Review Article

Prognostic Role of Optic Nerve Sheath Diameter for Neurological Outcomes in Post-Cardiac Arrest Patients: A Systematic Review and Meta-Analysis

Yan Wei Zhang, Sheng Zhang, Hui Gao, Chao Li, and Ming Xi Zhang

Emergency Department, Xingtai People’s Hospital, No. 16 Hongxing Road, Qiaodong Qu, Xingtai 054031, China

Correspondence should be addressed to Sheng Zhang; zs6600a@163.com

Received 21 June 2020; Revised 6 December 2020; Accepted 14 December 2020; Published 24 December 2020

Academic Editor: Chia-Te Kung

Copyright © 2020 Yan Wei Zhang et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Objective. The present study investigated whether optic nerve sheath diameter (ONSD) could be used to predict neurological outcomes in post-cardiac arrest (CA) patients.

Methods. We performed a comprehensive literature search in the Cochrane Library, ScienceDirect, PubMed, and Web of Science from inception to June 2020 for eligible articles. Stata 14.0 software was used to calculate the pooled odds ratios (ORs) and 95% confidence intervals (95% CIs), sensitivity, specificity, summary receiver operating characteristic (SROC) curve, subgroup analysis, sensitivity analysis, and publication bias.

Results. Eight studies involving 473 patients were considered eligible for this meta-analysis. The pooled result using a random-effects model showed that broadened ONSD is associated with poor neurological outcomes in post-CA patients (OR = 15.62, 95% CI: 5.50–44.34, \(P < 0.001\); \(I^2 = 58.4\%, P = 0.018\)), with a sensibility of 0.60 (95% CI: 0.45–0.73) and specificity of 0.94 (95% CI: 0.83–0.98). The area under the curve of the SROC curve for ONSD was 0.87 (95% CI: 0.84–0.90). Subgroup analysis revealed that sample size and time of ONSD measurement may be the source of heterogeneity. Sensitivity analysis demonstrated the stability of the results of this meta-analysis. No publication bias using Deeks’ funnel plot was noted across the studies (\(P = 0.23\)).

Conclusion. This meta-analysis confirmed that ONSD can be used to predict neurological outcomes in post-CA patients.

1. Introduction

Cardiac arrest (CA) is a health problem worldwide and is associated with high rates of mortality and morbidity. Even among those who attain return of spontaneous circulation (ROSC) after CA, in-hospital mortality remains over 50%, with a large proportion of survivors suffering permanent and severe neurological disability [1, 2]. Therefore, a valid prognostic index that can be employed early after ROSC must be developed.

Although invasive methods are considered the gold standard in intracranial pressure (ICP) monitoring, they are associated with significant risks, such as bleeding and infection [3]. The optic nerve is a part of the central nervous system and is surrounded by the dural sheath. Some reports [4–11] showed that the optic nerve sheath diameter (ONSD) is related to neurological outcomes in post-CA patients. However, the results are inconsistent. To address this discrepancy, the present study was aimed at assessing ONSD and neurological outcomes in post-CA patients.

2. Methods

2.1. Study Design. This meta-analysis was conducted on the basis of the checklists of the Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies statement [12]. All analyses were based on previous published studies; thus, no ethical approval and patient consent are required.

2.2. Literature Search. We performed a comprehensive literature search in the Cochrane Library, ScienceDirect, PubMed, and Web of Science from inception to June 2020.
for eligible articles that assessed the association between ONSD and neurological outcomes in post-CA patients. The search strategy included a combination of the following terms: optic nerve sheath diameter AND (cardiac arrest OR resuscitation). Additionally, we searched the reference lists of selected papers and systematic reviews for potentially relevant studies missed by the original search.

All the studies have to fulfill the following criteria: (1) clinical trials assessing the diagnostic accuracy of ONSD for neurological outcomes in post-CA patients and (2) studies with complete information for the assessment of odds ratios (ORs) with 95% confidence intervals (CIs). The exclusion criteria were as follows: (1) duplicated publications or data; (2) without sufficient calculable data; and (3) commentaries, case reports, editorials, review articles, letters to the editor, expert opinions, and animal experiments.

2.3. Data Extraction and Quality Assessment. Two reviewers used predefined data collection forms to extract data independently. Disagreements were solved through discussions and solicitation of opinions of a third researcher. The indispensible information extracted from all primary studies included the titles, first author’s name, publication year, study location, sample size, study design, cutoff value, time of ONSD measurement, method of ONSD measurement, and outcome parameters. ONSD was measured at a distance of 3 mm behind the eyeball, immediately below the sclera in a perpendicular vector in reference to the linear axis of the nerve [13].

The methodological quality of the included studies was assessed using the Revised Quality Assessment of Studies of Diagnostic Accuracy Included in Systematic Reviews- (QUADAS-2) tool [14]. Any disagreements were resolved by consensus, involving a third reviewer if necessary.

2.4. Statistical Analysis. Stata version 14.0 (StataCorp, College Station, Texas) was used in all statistical analyses. Pooled ORs and 95% CIs were used to assess the strength between the ORs and 95% CIs were used to assess the strength between

Records identified through database searching (n = 82) Additional records identified through other sources (n = 17)

Records after duplicates removed (n = 62)

Records screened (n = 37) Records excluded (n = 27)

Full-text articles assessed for eligibility (n = 10) Full-text articles excluded with reasons: Irrelevant topic (n = 1) Unavailable date (n = 1)

Studies included in qualitative synthesis (n = 8) Studies included in quantitative synthesis (meta-analysis) (n = 8)

Figure 1: Flow chart of the study selection process.

3. Results

3.1. Literature Search. Figure 1 presents the details regarding the screening process. A total of 99 potentially relevant records were initially identified by keyword search. Among them, 89 were excluded due to nonrelevance to the current study and/or duplication. Among 10 full studies, one was excluded for insufficient data, and one was excluded for focusing on an irrelevant topic. Finally, eight studies [4–11] were included in this meta-analysis.

3.2. Characteristics of the Included Studies. Table 1 shows the main characteristics of the included studies [4–11]. All these studies [4–11] were published between 2014 and 2019. Among them, six studies [4, 7–11] were based in Asia, and two [5, 6] were based in Europe. The sample sizes of the included studies ranged from 17 to 119. The cutoff values of ONSD were inconsistent across all studies, ranging from 4.90 to 6.69.

3.3. Quality Assessment. Before data analysis and synthesis, the quality of eligible studies was evaluated using the QUADAS-2 questionnaire (Figure 2). Six studies [4, 6, 8, 9, 11] were rated as having unclear risks of overall bias due to unmentioned consecutive patients, and six studies [4, 5, 8, 10, 11] were rated as having high risks of bias in the index test due to no preset specificity.

3.4. ONSD and Neurological Outcomes. Meta-analysis using the random-effects model showed that broadened ONSD was associated with poor neurological outcomes in post-CA patients (OR = 15.62, 95% CI: 5.50–44.34, P < 0.001; I² = 58.4%, P = 0.018; Figure 3), with a sensibility of 0.60 (95% CI: 0.45–0.73) and specificity of 0.94 (95% CI: 0.83–0.98). As shown in Figure 4, the area under the curve (AUC) of the summary receiver operating characteristic curve for ONSD was 0.87 (95% CI: 0.84–0.90).

3.5. Subgroup Analysis. Subgroup analysis was conducted on the basis of sample size (≤60 or >60), study design...
| Author (year) | Publication year | Country | Design      | Method of ONSD measurement | Time of ONSD measurement | Sample size | Cutoff (mm) | Poor prognosis | Good prognosis |
|--------------|-----------------|---------|-------------|--------------------------|-------------------------|-------------|------------|---------------|---------------|
| Chae et al. [4] | 2016 | Korea | Retrospective | CT | Within 6 h after ROSC | 119 | 5.9 | 5.8 (0.6) | 5.6 (0.5) |
| Chelly et al. [5] | 2016 | France | Prospective | Ultrasound | At 24 h after CA | 36 | 5.5 | 7.2 (6.8–7.4) | 6.5 (6.0–6.8) |
| Ertl et al. [6] | 2019 | Germany | Prospective | Ultrasound | At 24 h after CA | 49 | 5.75 | 5.88 ± 0.44 | 5.36 ± 0.43 |
| Kim et al. [7] | 2014 | Korea | Retrospective | CT | Within 24 h after ROSC | 91 | 6.21 | 6.29 ± 0.46 | 5.57 ± 0.30 |
| Park et al. [8] | 2019 | Korea | Prospective | Ultrasound | At 24 h after ROSC | 36 | 4.90 | 5.24 ± 0.56 | 3.78 ± 0.83 |
| Ryu et al. [9] | 2017 | Korea | Retrospective | CT | Within 24 h after ECPR | 42 | 6.69 | 6.07 (5.71–6.64) | 5.57 (5.14–5.98) |
| Ueda et al. [10] | 2015 | Japan | Retrospective | Ultrasound | At 12–72 h after CA | 17 | 5.4 | 6.1 (5.4–7.2) | 5.0 (4.4–6.1) |
| You et al. [11] | 2018 | Korea | Retrospective | Ultrasound | Before TTM | 83 | 5.11 | 5.29 (4.50–5.76) | 4.48 (4.27–5.09) |

CA: cardiac arrest; ECPR: extracorporeal cardiopulmonary resuscitation; NA: not available; ONSD: optic nerve sheath diameter; ROSC: return of spontaneous circulation; TTM: target temperature management.
(retrospective or prospective), cutoff value (≤5.5 or >5.5 mm), time of ONSD measurement (≤24 h after ROSC or >24 h after ROSC), and method of ONSD measurement (ultrasound or computed tomography), and the results indicated that these factors did not affect the predictive value of ONSD for neurological outcomes in post-CA patients (Table 2). In addition, subgroup analysis revealed that sample size and time of ONSD measurement may be the source of heterogeneity.

3.6. Sensitivity Analysis. As shown in Figure 5, the results of the sensitivity analysis did not show any significant impact from any single research study and confirmed the results of the overall performance of the ONSD.

3.7. Publication Bias. As shown in Figure 6, the P value for Deeks’ funnel plot asymmetry test was 0.23, indicating that no publication bias was observed in this meta-analysis.

4. Discussion

The prediction of neurological outcomes in comatose patients that were resuscitated is very important to reduce unnecessary costs, facilitate organ donation, and direct counseling with the patients’ families. In this meta-analysis,
we found that increased mean broadened ONSD was associated with poor neurological outcomes in post-CA patients with a sensitivity of 60%, specificity of 94%, and AUC of 0.87.

The variation in ICP is correlated with the ONSD because increased ICP is transmitted to the subarachnoid space surrounding the optic nerve, causing optic nerve sheath expansion. ONSD expansion can be compared to papilledema, but unlike papilledema, ONSD expansion occurs within seconds of an acute rise of ICP [15]. Some studies reported that a remarkable linear relationship exists between invasive ICP measurement and simultaneous ultrasonographic measurements of ONSD with a correlation coefficient of 0.42–0.78 [16–20].

However, the normative values for a normal ONSD and its associated factors remain unclear. Kim et al. [21] found that the ONSD of healthy adults was 4.11 mm with a range of 4.09–4.14 mm, whereas Bäuerle et al. [22] reported that the mean ONSD was 5.4 mm with a range of 4.3–7.6 mm. Recently, a meta-analysis included a total of 34 studies with cumulatively 2,450 patients without elevated ICP and reported that the pool of mean ONSD measurements was 4.78 mm (95% CI: 4.63–4.94) [23]. In addition, the ONSD was independently associated with eyeball transverse diameter rather than sex, body mass index, or height [21–23].

Despite relatively reliable sensitivity and specificity, a consistent ONSD cutoff to predict neurological outcomes in post-CA patients remains to be identified. Some of the included studies determined an optimal cutoff anywhere from 4.90 mm to 6.69 mm. A typical optic nerve sheath is less than 5 mm and is considered to be a good neurological outcome for post-CA patients. Future studies should establish the best cutoff values for ONSD that correlate with poor neurological outcome and that can be standardized for diverse subgroups categorized by age, temperature treatment, and condition [24].

We acknowledge several limitations to our large meta-analysis. First, our results are subject to limitations inherent to any meta-analysis on the basis of pooling of data from different studies with different inclusion criteria, different designs, variable follow-up duration, and different patient populations. Second, most studies included in the present meta-analysis were retrospective and had a relatively small

### Table: Studies and Results

| Study     | OR (95% CI)       | Weight |
|-----------|-------------------|--------|
| Chae 2016 | 3.15 (1.29, 7.71) | 20.90  |
| Chelly 2016 | 39.67 (5.79, 271.63) | 13.42 |
| Ertl 2019 | 102.29 (5.54, 1890.04) | 8.43 |
| Kim 2014  | 59.33 (3.46, 1016.61) | 8.72 |
| Park 2019 | 85.00 (7.97, 906.81) | 10.87 |
| Ryu 2017  | 11.59 (0.60, 224.68) | 8.25 |
| Ueda 2015 | 13.33 (1.07, 166.37) | 10.10 |
| You 2018  | 5.28 (1.74, 16.01)  | 19.30 |
| Overall (I² = 58.4%, p = 0.018) | 15.62 (5.50, 44.34) | 100.00 |

**Figure 3:** Forest plot of the association between optic nerve sheath diameter and neurological outcomes.

**Figure 4:** Summary receiver operating characteristic curve of the meta-analyzed sensitivity and specificity for optic nerve sheath diameter applications.
Table 2: Subgroup analysis.

|                                | N  | OR (95% CI)            | P       | I² (P value) |
|--------------------------------|----|------------------------|---------|--------------|
| Sample size                    |    |                        |         |              |
| <60                            | 5  | 36.76 (12.32–109.66)   | <0.001  | 0.0% (0.706) |
| ≥60                            | 3  | 5.71 (1.80–18.13)      | 0.003   | 54.7% (0.110)|
| Study design                   |    |                        |         |              |
| Retrospective                  | 5  | 5.95 (2.58–13.71)      | <0.001  | 24.8% (0.256)|
| Prospective                    | 3  | 61.40 (16.26–231.93)   | <0.001  | 0.0% (0.818) |
| Cutoff value                   |    |                        |         |              |
| ≤5.5 mm                        | 4  | 17.86 (4.59–69.54)     | <0.001  | 51.8% (0.101)|
| >5.5 mm                        | 4  | 16.61 (2.18–126.74)    | 0.007   | 68.5% (0.023)|
| Time of ONSD measurement       |    |                        |         |              |
| ≤24 h after ROSC               | 4  | 5.78 (2.18–15.28)      | <0.001  | 37.4% (0.188)|
| >24 h after ROSC               | 4  | 44.08 (13.60–142.86)   | <0.001  | 0.0% (0.680) |
| Method of ONSD measurement     |    |                        |         |              |
| Computed tomography            | 3  | 9.25 (1.28–66.70)      | <0.001  | 59.6% (0.084)|
| Ultrasound                     | 5  | 22.83 (6.22–83.88)     | <0.001  | 51.2% (0.085)|

CI: confidence intervals; OR: odd ratio; ROSC: return of spontaneous circulation.
sample size, with the potential for patient selection bias. Third, most studies originated from Asia, potentially limiting the generalizability to other healthcare systems.

In conclusion, our findings demonstrate that ONSD is a valuable and noninvasive marker to predict neurological outcomes in post-CA patients.

**Data Availability**

The data used to support the findings of this study are available from the corresponding author upon request.

**Conflicts of Interest**

The authors have declared that no competing interests exist.

**References**

[1] G. Lilja, N. Nielsen, H. Friberg et al., "Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33°C versus 36°C," *Circulation*, vol. 131, no. 15, pp. 1340–1349, 2015.

[2] G. S. Jun, J. G. Kim, H. Y. Choi et al., “A comparison of intravascular and surface cooling devices for targeted temperature management after out-of-hospital cardiac arrest: a nationwide observational study,” *Medicine*, vol. 98, no. 30, p. e16549, 2019.

[3] M. Harary, R. G. F. Dolmans, and W. B. Gormley, “Intracranial pressure monitoring-review and avenues for development,” *Sensors*, vol. 18, no. 2, p. 465, 2018.

[4] M. K. Chae, E. Ko, J. H. Lee 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*, vol. 104, pp. 40–45, 2016.

[5] J. Chelly, N. Deye, J. P. Guichard et al., “The optic nerve sheath diameter as a useful tool for early prediction of outcome after cardiac arrest: a prospective pilot study,” *Resuscitation*, vol. 103, pp. 7–13, 2016.

[6] M. Ertl, S. Weber, G. Hammel, C. Schroeder, and C. Krogias, “Transorbital sonography for early prognostication of hypoxic-ischemic encephalopathy after cardiac arrest,” *Journal of Neuroimaging*, vol. 28, no. 5, pp. 542–548, 2018.

[7] H. Y. Kim, H. J. Lee, K. C. Hong et al., "Feasibility of optic nerve sheath diameter measured on initial brain computed
tomography as an early neurologic outcome predictor after cardiac arrest,” *Academic Emergency Medicine*, vol. 21, no. 10, pp. 1121–1128, 2014.

[8] J. S. Park, Y. Cho, Y. You et al., “Optimal timing to measure optic nerve sheath diameter as a prognostic predictor in post-cardiac arrest patients treated with targeted temperature management,” *Resuscitation*, vol. 143, pp. 173–179, 2019.

[9] J. A. Ryu, C. R. Chung, Y. H. Cho et al., “The association of findings on brain computed tomography with neurologic outcomes following extracorporeal cardiopulmonary resuscitation,” *Critical Care*, vol. 21, no. 1, 2017.

[10] T. Ueda, E. Ishida, Y. Kojima, S. Yoshikawa, and H. Yonemoto, “Sonographic optic nerve sheath diameter: a simple and rapid tool to assess the neurologic prognosis after cardiac arrest,” *Journal of Neuroimaging*, vol. 25, no. 6, pp. 927–930, 2015.

[11] Y. You, J. Park, J. Min et al., “Relationship between time related serum albumin concentration, optic nerve sheath diameter, cerebrospinal fluid pressure, and neurological prognosis in cardiac arrest survivors,” *Resuscitation*, vol. 131, pp. 42–47, 2018.

[12] M. D. F. McInnes, D. Moher, B. D. Thombs et al., “Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies,” *JAMA*, vol. 319, no. 4, pp. 388–396, 2018.

[13] M. Ertl, F. Barinka, E. Torka et al., “Ocular color-coded sonography - a promising tool for neurologists and intensive care physicians,” *Ultraschall in der Medizin - European Journal of Ultrasound*, vol. 35, no. 5, pp. 422–431, 2014.

[14] P. F. Whiting, A. W. Rutjes, M. E. Westwood et al., “QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies,” *Annals of Internal Medicine*, vol. 155, no. 8, pp. 529–536, 2011.

[15] T. Geeraerts, J. Duranteau, and D. Benhamou, “Ocular sonography in patients with raised intracranial pressure: the papilloedema revisited,” *Critical care*, vol. 12, no. 3, 2008.

[16] H. C. Hansen and K. Helmke, “Validation of the optic nerve sheath response to changing cerebrospinal fluid pressure: ultrasound findings during intrathecal infusion tests,” *Journal of Neurosurgery*, vol. 87, no. 1, pp. 34–40, 1997.

[17] T. Soldatos, D. Karakitsos, K. Chatzimichail, M. Panathanasiou, A. Goulammos, and A. Karabinis, “Optic nerve sonography in the diagnostic evaluation of adult brain injury,” *Critical care*, vol. 12, no. 3, p. R67, 2008.

[18] H. H. Kimberly, S. Shah, K. Marill, and V. Noble, “Correlation of optic nerve sheath diameter with direct measurement of intracranial pressure,” *Academic Emergency Medicine*, vol. 15, no. 2, pp. 201–204, 2008.

[19] R. Moretti, B. Pizzi, F. Cassini, and N. Vivaldi, “Reliability of optic nerve ultrasound for the evaluation of patients with spontaneous intracranial hemorrhage,” *Neurocritical Care*, vol. 11, no. 3, pp. 406–410, 2009.

[20] J. P. Jeon, S. U. Lee, S. E. Kim et al., “Correlation of optic nerve sheath diameter with directly measured intracranial pressure in Korean adults using bedside ultrasonography,” *PLoS One*, vol. 12, no. 9, p. e0183170, 2017.

[21] D. H. Kim, J. S. Jun, and R. Kim, “Ultrasoundographic measurement of the optic nerve sheath diameter and its association with eyeball transverse diameter in 585 healthy volunteers,” *Scientific Reports*, vol. 7, no. 1, 2017.

[22] J. Bäuerle, P. Lochner, M. Kaps, and M. Nedelmann, “Intra- and interobserver reliability of sonographic assessment of the optic nerve sheath diameter in healthy adults,” *Journal of Neuroimaging*, vol. 22, no. 1, pp. 42–45, 2012.

[23] C. Schroeder, A. H. Katsanos, D. Richter, G. Tsivgoulis, R. Gold, and C. Krogias, “Quantification of optic nerve and sheath diameter by transorbital sonography: a systematic review and metaanalysis,” *Journal of Neuroimaging*, vol. 30, no. 2, pp. 165–174, 2020.

[24] J. Yu, J. Y. Park, D. H. Kim et al., “Dexmedetomidine attenuates the increase of ultrasonographic optic nerve sheath diameter as a surrogate for intracranial pressure in patients undergoing robot-assisted laparoscopic prostatectomy: a randomized double-blind controlled trial,” *Medicine*, vol. 98, no. 33, 2019.