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Review

Diagnostic performance of optic nerve sheath diameter for predicting neurologic outcome in post-cardiac arrest patients: A systematic review and meta-analysis

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Abstract

Aims: We evaluated the diagnostic performance of optic nerve sheath diameter (ONSD) for prediction of neurologic outcome in post-cardiac arrest patients and relative prediction performance according to ONSD measurement modality.

Data sources: PubMed and EMBASE databases were searched for diagnostic accuracy studies that used ocular ultrasound or brain computed tomography (CT) for prediction of neurologic outcome. Bivariate modelling and hierarchical-summary and receiver-operating-characteristic modelling were performed to evaluate diagnostic performance. A pooled diagnostic odds ratio with a 95% confidence interval not including 1 was considered informative. Subgroup analysis was performed according to the modality (ocular US vs. brain CT). Methodologic quality was assessed using the Quality Assessment of Diagnostic Accuracy Studies–2 tool. We performed meta-regression analyses for heterogeneity exploration.

Results: Eight studies including 766 patients were included. For prediction of poor neurologic outcome, ONSD showed pooled sensitivity 0.41, pooled specificity 0.99, and area under the receiver-operating-characteristic curve 0.86. According to the pooled diagnostic odds ratios, ONSD was informative for prediction of neurologic outcome. In subgroup analysis, ONSD on ocular ultrasound showed significantly higher sensitivity and similar specificity than that on brain CT. On meta-regression analysis, locale, time to examination after return of spontaneous circulation, cause of cardiac arrest, and reference standard were sources of heterogeneity.

Conclusion: ONSD may be useful for predicting neurologic outcomes in post-cardiac arrest patients. Measuring the ONSD specifically using ocular ultrasound, application in patients with cardiac-origin cardiac arrest, and using the Glasgow-Pittsburgh Cerebral Performance Categories for neurologic outcome evaluation are recommended for more accurately predicting neurologic outcomes.

Keywords: Meta-analysis, Post-cardiac arrest, Neurologic outcome, Optic nerve sheath diameter, Ultrasonography, Computed tomography

Introduction

Hypoxic-ischemic is the most common cause of death after cardiac arrest (CA). Some post-CA patients may have a good neurological outcome with no need for aggressive interventions. In contrast, avoiding aggressive interventions is economically and morally advised in patients with poor neurological outcomes. Thus, prediction of the neurological outcome in resuscitated post-CA patients is crucial. However, this remains challenging.[1,2]

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Raised intracranial pressure (ICP) in post-CA patients is associated with poor neurological outcomes.[3–5] For this reason, raised ICP can cause secondary ischemic injury by decreasing cerebral blood flow, which would result in lessened cerebral oxygen delivery.[6,7] However, direct measurement of raised ICP requires an invasive procedure which involves insertion of an ICP monitoring catheter. Some findings in brain CT are traditionally used for indirectly detecting raised ICP such as the presence of a midline shift of >5 mm and basal cistern and sulcal effacement. None of these methods is considered reliable in predicting raised ICP.[8,9]

We here introduce the measurement of optic nerve-sheath diameter (ONSD) on brain computed tomography (CT) or ocular ultrasonography (US) as an indirect measurement of raised ICP, and demonstrate it to be a reliable and useful tool.[3,10] Because the optic nerve sheath connects to the dura mater that surrounds the brain and cerebrospinal fluid (CSF), a fluid-filled cavity is present between the optic nerve and the optic nerve sheath. Therefore, raised ICP will tend to inflate the sheath, leading to increases in the ONSD.[11,34,35]

So far, a few published meta-analyses[12–15] have demonstrated a relationship between ONSD as seen with US and raised ICP; however, these studies were not focused on post-CA patients and evaluated only the relationship between ONSD and raised ICP. Thus, they not only did not evaluate the relationship in post-CA patients, but also did not evaluate the relationship between ONSD and neurologic outcome. Therefore, the diagnostic performance of ONSD for predicting neurologic outcome should be fully explored and presented as high-level evidence through the quantitative synthesis of data from existing studies. Additionally, the pooling of results will be interesting because the published studies have used different modalities (ocular US vs. brain CT) and cut-off values.

This systematic review and meta-analysis aimed to assess the diagnostic performance of ONSD for predicting neurologic outcome in post-CA patients.

Methods

This meta-analysis followed the revised guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Accuracy Studies (PRISMA-DTA), statement.[16]

Data sources

The PubMed and EMBASE databases were searched up to November 1, 2018, to identify English-language studies on using ONSD to predict neurologic outcomes in post-CA patients. The search terms "optic nerve sheath diameter," "arrest," or "resuscitation" were combined with "diagnosis," or "prediction". The full search strategy is described in Supplemental Table 1. The bibliographies of the identified articles were screened to identify additional relevant studies. Two investigators screened the titles and abstracts for potential eligibility, and any disagreements were resolved through discussion.

Study selection

We included studies that fulfilled the following criteria: (1) patients with post-CA; (2) use of mean ONSD (average ONSD of left and right eyes) on ocular US or brain CT as the index test; (3) use of the Glasgow-Pittsburgh Cerebral Performance Categories (CPC), the Glasgow Outcome Scale (GOS), or the modified Rankin Scale (MRS) at discharge as the reference standard for neurologic outcome; (4) availability of sufficient information to reconstruct 2×2 contingency tables regarding sensitivity and specificity; and (5) original research article as the publication type.

The exclusion criteria were as follows: (1) case report or case series; (2) review articles, guidelines, consensus statements, letters, editorials, clinical trials, or conference abstracts; (3) studies not pertaining to the field of interest; (4) studies with insufficient information for reconstructing 2×2 contingency tables; and (5) not human study.

Quality assessment and data extraction

Two investigators independently extracted data on the patient and study characteristics. The same investigators evaluated the methodological quality using the Quality Assessment of Diagnostic Accuracy Studies-2 tool.[17] Any disagreements between the reviewers were resolved through discussion. A standardized form was used to extract data on (1) patient characteristics, including patient number, origin of cardiac arrest, place of cardiac arrest, mean age, age range, and sex; (2) study characteristics, including study origin, publication year, study design, reference standard, and blinding to reference standard; and (3) interpretative characteristics, including modality, interpreter, ONSD measurement method, and ONSD cut-off value.

We extracted the study outcomes to construct 2×2 tables (i.e., true-positive, true-negative, false-positive, and false-negative results). We calculated the 2×2 tables using the Bayesian method if only sensitivity and specificity were presented in an eligible study. In evaluating the diagnostic performance of ONSD, the result with the highest specificity was extracted. The determination of cut-off values assumed 100% specificity for prediction of poor neurological outcomes at discharge, to ensure that all patients with minimal chances of favourable neurological outcomes are identified.[18,19]

Data synthesis and analysis of the diagnostic performance

The patient demographic characteristics and extracted covariates were summarized using standard descriptive statistics. The studies were stratified using vertebral compression factor analysis where available. Continuous variables were expressed as means and 95% CIs, whereas categorical variables were expressed as frequencies or percentages unless stated otherwise.

We used a bivariate, random-effects model for analyzing and pooling the diagnostic performance measures (sensitivity and specificity) across studies. To derive summary estimates of the diagnostic performance, we plotted estimates of the observed sensitivities and specificities for each test on forest plots and on hierarchical-summary ROC (HSROC) curves derived from individual study results.[20–22] These results were plotted using HSROC curves with 95% CI and prediction regions. In addition, pooled sensitivities, specificities, diagnostic odds ratios (DORs), areas under the curve, and positive and negative likelihood ratios were calculated. Features showing a pooled DOR with a 95% CI not including 1 were considered to be informative.

Heterogeneity was determined using Cochran's Q test ($p < 0.05$ indicated the presence of heterogeneity) and the I^2 test (0–40%, possibly no heterogeneity; 30%–60%, moderate heterogeneity; 50%–90%, substantial heterogeneity; and 75%–100%, considerable heterogeneity).[23] When heterogeneity was noted, it was analyzed according to a "threshold effect" by visual assessment of the coupled forest plots of

sensitivity and specificity. A meta-analysis of diagnostic test accuracy studies was simultaneously used to evaluate pairs of outcomes (i.e., sensitivity and specificity).[20-22] Sensitivity and specificity are commonly inversely correlated and influenced by the threshold (cut-off) value. In addition, Spearman's correlation coefficient between the sensitivity and false-positive rate was calculated to determine any threshold effect; a coefficient >0.6 was considered to indicate a considerable threshold effect.[24] To test for publication bias, we omitted Deeks' funnel plot[25] of individual studies according to the method of PRISMA-DTA.

Subgroup analysis

We additionally performed subgroup analysis in which we compared the diagnostic performance of ONSD between determination by ocular US and determination by brain CT.

Meta-regression analysis

Meta-regression analyses were performed to investigate the potential causes of heterogeneity using several covariates, as follows: (1) locale (South Korea vs. countries other than South Korea), (2) study design (prospective vs. retrospective), (3) number of study centres (multi-centre vs. single centre), (4) number of patients (≥50 vs.<50), (5) proportion of CAs of cardiac origin (≥50% vs.<50%), (6) proportion of cases with poor neurologic outcomes (≥60% vs.<60%), (7) mean time to examination after return of spontaneous circulation (ROSC) (≤6 h vs.>6 h), (8) reference standard (CPC vs. GOS), and (9) cut-off value of the ONSD (≥6 mm vs.<6 mm).

All statistical analyses were performed by the same author, who had three years of experience in performing systematic reviews and meta-analyses. The statistical analyses were performed using the "midas'' and "metandi" modules in STATA software, version 10.0, and the "mada'' package in R software version 3.4.1. Results were considered statistically significant at a p-value of < 0.05.

Results

Literature

Fig. 1shows a flow diagram summarizing the literature search. During the initial search, 391 studies were identified. After removing 65 duplicates, we reviewed 326 titles and abstracts and excluded 317 studies for the following reasons: case reports, letters, editorials, and conference abstracts (n=109); review articles, guidelines, and consensus statements (n=58); not in the field of interest (n=131), and animal study (n=19). After reviewing the full text of nine eligible articles, we excluded one study for the following reasons: study did not provide sufficient information for reconstructing a 2 × 2 contingency table.[26] Ultimately, eight original research articles,[3,10,27–32] including a total of 766 post-CA patients, were included in the meta-analysis.

Characteristics of the studies

The patient characteristics are summarized in Table 1. The number of patients enrolled in the studies ranged from 17 to 329 (mean age, 51–74.8 years). The proportion of CAs of cardiac origin was 36.1%–91.8%. The studies and their interpretive characteristics are summarized in Tables 2 and 3, respectively. All studies performed consecutive recruitment with prospectively or retrospectively designed participants. Three studies[10,28,31] from eight journal articles used ocular US and five[3,27,29,30,32] used brain CT for evaluating ONSD. Seven studies[3,10,27–31] from eight journal articles measured the ONSD at a position 3 mm behind the sclera and in one,[32] location was not reported. All studies used the average ONSD of the right and left eyes for evaluating diagnostic performance. Seven studies[3,10,27–30,32] from eight articles used CPC and one[31] used GOS for evaluation of the neurologic outcome. No studies used MRS as the reference standard for neurologic outcome.

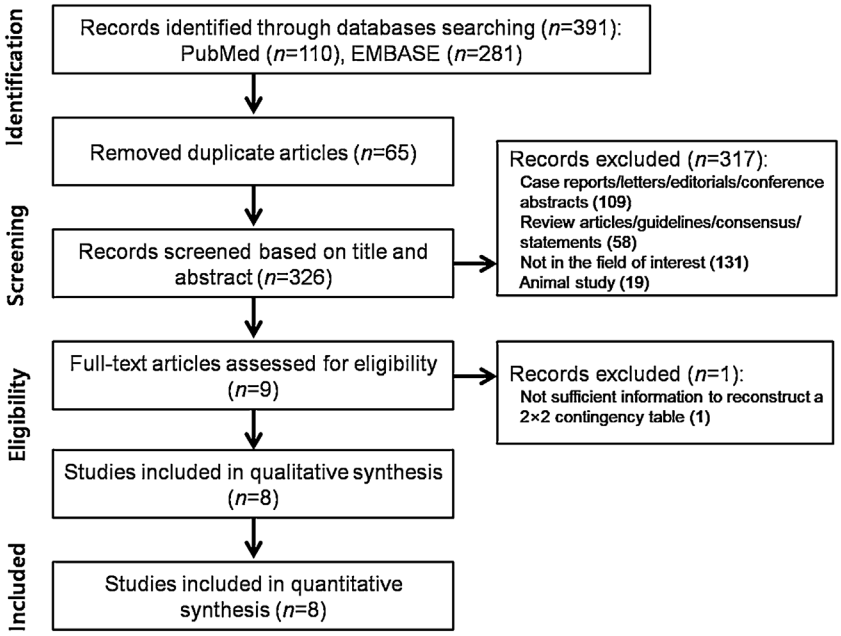

Fig. 1 – Flow diagram showing the study selection process for the meta-analysis.

Table 1 – The included patients' demographic characteristics.

Author	No. of patients	Percentage of cardiac origin CA (%)	No. of good/poor neurological outcomes	Place of cardiac arrest	TTM	ECMO	Time to examination after ROSC (h)	Mean age (years)	Age range (years)	No. of men/ women
Chae et al.[27]	119	56.3	45/74	NR	Yes	No	≤6	53.5	18–75	73/46
Chelly et al.[28]	36	36.1	19/17	OHCA, IHCA	Yes	No	≤24	58	45–69	25/11
Ertl et al.[10]	49	91.8	24/25	NR	Yes or no	No	≤11	65	20–96	35/14
Hwan Kimet al.[3]	91	38.5	23/68	NR	Yes or no	No	≤24	58.2	44–71	57/34
Lee et al.[29]	329	61.7	99/230	OHCA	Yes	No	≤2	58.6	18–87	230/99
Ryu et al.[30]	42	83.3	19/23	OHCA, IHCA	Yes or no	Yes	≤48	51	34–65	29/13
Ueda et al.[31]	17	64.7	6/11	OHCA, IHCA	Yes or no	No	12-72	74.8	55–92	9/8
You et al.[32]	83	36.1	28/55	NR	Yes	No	NR	52	42–68	59/24

No., number; CA, cardiac arrest; TTM target temperature management; ECMO, extracorporeal membrane oxygenation, OHCA, out-of-hospital cardiac arrest; IHCA in-hospital cardiac arrest; NR, not reported.

Table 2 – Characteristics of the included studies.

Author	Year	Locale	Study period	Study design	Neurologic outcome	Definition of poor neurologic outcome	Blinding
Chae et al.[27]	2016	South Korea	October 2009–December 2013	Retrospective, consecutive, single-centre	CPC	CPC≥3	Blinding
Chelly et al.[28]	2016	France	November 2011–September 2013	Prospective, consecutive, multi-centre	CPC	CPC 5	Blinding
Ertl et al.[10]	2018	Germany	September 2015-August 2017	Prospective, consecutive, multi-centre	CPC	CPC 5	Blinding
Hwan Kim et al.[3]	2014	South Korea	November 2012–October 2013	Prospective, consecutive, single-centre	CPC	CPC≥3	Blinding
Lee et al.[29]	2018	South Korea	November 2015–October 2016	Prospective, consecutive, multi-centre	CPC	CPC≥3	Blinding
Ryu et al.[30]	2017	South Korea	February 2005–December 2015	Retrospective, consecutive, single-centre	CPC	CPC≥3	Blinding
Ueda et al.[31]	2015	Japan	May 2013–September 2014	Retrospective, consecutive, single-centre	GOS	GOS<4	Not reported
You et al.[32]	2018	South Korea	January 2014–January 2018	Retrospective, consecutive, single-centre	CPC	CPC≥3	Blinding

CPC, Glasgow-Pittsburgh Cerebral Performance Categories; GOS, Glasgow Outcome Scale score.

Quality assessment

Fig. 2 shows the risk of bias and applicability concerns for the eight included studies. Overall, no studies were found to be seriously flawed according to the QUADAs-2 tool. All the studies satisfied ≥6 of the 7 items. Regarding patient selection, index test, and reference standard domains, all studies were considered to have a low risk of bias. Regarding the flow and timing domain, one study[31] was considered to have a risk of bias because the time to examination after ROSC varied over a wide range (12–72 h) and one[32] was considered to have an unclear risk of bias because the time to examination after ROSC was not reported. All studies exhibited low applicability to our research question in the patient selection, index test, and reference standard domains.

Diagnostic performance of ONSD for the prediction of poor or good neurologic outcome

The pooled sensitivity and specificity were 0.41 (95% CI, 0.20–0.67) and 0.99 (95% CI, 0.82–1.0), respectively. According to the pooled DORs with 95% CIs, ONSD was informative for prediction of the neurologic outcome (DOR, 83; 95% CI, 4–1525). The pooled positive and negative likelihood ratios were 49.0 (95% CI, 2.4–958.9) and 0.59

Table 3 – Interpretative characteristics of the included studies.

Author	Modality	Interpreter	ONSD measurement	Mean ONSD for good neurologic outcome (mm)	Mean ONSD for poor neurologic outcome (mm)	ONSD cut-off value (mm)
Chae et al.[27]	CT	Emergency physicians	3 mm behind the globe	5.6	5.8	7
Chelly et al.[28]	US	Intensive care unit physicians	3 mm behind the globe	6.5	7.2	6.7
Ertl et al.[10]	US	Neurologist	3 mm behind the globe	5.36	5.88	5.75
Hwan Kim et al.[3]	CT	Emergency physicians	3 mm behind the globe	5.57	6.29	6.21
Lee et al.[29]	CT	Emergency physicians	3 mm behind the globe	5.61	5.69	6.9
Ryu et al.[30]	CT	Cardiologists	3 mm behind the globe	5.57	6.07	6.69
Ueda et al.[31]	US	Emergency physicians or internal medicine physicians	3 mm behind the globe	5	6.1	5.4
You et al.[32]	CT	Emergency physician	Not reported	4.48	5.29	5.11

US, ultrasonography; CT, computed tomography; ONSD, optic nerve sheath diameter.

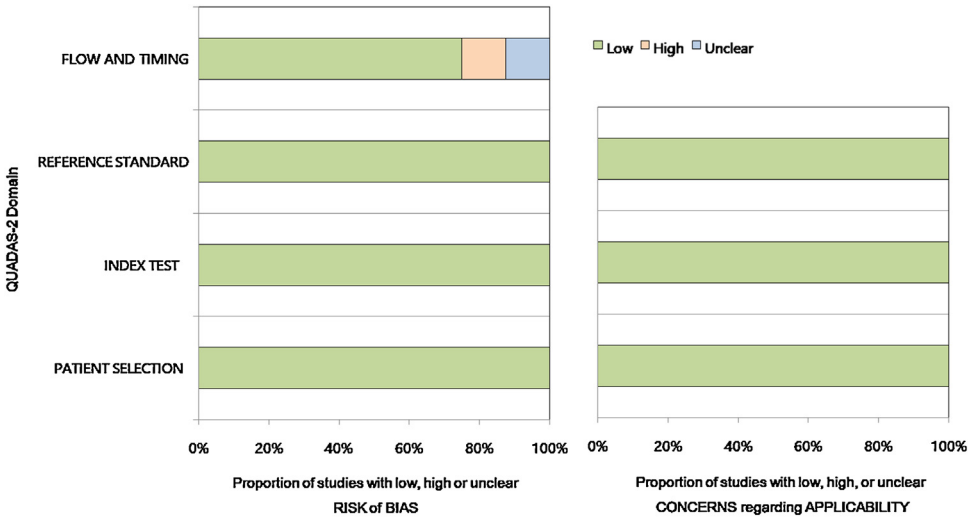

Fig. 2 – Grouped bar charts show the risk of bias (left) and the concerns re applicability (right) of the eight included studies using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS)-2 domains.

(95% CI, 0.39–0.90), respectively. The Q test revealed significant heterogeneity (Q = 55.364, $p < 0.001$). Sensitivity ($I^2 = 95.72\%$) and specificity ($I^2 = 94.60\%$) indicated considerable heterogeneity. A threshold effect was shown by visual analysis of the coupled forest plot of sensitivity and specificity (Fig. 3) as well as a corresponding correlation coefficient of 0.491 (95% CI, −0.295 to 0.815) between sensitivity and the false-positive rate. The area under the HSROC curve was 0.86 (95% CI, 0.83–0.89; Fig. 4).

Subgroup analysis: ocular US vs. Brain CT

For ocular US, the pooled sensitivity and specificity were 0.77 (95% CI, 0.53–1.00) and 0.98 (95% CI, 0.83–1.00), respectively. For brain CT, the pooled sensitivity and specificity were 0.24 (95% CI, 0.07–0.41) and 1.00 (95% CI, 0.98–1.00), respectively. The sensitivity was significantly higher on brain CT than on ocular US ($p < 0.01$). The specificity was not significantly higher on ocular US than on brain CT ($p = 0.80$).

Meta-regression analysis results

The results of the meta-regression analyses (Table 4) showed that the significant sources of heterogeneity in sensitivity were locale ($p = 0.01$) and the time to examination after ROSC ($p < 0.01$), with lower sensitivity reported in studies with South Korean patients and in studies with short-term examination after ROSC (≤6 h). The significant sources of heterogeneity in specificity were cause of cardiac arrest ($p = 0.01$) and reference standard ($p < 0.01$), with higher

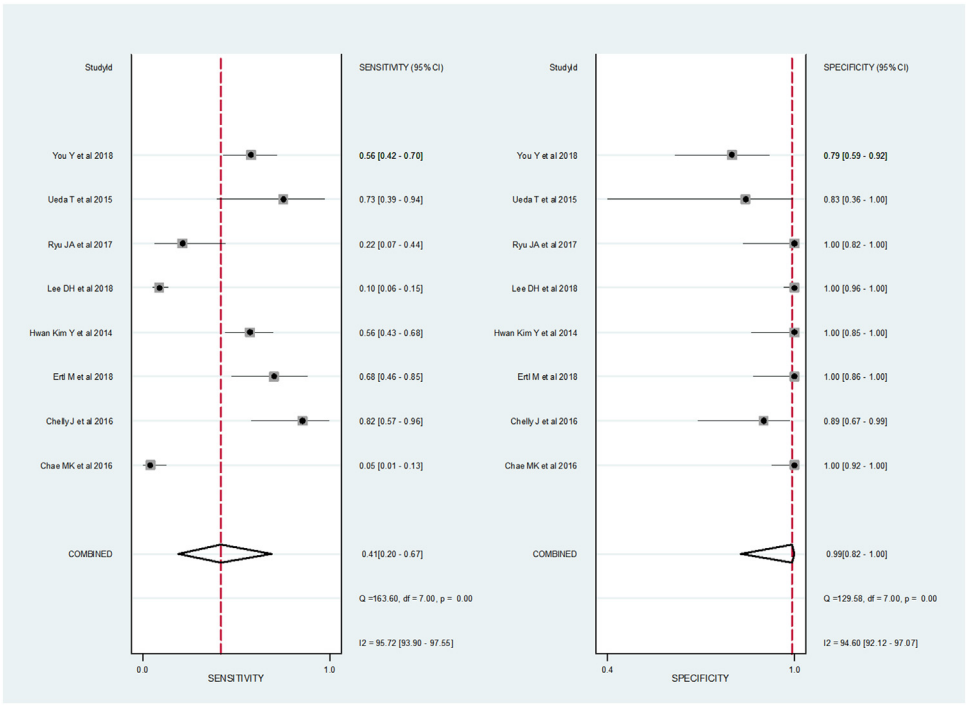

Fig. 3 – Coupled forest plots of pooled sensitivity and specificity of the optic nerve sheath diameter (ONSD) measurement for predicting poor or good outcomes in patients with post-cardiac arrest (CA). Dots in squares represent sensitivity and specificity. Horizontal lines represent the 95% confidence interval (CI) for each included study. The combined estimate ("Combined") is based on the random-effects model and is indicated using diamonds. Corresponding heterogeneities (I^2) with 95% CIs are provided in the bottom right corners: $I^2 = 100\% \times (Q\text{–}df)/Q$, where Q is Cochran's heterogeneity statistic and df is the degrees of freedom.

specificity reported in studies with a relatively high proportion (≥50%) of CAs of cardiac origin and having CPC as the reference standard, than in studies with a relatively low proportion (<50%) of cardiac origin and having GOS as the reference standard. Other factors, including study design, number of study centres, total patient number, proportion of patients with poor neurologic outcome, and cut-off value of ONSD were not significantly different (sensitivity, $p = 0.09$–0.61; specificity, $p = 0.18$–0.95)

Discussion

The present meta-analysis revealed ONSD to be useful for prediction of the neurologic outcome in post-CA patients (sensitivity, 41%; specificity, 99%). In subgroup analysis, ONSD on ocular US (sensitivity, 77%; specificity, 98%) showed significantly higher sensitivity and similar specificity vs. that on brain CT (sensitivity, 24%; specificity, 100%).

The mechanism of the ONSD enlargement in raised ICP is well known. The optic nerve and optic nerve sheath are cylindrical structures that connect the eyeball to the cranium directly, running posterior-centrally and relatively upward toward the optic chiasm. The optic nerve is surrounded by the optic nerve sheath, which is filled with CSF and directly communicates with the subarachnoid space. The ONSD reflects raised ICP due to inflation of the optic nerve sheath with CSF.[33,34]

Our results may have important clinical implications because critical care management of post-CA patients with good neurologic outcome focuses on prevention and prompt treatment of secondary insults.[1,2] In post-CA patients, raised ICP is correlated with neurological prognosis.[35,36] The finding of an enlarged ONSD in brain-injured patients is a predictor of raised ICP.[37] It was directly related to patients' mortality, indicating a 2.0–22.7 fold increased mortality vs. patients with a normal ONSD.[38,39] Thus, detecting ONSD enlargement as early as possible is crucial. It appears that ONSD measurement from ocular US or brain CT is advantageous because it provides a simple, effective, and real-time prediction method.

Our subgroup analysis revealed that ocular US was more useful than brain CT for prediction of neurologic outcome. We speculate that the brain CT was obtained parallel to the tuberculum sellae-occipital protuberance line, not parallel to the optic nerve. Consequently, the brain CT might demonstrate an oblique image rather than horizontal or it might not visualize the whole optic nerve sheath. In contrast, the ocular US was obtained with the imaging plane perpendicular to the optic nerve; thus, the ONSD might be more accurately determined with ocular US. We recommend that ONSD be measured with ocular US to diagnose raised ICP more accurately and thus better predict neurologic outcome.

Our meta-regression analysis revealed that the proportion of cardiac-origin CAs and the reference standard were sources of heterogeneity in terms of specificity. In particular, the pooled specificity of the ONSD was higher in studies with a relatively high proportion of cardiac-origin CAs and a CPC reference vs. those with a relatively low proportion of cardiac-origin CAs and a GOS reference. Therefore, for best specificity of the ONSD in predicting the neurologic outcome, patients with cardiac-origin CAs and use of CPC as the evaluation method for neurologic outcome are preferred.

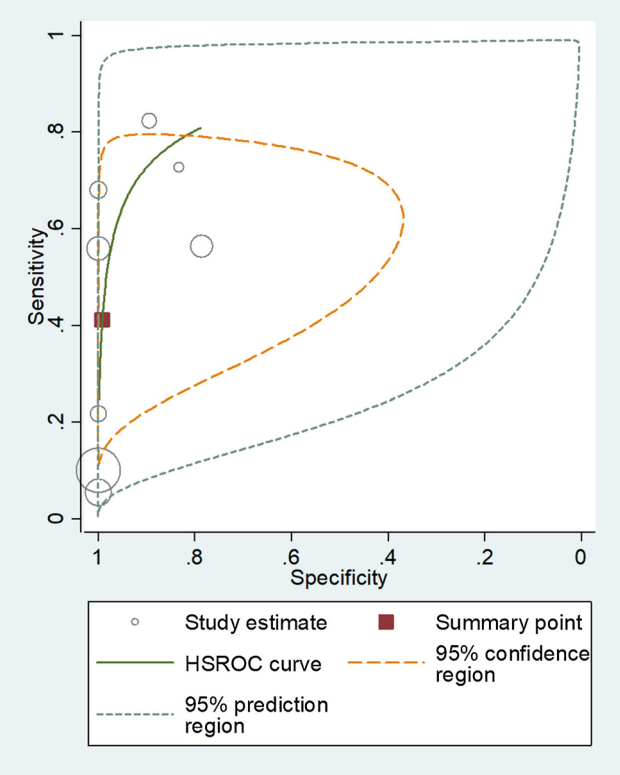

Fig. 4 – Hierarchical-summary, receiver operating characteristic curve of the diagnostic performance of ONSD measurement for predicting poor or good neurologic outcomes in patients with post-CA. The summary point (red box) indicates that the summary sensitivity was 0.41 and the summary specificity was 0.99. The 95% confidence region represents the 95% CIs of summary sensitivity and specificity, and the 95% prediction region represents the 95% CIs of sensitivity and specificity for each included study. The study estimates indicate the sensitivity and specificity estimated using the data from each study. The size of the marker is scaled according to the total number of patients in each study (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

The proposed cut off ONSDs for prediction showed variation. Most studies ($n=7$) used 5.4 mm or more for differentiating poor from good neurologic outcomes. It is certain that ONSD <5 mm indicates no significant enlargement of the ONSD and predicts a good neurologic outcome. Since we did not have the raw data from the studies, a single cut-off value for the ONSD could not be calculated based on this meta-analysis.

Four previous meta-analyses[12–15] have evaluated the diagnostic performance of ONSD for raised ICP, although those studies had several limitations. First, they only included acute neurological patients such as those with spontaneous haemorrhage, stroke, or tumour. From prognosis to treatment plan, patients with acute neurological disease are different from post-CA patients; thus, acute neurological patients must be considered a different category. Second, these authors evaluated only the usefulness of the sonographic ONSD, not of measurements by brain CT. Also, we find no investigation comparing the diagnostic performance of the ONSD between the ocular US and brain CT measurement methods. Third, the authors did not perform a thorough analysis of the potential sources of heterogeneity, not distinguishing between sensitivity and specificity for the covariate effects, which precluded any recommendations regarding methods to increase the diagnostic performance of ONSD. Finally, two of them[12,13] did not use a hierarchical model (e.g., the bivariate or HSROC model), which are recommended statistical tools for the meta-analysis of studies regarding diagnostic accuracy.[20,21]

The present study has several limitations. The first is the relatively small number of included studies. Nevertheless, we were able to draw several important conclusions regarding the diagnostic performance of ONSD and related factors (modality), which we believe provide a useful overview because we used broad search terms and only included easily accessible studies (i.e., published in English and available in the PubMed and EMBASE databases). The second limitation is that almost all the included studies revealed positive results, and that fact could be attributed to publication bias, which is impossible to quantify. Although we omitted Deeks' funnel plots according to the PRISMA-DTA guidelines, we observed a low probability of publication bias ($p=0.48$), which suggests that this factor did not undermine our results. The third limitation is the presence of methodological differences among the included studies; extensive meta-regression analysis revealed that these variables were significant sources of heterogeneity. This methodological diversity could have affected the pooled estimates, especially since the effect of patient management such as target temperature management and extracorporeal membrane oxygenation were not assessed in the meta-regression analysis due to a computational failure in the STATA program. Moreover, not all technical parameters were assessed here because not all studies reported values for gain, dynamic range, ocular-US mechanical index, kVP, mAs, and brain-CT slice thickness. Further prospective

Table 4 – Meta-regression analyses for potential sources of heterogeneity.

Covariate	No. of studies	Sensitivity (95% CI)	*p*-Value	Specificity (95% CI)	*p*-Value
Locale			**0.01**		0.46
South Korea	5	0.24 [0.07– 0.41]		1.00 [0.98–1.00]	
Countries other than South Korea	3	0.77 [0.53–1.00]		0.96 [0.83–1.00]	
Study design			0.37		0.72
Prospective	4	0.52 [0.16–0.87]		1.00 [0.98–1.00]	
Retrospective	4	0.30 [0.10–0.60]		0.97 [0.89–1.00]	
No. of study center			0.61		0.90
Multi-centre	3	0.50 [0.07–0.93]		1.00 [0.98–1.00]	
Single-centre	5	0.36 [0.06–0.67]		0.99 [0.93–1.00]	
No. of patients			0.09		0.60
≥50	4	0.25 [0.02–0.48]		1.00 [0.98–1.00]	
<50	4	0.63 [0.32–0.94]		0.99 [0.94–1.00]	
Proportion of cardiac origin cardiac arrest			0.10		**0.01**
≥50%	8	0.28 [0.05–0.50]		1.00 [0.99–1.00]	
<50%	4	0.65 [0.32–0.98]		0.93 [0.76–1.00]	
Proportion of poor neurologic outcomes			0.27		0.95
≥60%	5	0.32 [0.05–0.59]		0.99 [0.95–1.00]	
<60%	3	0.59 [0.19–0.98]		0.99 [0.97–1.00]	
Time to examination after ROSC			<**0.01**		0.94
≤6 h	2	0.07 [0.00–0.15]		1.00 [1.00–1.00]	
> 6 h	5	0.61 [0.44–0.78]		0.99 [0.95–1.00]	
Reference standard			0.23		**0.01**
CPC	7	0.37 [0.12–0.61]		0.99 [0.97–1.00]	
GOS	1	0.74 [0.17–1.00]		0.87 [0.25–1.00]	
Cut-off value of ONSD			0.11		0.18
≥6 mm	5	0.28 [0.05–0.51]		1.00 [0.99–1.00]	
<6 mm	3	0.65 [0.31–0.99]		0.96 [0.69–1.00]	

Boldface type indicates statistical significance ($p < 0.05$). CI, confidence interval; No., number; ONSD, optic nerve sheath diameter; ROSC, return of spontaneous circulation; CPC, Glasgow-Pittsburgh Cerebral Performance Categories; GOS, Glasgow Outcome Scale score.

studies with larger sample sizes and standardization of patient management are needed to establish the optimal parameters and cut-off value for ONSD.

Conclusion

The present meta-analysis revealed that ONSD may be a useful method for predicting neurologic outcomes in post-CA patients. For increased accuracy, measurement of the ONSD should be by ocular US, the method should be confined to patients with cardiac-origin CA, and CPC should be used for neurologic outcome evaluation. These rules will lead to more accurate differentiation of good and poor neurologic outcomes.

Conflict of interests

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Conflicts of interest

All authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

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REFERENCES

1. Kamps MJ, Horn J, Oddo M, et al. Prognostication of neurologic outcome in cardiac arrest patients after mild therapeutic hypothermia: a meta-analysis of the current literature. Intensive Care Med 2013;39:1671–82.

2. Sandroni C, Cavallaro F, Callaway CW, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 1: patients not treated with therapeutic hypothermia. Resuscitation 2013;84:1310–23.
3. Hwan Kim Y, Ho Lee J, Kun Hong C, et al. Feasibility of optic nerve sheath diameter measured on initial brain computed tomography as an early neurologic outcome predictor after cardiac arrest. Acad Emerg Med 2014;21:1121–8.
4. Iida K, Satoh H, Arita K, Nakahara T, Kurisu K, Ohtani M. Delayed hyperemia causing intracranial hypertension after cardiopulmonary resuscitation. Crit Care Med 1997;25:971–6.
5. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009;37:S186–202.
6. Balestreri M, Czosnyka M, Hutchinson P, et al. Impact of intracranial pressure and cerebral perfusion pressure on severe disability and mortality after head injury. Neurocrit Care 2006;4:8–13.
7. Treggiari MM, Schutz N, Yanez ND, Romand JA. Role of intracranial pressure values and patterns in predicting outcome in traumatic brain injury: a systematic review. Neurocrit Care 2007;6:104–12.
8. Hiler M, Czosnyka M, Hutchinson P, et al. Predictive value of initial computerized tomography scan, intracranial pressure, and state of autoregulation in patients with traumatic brain injury. J Neurosurg 2006;104:731–7.
9. Miller MT, Pasquale M, Kurek S, et al. Initial head computed tomographic scan characteristics have a linear relationship with initial intracranial pressure after trauma. J Trauma 2004;56:967–72 discussion 72-3.
10. Ertl M, Weber S, Hammel G, Schroeder C, Krogias C. Transorbital sonography for early prognostication of hypoxic-ischemic encephalopathy after cardiac arrest. J Neuroimaging 2018;28:542–8.
11. Helmke K, Hansen HC. Fundamentals of transorbital sonographic evaluation of optic nerve sheath expansion under intracranial hypertension II. Patient study. Pediatr Radiol 1996;26:706–10.
12. Dubourg J, Javouhey E, Geeraerts T, Messerer M, Kassai B. Ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure: a systematic review and meta-analysis. Intensive Care Med 2011;37:1059–68.
13. Kim SE, Hong EP, Kim HC, Lee SU, Jeon JP. Ultrasonographic optic nerve sheath diameter to detect increased intracranial pressure in adults: a meta-analysis. Acta Radiol 2019;60:221–9.
14. Ohle R, McIsaac SM, Woo MY, Perry JJ. Sonography of the optic nerve sheath diameter for detection of raised intracranial pressure compared to computed tomography: a systematic review and meta-analysis. J Ultrasound Med 2015;34:1285–94.
15. Robba C, Santori G, Czosnyka M, et al. Optic nerve sheath diameter measured sonographically as non-invasive estimator of intracranial pressure: a systematic review and meta-analysis. Intensive Care Med 2018;44:1284–94.
16. McInnes MDF, Moher D, Thombs BD, et al. Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies: the PRISMA-DTA statement. JAMA 2018;319:388–96.
17. 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;155:529–36.
18. Lee BK, Kim WY, Shin J, et al. Prognostic value of gray matter to white matter ratio in hypoxic and non-hypoxic cardiac arrest with non-cardiac etiology. Am J Emerg Med 2016;34:1583–8.
19. Na MK, Kim W, Lim TH, et al. Gray matter to white matter ratio for predicting neurological outcomes in patients treated with target temperature management after cardiac arrest: a systematic review and meta-analysis. Resuscitation 2018;132:21–8.
20. Kim KW, Lee J, Choi SH, Huh J, Park SH. Systematic review and meta-analysis of studies evaluating diagnostic test accuracy: a practical review for clinical researchers-part I. General guidance and tips. Korean J Radiol 2015;16:1175–87.
21. Lee J, Kim KW, Choi SH, Huh J, Park SH. 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;16:1188–96.
22. Suh CH, Park SH. Successful publication of systematic review and meta-analysis of studies evaluating diagnostic test accuracy. Korean J Radiol 2016;17:5–6.
23. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. Cochrane Collaboration; 2008.
24. Deville WL, Buntinx F, Bouter LM, et al. Conducting systematic reviews of diagnostic studies: didactic guidelines. BMC Med Res Methodol 2002;2:9.
25. 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;58:882–93.
26. Rush B, Wormsbecker A, Berger L, Wiskar K, Sekhon MS, Griesdale DE. Optic nerve sheath diameter on computed tomography not predictive of neurological status post-cardiac arrest. CJEM 2017;19:181–5.
27. Chae MK, Ko E, Lee JH, et al. Better prognostic value with combined optic nerve sheath diameter and grey-to-white matter ratio on initial brain computed tomography in post-cardiac arrest patients. Resuscitation 2016;104:40–5.
28. Chelly J, Deye N, Guichard JP, et al. The optic nerve sheath diameter as a useful tool for early prediction of outcome after cardiac arrest: a prospective pilot study. Resuscitation 2016;103:7–13.
29. Lee DH, Lee SH, Oh JH, et al. Optic nerve sheath diameter measured using early unenhanced brain computed tomography shows no correlation with neurological outcomes in patients undergoing targeted temperature management after cardiac arrest. Resuscitation 2018;128:144–50.
30. Ryu JA, Chung CR, Cho YH, et al. The association of findings on brain computed tomography with neurologic outcomes following extracorporeal cardiopulmonary resuscitation. Crit Care 2017;21:15.
31. Ueda T, Ishida E, Kojima Y, Yoshikawa S, Yonemoto H. Sonographic optic nerve sheath diameter: a simple and rapid tool to assess the neurologic prognosis after cardiac arrest. J Neuroimaging 2015;25:927–30.
32. You Y, Park J, Min J, et al. Relationship between time related serum albumin concentration, optic nerve sheath diameter, cerebrospinal fluid pressure, and neurological prognosis in cardiac arrest survivors. Resuscitation 2018;131:42–7.
33. Selhorst JB, Chen Y. The optic nerve. Semin Neurol 2009;29:29–35.
34. Sheth S, BFt Branstetter, Escott EJ. Appearance of normal cranial nerves on steady-state free precession MR images. Radiographics 2009;29:1045–55.
35. Gueugniaud PY, Garcia-Darennes F, Gaussorgues P, Bancalari G, Petit P, Robert D. Prognostic significance of early intracranial and cerebral perfusion pressures in post-cardiac arrest anoxic coma. Intensive Care Med 1991;17:392–8.
36. Naito H, Isotani E, Callaway CW, Hagioka S, Morimoto N. Intracranial pressure increases during rewarming period after mild therapeutic hypothermia in postcardiac arrest patients. Ther Hypothermia Temp Manag 2016;6:189–93.
37. Cardim D, Griesdale DE, Ainslie PN, et al. A comparison of non-invasive versus invasive measures of intracranial pressure in hypoxic ischaemic brain injury after cardiac arrest. Resuscitation 2019 pii: S0300-9572(18)30912-2. [Epub ahead of print].
38. Legrand A, Jeanjean P, Delanghe F, Peltier J, Lecat B, Dupont H. Estimation of optic nerve sheath diameter on an initial brain computed tomography scan can contribute prognostic information in traumatic brain injury patients. Crit Care 2013;17:R61.
39. Sekhon MS, McBeth P, Zou J, et al. Association between optic nerve sheath diameter and mortality in patients with severe traumatic brain injury. Neurocrit Care 2014;21:245–52.