	20. edema.ti,ab,kf.
	21. or/14-20
	22. intracranial pressure/
	23. ((intracranial or subarachnoid*) adj2 pressure).ti,ab,kf.
	24. intracranial hypertension/
	25. intracranial hypertension.ti,ab,kf.
	26. icp.ti,ab,kf.
	27. papilledema/
	28. papilledema*.ti,ab,kf.
	29. or/22-28
	30. (7 or 13) and 21 and 29

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Figure 1: PRISMA flow diagram

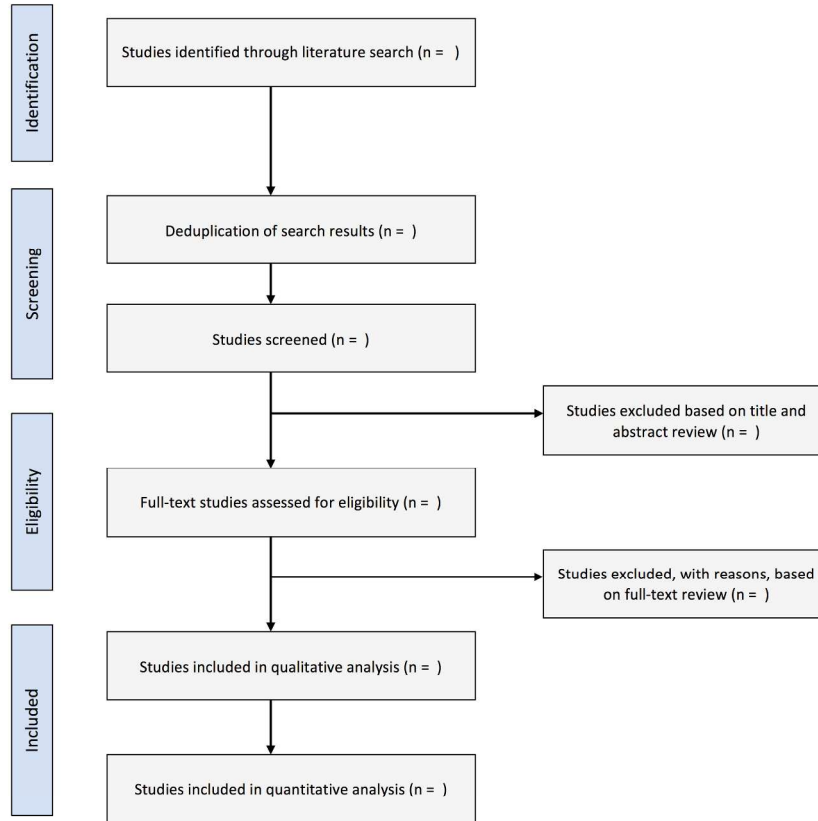


Figure 1: Flowchart of study selection

215x279mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Corresponding Page Number in Manuscript
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	3,5
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1,2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2,11
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	11,12
Sponsor	5b	Provide name for the review funder and/or sponsor	11,12
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	11,12
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	5,6
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	5,6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	5,6
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned	16, Table 1

		limits, such that it could be repeated	
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	8
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	6, 8, Figure 1
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	8
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	8
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	8
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	8,9
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	9-11
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2 , Kendall's τ)	9-11
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	10,11
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	10
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	11

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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