Review article

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Optic nerve and transcranial doppler ultrasonography for diagnosing increased intracranial pressure in adult traumatic brain injury patients: A systematic review and meta-analysis

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Abstract

***Objective*: To evaluate the accuracy of ultrasonography to assess the increase of intracranial pressure by assessing optic nerve sheath diameter (ONSD) and transcranial Doppler (TCD), consisting of the black box (BB) model, arterial diastolic flow velocity (FVd), critical closing pressure (CrCp), and pulsatility index (PI) as parameters, in adult traumatic brain injury (TBI) patients.**

***Methods*: A systematic search through the electronic databases including Medline through PubMed and Embase for studies evaluating the use of optic nerve and TCD USG to evaluate increased intracranial pressure (ICP) compared with the invasive method. Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the risk of bias.**

***Results*: Ten studies consisting of 727 patients were included in this study. The overall pooled sensitivity and specificity for the prediction of elevated ICP by measuring ONSD were 94% (95% CI: 89%-97%) and 88% (95% CI: 81%-95%), respectively. Positive and negative likelihood ratios were 12.7 (95% CI: 6.6-25.3; Cochran Q-statistic =14.6; *p*=0.04) and 0.06 (95% CI: 0.03-0.10; Cochran Q-statistic =14.1; *p*=0.05), respectively. All I^2 values were >0.50. The area under the receiver operating characteristic (ROC) curve was 0.92 (95% CI: 0.81-0.98) as shown in the summary ROC (sROC) plot. A meta-analysis could not be performed for the TCD subgroup due to several incomplete sensitivity and specificity data and differences in the evaluated parameters. Four studies evaluated the role of TCD with mixed results. In one study, averaging the parameters of TCD displayed favorable results.**

***Conclusion*: ONSD can be used as a parameter to evaluate the increase of ICP in TBI patients. BB model, FVd, and CrCp are potential promising parameters of TCD ultrasonography for noninvasive ICP estimation as opposed to PI. However, more studies with complete accuracy results are required in the future.**

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Introduction

Traumatic brain injury (TBI) is defined as a blunt force to the head or penetrating head injury that disrupts the normal function of the brain. It occurs when the head hits an object or when an object pierces the skull and damages the brain tissue. (1) The secondary insult from traumatic brain injury results in an elevated intracranial pressure (ICP), leading to a reduced cerebral perfusion pressure (CPP) at any given mean arterial pressure (MAP). Although the critical parameter for brain function and survival is an adequate cerebral blood flow (CBF) to meet cerebral demand, CBF is relatively difficult to quantitate compared to ICP. However, CBF depends on CPP, which is related to ICP, therefore making ICP monitoring as the mainstay evaluation in TBI patients. (2) TBI is a major problem worldwide, affecting sixty-nine million individuals worldwide every year. The TBIs caused by road traffic accidents is by proportion highest in Africa and Southeast Asia (both 56%) and lowest in North America (25%). (3) In Indonesia, the number of injuries causing disability from 2007 until 2018 increases continuously, with head injury being the third most common after lower and upper extremity trauma. Drivers (72.7%) and passengers (19.2%) of motorcycle ranks the two first victims of road traffic accidents. The compliance to wear helmets itself is still fairly low, with some never wearing helmets at all (23.9%) and most only occasionally (42.4%), (4) even though helmet usage has been proven to prevent worse intracranial complications and functional deficits. (5) The outcome of the patients is usually worsened due to the elevation of ICP as a secondary insult to TBI. (6) It is possible to reduce morbidity or mortality by diagnosing signs of secondary insults as early as possible. The current gold standard to measure ICP is by utilizing invasive intracranial devices. However, the method is invasive and not widely available in every health care centre. Other alternatives like computed tomography (CT) scan and magnetic resonance imaging (MRI), albeit less invasive, are expensive and require additional expertise that may not be present in rural areas. (7) Performing physical examination to evaluate signs of elevated ICP is subjective and not always reliable. (8) One of the proposed alternative diagnostic modalities that have been suggested in previous studies is ultrasonography (USG). The method is less invasive, widely available, and cheaper compared to the current golden standard of diagnosis. (9) A systematic review of optic nerve sheath diameter (ONSD) ultrasonography (USG) for detection of raised intracranial pressure have been published, however, this review did not take other possible parameters of non-invasive evaluation using USG that could be assessed, such as the black box (BB) model, arterial diastolic flow velocity (FVd), critical closing pressure (CrCp), and pulsatility index (PI), all of which are measured using transcranial Doppler (TCD) ultrasonography with each respective formula. (10) In this updated systematic review, we evaluate the accuracy of ultrasonography to assess the increase of intracranial pressure by assessing ONSD and TCD evaluation in adult TBI patients.

Methods

The conduction of this systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis of Diagnostic Test Accuracy (PRISMA-DTA). The protocol of this systematic review was registered in PROSPERO with the ID number: CRD42020184714.

Search Strategy

We performed a comprehensive literature search through the electronic databases including Medline through PubMed and Embase in April 2020. The following keywords were used: “brain injuries” OR “traumatic brain injury”, AND “ultrasonography” OR “USG” AND “intracranial hypertension” OR “intracranial pressure” OR “raised intracranial pressure” AND “diagnosis” OR “sensitivity” OR “specificity” OR “predictive value” OR “likelihood ratio” OR “false positive” OR “true positive”. There were no any language or other restrictions during the search. The study search and selection were independently performed and cross-checked by 6 reviewers to ensure eligibility. Any disagreements were resolved by a discussion between the reviewers. A search flow diagram displaying the amount of literatures screened and included were shown in **Figure 1**.

Eligibility criteria

Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess to the risk of bias and applicability concern of the studies. (11) The quality of each study is assessed independently by six investigators. Studies were considered eligible if they met the following criteria: 1) Prospective or retrospective study design, 2) The subjects were adult TBI patients, 3) ONSD measurement using USG or TCD was used for evaluation, 4) Invasive method evaluating ICP was used as a comparator, and 5) The outcome of the study was elevated ICP evaluation.

Statistical analysis

All studies were included based on the eligibility criteria and assessed manually for duplication. Quantitative synthesis or meta-analysis were used for studies with adequate results of sensitivity, specificity, receiver operating characteristic (ROC) curve and area under the curve (AUC).The sensitivity of the findings was defined as the probability that the index test results would be positive in a diseased case, whereas specificity was defined as the probability that the index test would be negative in a non-diseased case. The sensitivity and specificity findings would be displayed in a forest plot with each confidence interval (CI) respectively. Summary ROC (sROC) plot was used to display the results of each study in ROC space, depicting the scatter of the results. (12) The meta-analysis was performed using statistical software Review Manager (Revman) 5.3 by Cochrane Collaboration.

Results

Overview of literature search

Our search strategy identified 1028 studies, 10 of which were selected for further evaluation on the basis of inclusion criteria and content as shown in **Figure 1**. We excluded review articles, study in children, and studies that did not fit our methodologic criteria. All studies were conducted in the Emergency Departments or in hospital wards or in the Intensive Care Unit (ICU).

Characteristics and eligibility of selected studies

In this systematic review we evaluated several parameters to measure intracranial pressure: ONSD and TCD which consists of several parameters. **Table 1** displays the main characteristics of eligible studies. Overall, there were 727 adults across the ten studies. The average age of the samples was 35 years (range: 21-80 years) and 62% of them were male. One study was conducted in multiple centers and the remaining were single-center studies. Six studies were conducted in Europe and four studies were conducted in Asia. The quality of most of the studies included in this meta-analysis was high based on the risk of bias assessment using the QUADAS tool as shown in **Figure 2**. All studies described their selection criteria with sufficient detail and conducted ICP monitoring immediately after ultrasound was obtained. One study used the same radiologist to read both the ICP and ultrasound. Seven studies assessed ultrasound results independently and were blinded to ICP results. Ultrasound techniques were described in sufficient detail in each of these studies. Sonographers were not blinded to clinical data. Unfortunately, we were unable to perform a meta-analysis of TCD ultrasonography ICP evaluation due to multiple evaluated parameters of TCD that varied between studies. There were also incomplete data of sensitivity, specificity, and AUC from some studies.

Optic nerve sheath diameter meta-analysis

The overall pooled sensitivity and specificity shown in **Figure 2** for the prediction of elevated ICP were 94% (95% CI: 89%-97%) and 88% (95% CI: 81%-95%), respectively. Positive and negative likelihood ratios were 12.7 (95% CI: 6.625.3; Cochran Q-statistic =14.6; p=0.04) and 0.06 (95% CI: 0.03-0.10; Cochran Q-statistic =14.1; p=0.05), respectively. All I^2 values were >0.50. The area under the receiver operating characteristic curve was 0.92 (95% CI: 0.81-0.98) as shown in the sROC plot in **Figure 3**, indicating that ONSD was considered an outstanding diagnostic test to predict elevated ICP.

TCD ultrasonography qualitative synthesis

A total of four included studies attempted to utilize TCD ultrasonography as a non-invasive ICP estimator, three of which were conducted by Cardim, et al and the other one was conducted by Martin, et al. (13-16) Due to several incomplete sensitivity and specificity data and evaluated parameter differences among the included studies, a meta-analysis could not be performed for the TCD subgroup.

The first study prospectively collected 40 TBI patients to be evaluated. (13) The TCD methods used in this study were: BB model, FVd, CrCp, and PI. In the BB model, the intracranial compartment was examined as though it were a black-box system. Arterial blood pressure (ABP) was considered as an input signal to the compartment, whereas the ICP was considered as an output signal. Both ABP and ICP were managed by hemodynamic parameters, displaying flow velocity patterns. The output data was displayed as a full waveform measured in mmHg. The estimation of ICP was generated using a plugin specifically developed for ICM+ software. The second method was based on the formula described by Czosnyka, et al, which measured cerebral perfusion pressure (CPP) followed by non-invasive ICP (nICP). TCD was able to evaluate non-quantitative measurements cerebral blood flow (CBF), which could be monitored using blood flow velocity. Specific patterns of TCD waveform indicated insufficient cerebral perfusion due to a decrease in CPP. In this occurrence, there was a diastolic flow velocity drop with an unchanged systolic flow velocity. In this method, by measuring the blood flow velocity of middle cerebral artery (MCA), FVd could be used for CPP estimation and eventually ICP. CPP was calculated as MAP x FVd/mean flow velocity (FVm) + 14 mmHg, and ICP was estimated as the difference between MAP and CPP (nICP=MAP-CPP). (17) The CrCp method was similar to the FVd method, in which it calculated ICP based on CPP. Based on the Burton's model, CrCp was equal to the sum of ICP and vascular wall tension. The method indicated ABP threshold which was the limit where the brain microvascular blood pressure was unable to prevent the cessation of blood flow. The association with wall tension was able to provide information regarding the cerebral hemodynamics state of certain neurological problems. (17) The PI method explained changes in the morphology of TCD waveform due to cerebral vascular resistance changes, both quantitatively and qualitatively. It was calculated from the difference of systolic flow velocity (FVs) and FVd divided by FVm. This method was based on the observation that during the elevation of ICP, PI also increased. (18) All non-invasive evaluation using TCD was compared with an invasive ICP monitoring using an intraparenchymal probe. In the first study, Pearson correlation, Bland-Altman analysis, and ROC analysis for an ICP threshold of 17 mmHg were used to analyze the results. BB model, FVd, and CrCp methods showed moderate (R=0.39, 0.39, 0.35, respectively), but significant correlation ($p<0.05$) with measured ICP. However, PI had an insignificant correlation with measured ICP ($p>0.05$). Based on the Bland-Altman analysis, the BB model, PI, and CrCp had low bias compared to the FVd-based method. However, out of the evaluated parameters in the study, FVd had the best predictor value (AUC=0.70) compared to BB (AUC=0.66), CrCP (AUC=0.64), and PI (AUC=0.43). Analyzing each parameter independently showed that BB had the strongest relationship with measured ICP as a number, in which the average value of ICP was assessed during a single session, out of the four methods. The bias was close to zero and the 95% CI for prediction was small. The AUC result of BB was deemed reasonable with significant asymptotic probabilities for ROC analysis, indicating the model's ability to identify differences between normal and high ICP results. Both FVd and CrCp displayed biases significantly different from zero. CrCp also did not show significant asymptotic probabilities for AUC. Based on the 95% CI, FVd had the largest prediction error, whereas CrCp had the smallest. PI was considered to be a did not display any consistent statistical parameter to estimate ICP as to correlation with mean values, CI, and AUC. This study also averaged the best estimation for ICP as a number by combining the results from BB, FVd, and CrCp. PI was excluded from the combination as it did not yield any improvements in the estimation. In comparison to a single method, the new estimator was potentially more reliable since it took advantage of a multiple set of inputs. The study claimed that despite the limitation of TCD-based ICP methods, they may have a potential as an assessment tool in diagnosing intracranial hypertension in TBI patients. The best estimator out of the four methods were the BB model. Both FVd and CrCp indicated intermediate accuracy, while PI displayed a good correlation in time domain during variations of ICP. They suggested that a new method consisting of combining the average results of BB, FVd, CrCp would demonstrate a better statistical indicator to evaluate ICP.

The second study analyzed the same four parameters from the first study. Thirty-six adult TBI patients were analyzed retrospectively. (14) TCD monitoring was used to identify plateau waves of the patients, which were identified as spontaneous and sudden increases of ICP. Several noninvasive methods evaluated in this study were similar to the first study. The results in this study were divided into correlations in time, correlations between the ICP differences of the invasive and non-invasive methods, and ROC analysis. The correlations in time, representing the ability of a non-invasive method to replicate relative changes found in a direct ICP over time, showed good results among all methods (R>0.60). Significant correlations of the difference between the non-invasive and invasive ICP were shown by CrCp and BB model as opposed to PI and FVd. The best AUC value for predicting intracranial hypertension (ICP≥35 mmHg) was displayed by PI, compared to other parameters, albeit they still presented reasonable prediction abilities (AUC>0.70). Both CrCp and PI showed null values for negative predictive value and specificity, which showed that there was an underestimation of real pressure observed. All methods showed adequate positive predictive values (65, 69, 58, and 58% for BB, FVd, CrCp, and PI, respectively). The study was, however, limited by the use of radial artery ABP, which was zeroed at the level of the heart instead of the intracranial compartment.

In the third study, a total of 100 TBI patients were included. (15) Two experienced operators performed the TCD examination with a duplex USG machine to reduce interoperator variability. The method used in the study was the FVd-derived formula by Czonyka, et al. The findings in this study suggested that TCD-derived FVd was inadequate to accurately assess ICP noninvasively (AUC=0.345; 95% CI: 0.231-0.459) with 0% sensitivity and 74.4% specificity. Bland-Altman analysis comparing the invasive and non-invasive method showed that there were no any improvements in the subgroup comparisons. This study concluded that TCD-derived FVd should be used with caution and further studies were required to confirm the results.

The fourth study, conducted by Martin, et al evaluated PI as a predictor for elevated ICP in TBI patients. (16) Unlike the study done by Cardim, et al, this study only recruited severe TBI patients and further divided into two categories, patients with early high intracranial pressure (EHICP+) and patients without early high intracranial pressure (EHICP-). The results showed that PI didn't correlate with EHICP+ patients. Using maximal PI as a predictor for the occurrence of early high intracranial pressure (EHICP) after severe TBI was unfeasible (AUC=0.67, 95% CI: 0.52-0.81). This study claimed that early invasive monitoring of ICP still remained the best severe TBI-related outcome improvement strategy, however, further studies are still needed to confirm these results.

Discussion

Current types of commonly used ICP monitoring methods include intraventricular catheter (IVC), intraparenchymal monitor, subarachnoid screw (bolt), subdural catheter, and epidural catheter. These invasive methods, with IVC being the most invasive and accurate, are not without risks and complications, as with any other surgical procedures. Complications include infection, haemorrhage, malfunction or obstruction, and malposition. (19) Moreover, the method is expensive and not available in health centers with limited facilities. However, there are multiple promising methods of assessing ICP elevation non-invasively that are heavily being studied. We believe that currently there is yet to be a non-invasive ICP monitoring that could fully replace ICP monitoring. Nevertheless, non-invasive methods have a potential role in centers where invasive methods could not be performed. This is common in developing countries, especially in Indonesia where the number of rural hospitals with limited facilities are higher than tertiary hospitals. (20) In this systematic review, we discovered that studies attempting to evaluate non-invasive methods in determining increased ICP mainly utilized USG to measure ONSD and TCD to measure flow velocity using several methods.

ONSD to evaluate elevated ICP

This meta-analysis showed that ONSD measurement is capable to predict elevated ICP in adult TBI patients due to its high sensitivity and specificity as shown in **Figure 3**. The sROC plot in **Figure 4** also indicates excellent diagnostic values based on the AUC (0.92, 95% CI: 0.81-0.98). This study showed that ONSD can be used to predict elevated ICP, not just in TBI cases, but potentially in other disorders involving ICP elevation. ONSD has important clinical implications in patients with elevated ICP. Both the optic nerve and its sheath are cylindrical structures. The optic nerve is a white matter tract of the brain, also known as cranial nerve II. (18) The optic nerve sheath is the extension of the meningeal sheaths of the central nervous system, composed of dura mater, arachnoid mater, and pia mater, respectively from outward to inward. Thus, the optic nerve sheath also has subarachnoid space, in which the cerebrospinal fluid located. Hence, an elevation of intracranial pressure, therefore, will be directly transmitted to the subarachnoid space (SAS) surrounding the optic nerve and contained within its dural sheath, creating an enlargement in the optic nerve sheath diameter. (21) The results of this study have important clinical implication in neuro emergency care management. In previous studies, ONSD already proven to be independently associated with mortality and severity in neurology cases, such as traumatic brain injury and cerebrovascular accidents. (22) In one study, it is estimated that in each 1 mm increment in ONSD was associated with two-fold increment of hospital mortality. (23) Thus, early detection and continued monitoring of ICP is crucial to alleviate secondary injuries related to elevated ICP. There are multiple meta-analysis and systematic review publications regarding the use of ONSD to estimate ICP non-invasively. Robba, et al discovered the potential use of ONSD measured using USG for assessing intracranial hypertension when invasive alternatives are not available. (10) Evaluating studies focusing on adult TBI patients, Lee, et al claimed that measurement of the ONSD may be useful for predicting raised ICP. (24) Koziarz, et al performed a systematic review and meta-analysis which concluded that a normal sheath diameter measurement has a high sensitivity and a low negative likelihood ratio, whereas an elevated measurement, characterized by a high specificity and positive likelihood ratio, may indicate increased intracranial pressure. However, there is still a need for additional confirmatory tests. (25) A meta-analysis by Kim, et al concluded that ONSD can be used to rapidly detect ICP in adults. (26) The results of these previous reviews are similar to the findings in this study's meta-analysis.

TCD USG to evaluate elevated ICP

Even though both techniques utilized USG to evaluate ICP increase, TCD differs from ONSD as it allows for continuous monitoring of ICP overtime. TCD is fast, safe, and available in most centers. (15) However, even the use of TCD to evaluate ICP is still insufficiently investigated, even though many formulas have been created to estimate ICP using TCD. (14) Results from current studies are inconsistent and none seem to be adequate to re-

replace the invasive method. (15) Cardim, et al attempted to evaluate four different methods derived from TCD to assess ICP. They concluded that both FVd, BB, and CrCp have a potential, as opposed to PI, which was deemed unreliable. (13) Another study also discovered the weak correlation between PI and ICP. (27) A strong relation between PI and ICP was found in a prospective study investigating the relationship between ICP and TCD-derived PI in 67 patients with traumatic brain injury and 14 others with neurosurgical disorders by Bellner, et al. (28) The author suggested that the TCD-derived PI could be used as a guidance and as a tool in patients in neurointensive care. However, the findings were affected by external factors like MAP and the partial pressure of carbon dioxide (PaCO2). (29) The black box model was shown to be the best statistically as it showed the most consistent indicators for ICP prediction in the study by Cardim, et al. (13) To analyze the relationship and constant changes between the ABP flow velocity and ICP using the BB model, a dedicated software analysis is needed. (14) Even though the model has promising results to be used as a TCD parameter, it may not be applicable as a fast and easier alternative for physicians in limited centers to evaluate elevated ICP in TBI patients compared to other simpler methods. Multiple studies by Cardim, et al also found FVd-derived TCD to be promising. (13-15) As ICP elevates and cerebral perfusion pressure (CPP) correspondingly decreases, reductions of TCD flow velocity are obtained. Continuous elevations of ICP result first a decrease then followed by loss of diastolic flow, progression to an isolated systolic flow, and eventually to a fluctuating flow pattern in TCD waveform, which indicates the onset of intracranial circulatory arrest. (13) This method uses diastolic flow velocity for the estimation of CPP based on waveform analysis of blood flow velocity of MCA. In the first study by Cardim, et al, FVd was shown to have the best AUC value compared to other evaluated methods. (13) They performed another study in 2019 focusing on FVd alone, resulting differently. The findings suggested that TCD-derived FVd was insufficiently accurate to assess ICP noninvasively and should be used with caution. (15) CrCp demonstrated moderate but significant correlation with measured ICP in the study by Cardim, et al. (13) In the study also performed by Cardim, et al in 2017, it was discovered that CrCp, along with BB, had a better correlation to represent the non-invasive and invasive ICP differences. (14) Based on these varying results among the different methods, a new method based on averaging these parameters would be more promising to push TCD as a non-invasive replacement to evaluate ICP. (13)

Study limitations

The findings from the TCD-derived methods from multiple different publications vary in results. Additionally, the limited number of studies and several incomplete data hindered the possibility of performing a quantitative synthesis through meta-analysis. An updated systematic review and meta-analysis are needed in the future to determine the accuracy of the TCD-derived methods.

Conclusion

ONSD can be used as a parameter to evaluate the increase of ICP in TBI patients. BB model, FVd, and CrCp are potentially promising parameters of TCD ultrasonography for noninvasive ICP estimation as opposed to PI. However, more studies with complete accuracy results are required in the future to draw a conclusion from a meta-analysis as conclusions from the current available studies differ from one another with each method's respective superiorities and weaknesses.

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Declaration of conflicting interest

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Table 1. Included studies' characteristics

Study	Year	Study type	Diagnostic subgroup	Sample	Sensitivity	Specificity	AUC/AUROC
Amini (8)	2013	Prospective	ONSD	222	0.964	0.953	0.95
Maissan (30)	2015	Prospective	ONSD	18	0.94	0.98	0.99
Cardim (13)	2016	Prospective	TCD	40	N/A	N/A	BB: 0.66 FVd: 0.70 CrCp: 0.64 PI: 0.43 Avg: 0.73
Cardim (14)	2017	Retrospective	TCD	36	N/A	N/A	BB: 0.82 FVd: 0.77 CrCp: 0.79 PI: 0.81
Raffiz (31)	2017	Prospective	ONSD	41	ONSD 5.22 mm: 0.944, 5.47 mm: 0.944	ONSD 5.22 mm: 0.905, 5.47 mm: 0.952	ONSD: 0.964
Robba (32)	2017	Prospective	ONSD	64	0.866	0.826	0.91
Martin (16)	2019	Prospective	PI, ONSD	54	PI: 100% ONSD: 100%	N/A	PI: 0.67 ONSD: 0.73
Jie Du (33)	2019	Prospective	ONSD	52	0.80	0.793	0.87
Munawar (34)	2019	Prospective	ONSD	100	0.94	0.96	N/A
Cardim (15)	2019	Prospective	FVd	100	0.00	0.744	0.345

Legend: ONSD=optic nerve sheath diameter; TCD=transcranial Doppler; BB=black box model; FVd=diastolic flow velocity; CrCp=critical closing pressure; PI=pulsatility index; Avg=average; N/A=not available.

Figure 1. Flow diagram

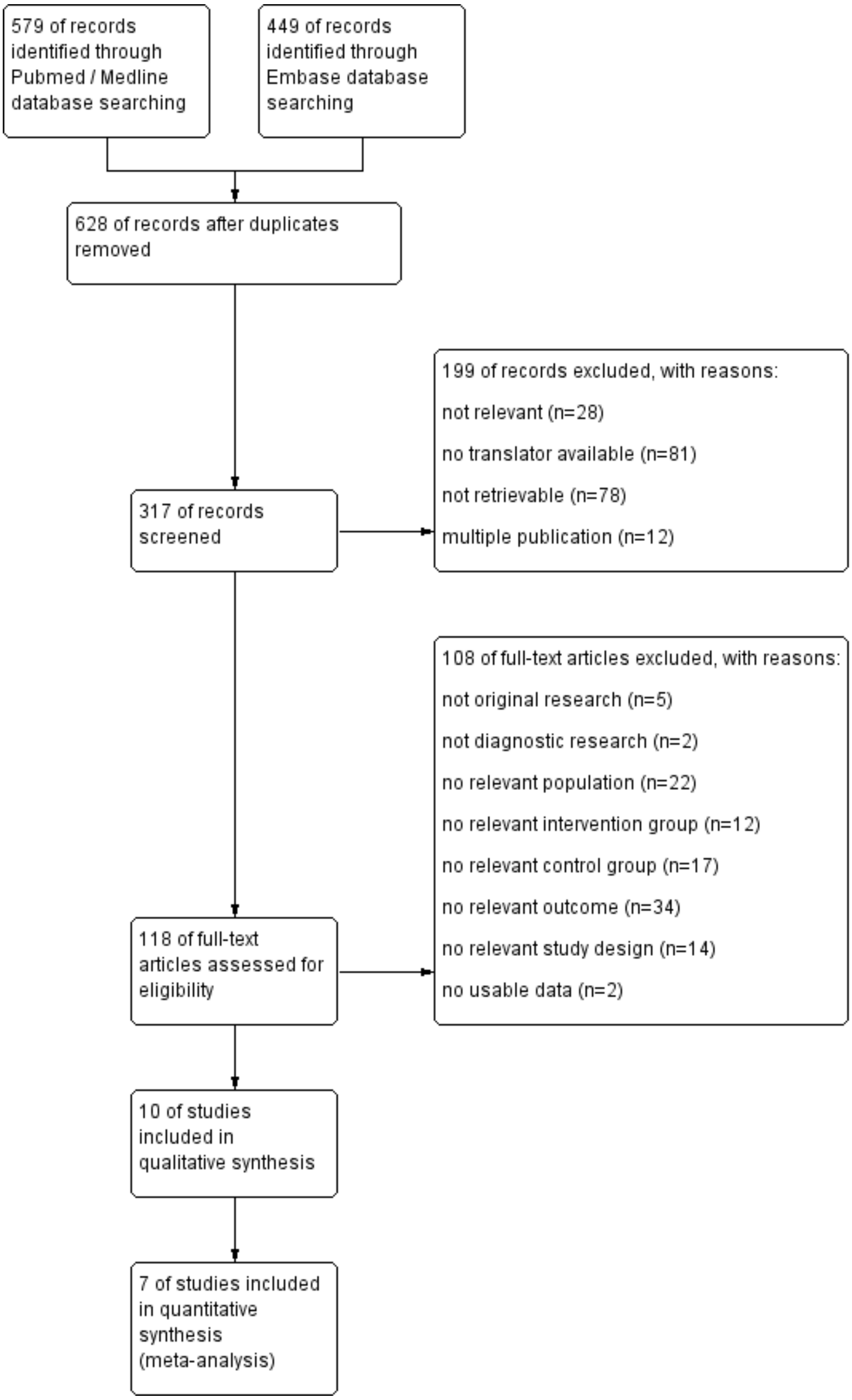


Figure 2. QUADAS-2 tool assessment of the included studies

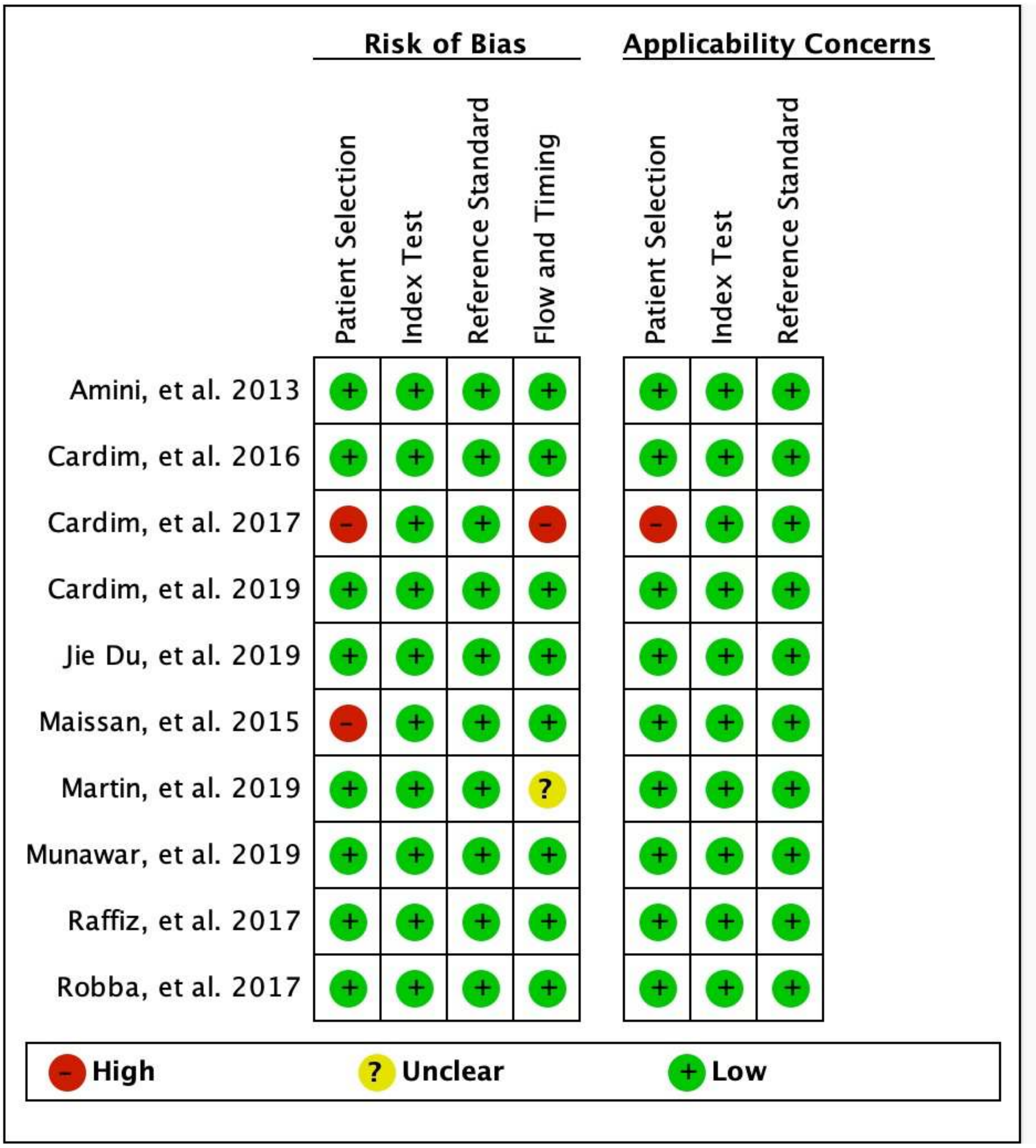
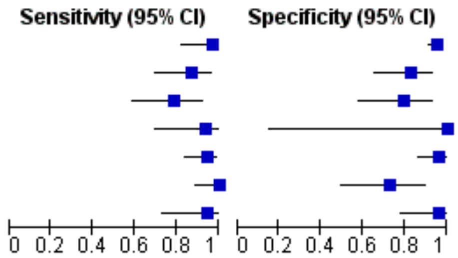


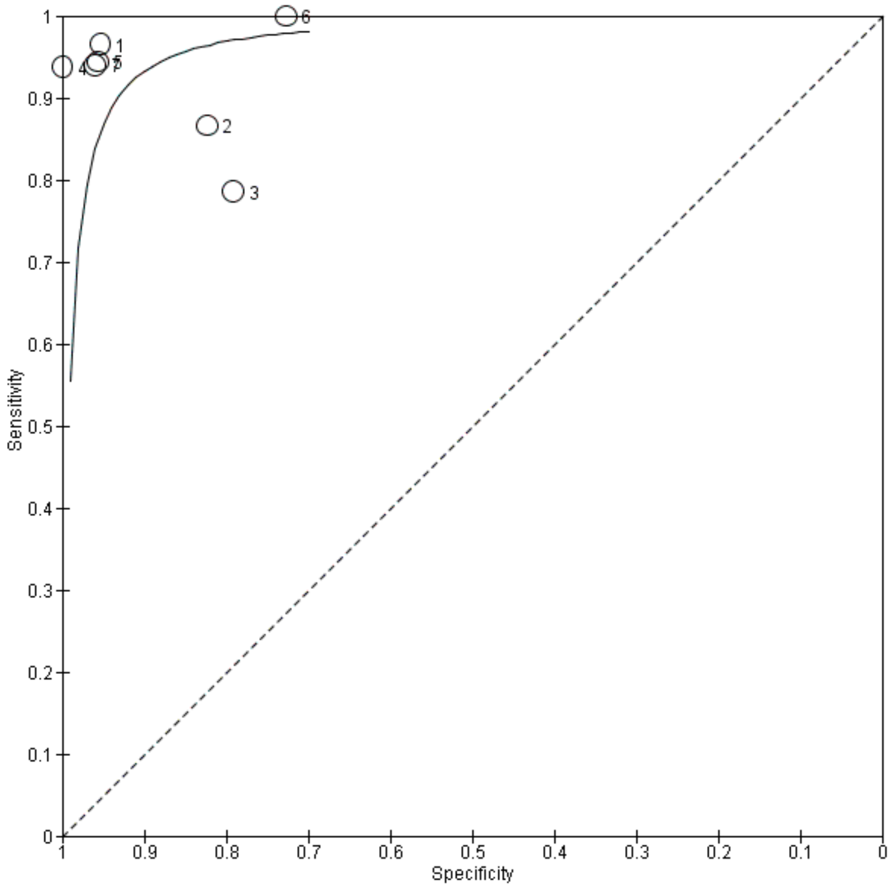
Figure 3. Sensitivity and specificity forest plot of the included studies evaluating ONSD

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Afshin 2013	28	9	1	184	0.97 [0.82, 1.00]	0.95 [0.91, 0.98]
Chiara 2017	26	6	4	28	0.87 [0.69, 0.96]	0.82 [0.65, 0.93]
Du 2019	22	5	6	19	0.79 [0.59, 0.92]	0.79 [0.58, 0.93]
Iscander 2015	15	0	1	2	0.94 [0.70, 1.00]	1.00 [0.16, 1.00]
Kamran 2019	47	2	3	48	0.94 [0.83, 0.99]	0.96 [0.86, 1.00]
Martin 2019	32	6	0	16	1.00 [0.89, 1.00]	0.73 [0.50, 0.89]
Raffiz 2016	17	1	1	22	0.94 [0.73, 1.00]	0.96 [0.78, 1.00]



Legend: ONSD= ONSD=optic nerve sheath diameter.

Figure 4. Summary ROC plot of the included studies evaluating ONSD



Legend: ROC=receiver operating characteristic; ONSD=optic nerve sheath diameter; O=nerve ultrasound; 1=Afshin 2013; 2=Chiara 2017; 3=Du 2019; 4=Iscander 2015; 5=Raffiz 2016; 6=Martin 2019; 7=Kamran 2019.

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