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Article

Predictive Utility of Changes in Optic Nerve Sheath Diameter after Cardiac Arrest for Neurologic Outcomes

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Abstract:

Optic nerve sheath diameter (ONSD) can help predict the neurologic outcome of patients with post-cardiac arrest (CA) return of spontaneous circulation (ROSC). We aimed to investigate the effect of ONSD changes before and after CA on neurologic outcomes in patients with ROSC after CA using brain computed tomography (CT). The study included patients hospitalized after CA, who had undergone pre- and post-CA brain CT from January 2001 to September 2020. The patients were divided into good and poor neurologic outcome (GNO and PNO, respectively) groups based on the neurologic outcome at hospital discharge. We performed between-group comparisons of the amount and rate of ONSD changes on brain CT and calculated the area under the curve (AUC) to determine their predictive value for neurologic outcomes. Among the 96 enrolled patients, 25 had GNO. Compared to the GNO group, the PNO group showed significantly higher amount (0.30 vs. 0.63 mm; p=0.030) and rate of change (5.26 vs. 12.29 %; p=0.041). The AUC for predicting PNO was 0.64 (95% CI=0.53–0.73; p=0.04) and patients with a rate of ONSD change >27.2% had PNO with 100% specificity and positive predictive value. Hence, ONSD changes may predict neurologic outcomes in patients with post-CA ROSC.

Keywords: Heart arrest; optic nerve sheath diameter; Patient outcome assessment

1. Introduction

Ischemia/reperfusion cerebral injury after cardiac arrest (CA) may cause cerebral edema [1,2], This results in an increase in intracranial pressure (ICP) and contributes to poor neurologic outcomes in patients with post-CA return of spontaneous circulation (ROSC) [3,4]. In these survivors, there is a need for early detection of increased ICP and prediction of neurologic outcomes to facilitate appropriate post-resuscitation care [5]. This can help prioritize allocation of limited medical resources to patients with expected good neurologic outcomes. There have been studies on various predictive factors for post-CA neurologic outcomes, including neurologic examination of brainstem reflexes, electrophysiological tests, and serum biomarkers, such as neuron specific enolase and S-100B [6-8]. However, these factors have been recommended as prognostic factors at 72 post-CA hours [8-10]. Moreover, early brain computed tomography (CT) of patients with post-CA

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ROSC may play a crucial role as a prognostic predictor. Further, the American Heart Association guidelines recommend early post-CA brain CT scans and confirm that a decrease in the grey-to white matter ratio (GWR) can help predict neurologic outcome [10-13]. Additionally, there have been studies regarding the role of optic nerve sheath diameter (ONSD) on brain CT for predicting neurologic outcomes in post-CA survivors [14-16].

Previous studies have shown the potential role of ONSD on brain CT as a useful tool for non-invasive ICP measurement [17,18]. Additionally, recent studies have demonstrated that the ONSD on brain CT is useful for early neurologic outcome prediction through evaluation of increased ICP in patients with post-CA ROSC [15,19]. A recent meta-analysis confirmed the utility of ONSD as a prognostic factor for neurologic outcomes in post-CA patients [20]. However, most of the studies included in the meta-analysis indicated that sole use of ONSD had limited predictive utility for prognosis. Furthermore, all these studies only measured the post-CA ONSD values without considering changes in an individual.

This study aimed to assess differences between pre- and post-CA ONSD in patients with ROSC after CA using brain CT imaging. Additionally, we aimed to investigate the impact of the amount and rate of post-CA ONSD changes on the neurologic outcome at discharge.

2. Materials and Methods

2.1 Study design and population

This retrospective observational cohort study investigated brain CT scans of patients hospitalized after CA at a single university-affiliated hospital in Korea between January 2001 and September 2020. This study was approved by the Institutional Review Board of Hanyang University Guri Hospital (IRB No. GURI 2020-12-008), which waived the requirement of informed consent due to the retrospective nature of the study.

We included adult patients hospitalized after CA who underwent pre- and post-CA brain CT. The exclusion criteria were as follows: (1) being transferred to another hospital after ROSC, (2) age < 19 years, (3) having traumatic/non-traumatic brain hemorrhage or brain tumor, (4) a history of ophthalmological disorders or surgeries that could affect ONSD, and (5) having the most recent pre-CA brain CT performed at an age < 19 years. Finally, eligible patients were divided into the good neurologic outcome (GNO) and poor neurologic outcome (PNO) groups based on the neurologic outcome at discharge; subsequently, we measured ONSD changes and performed between-group analysis. The primary outcome was the association between ONSD changes and the neurologic outcomes of patients hospitalized after CA.

2.2 Data collection

We retrospectively collected the following data from electronic medical records: age, gender, comorbidities (hypertension, diabetes, myocardial infarction), etiology (cardiac, respiratory), location of CA, whether the CA was witnessed, bystander CPR, first monitored shockable rhythm, CA duration including the no-flow (time between CA and CPR initiation) and low-flow time (time between active CPR and ROSC), and administered targeted temperature management (TTM). Based on the medical records, we determined the interval between the latest pre-CA brain CT and ROSC (month), which was termed as 'CT to ROSC', and between ROSC and post-CA brain CT (minute), which was termed as 'ROSC to CT'. Additionally, we collected data regarding the neurologic outcomes on discharge using the Glasgow-Pittsburgh Cerebral Performance Categories (CPC). Based on the CPC scale, we defined GNO and PNO as a CPC of 1 or 2 and 3–5, respectively.

2.3 ONSD measurements using brain CT

Brain CT scans were performed based on standard protocols using non-contrast 4-mm contiguous slices parallel to the orbital floor from the skull base to the vertex. The pre-CA and post-CA ONSDs were bilaterally measured at 3 mm behind the globe on brain

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CT using the picture archiving and communication system (PACS) ruler tool (PiView STAR, INFINITT, Seoul, Korea). Images were magnified at 450% and changed to the "mediastinum" window (window width: 440; window level: 45) using the PACS tool. The ONSDs of the right and left eyes were averaged to obtain the mean value. All measurements were performed by emergency physicians blinded to the patient information, including the neurologic outcome. Additionally, we calculated the amount and rate of ONSD change. We defined the amount of change as the difference between the pre-CA and post-CA ONSD. Moreover, the rate of ONSD change was calculated as follows:

$$Rate\ of\ ONSD\ change = \left(\frac{Post{-}CA\ ONSD - Pre{-}CA\ ONSD}{Pre{-}CA\ ONSD}\right) x\ 100$$

We used the following three CT equipment: SOMATOM Sensation 16, SOMATOM Definition DS, and SOMATOM Definition Edge (Siemens Healthcare, Erlangen, Germany). The following parameters were used: 120 kVp, 250-500 mAs, and 4 to 4.5-mm slice thickness. All CT images were stored as the Digital Imaging and Communication in Medicine format in the PACS.

2.4 Sample size

We calculated the sample size based on a pilot study on 33 participants using G*Power (3.1.9.6; Heine Heinrich University, Düsseldorf, German). The mean ONSD of patients with GNO and PNO were 4.75 ± 1.45 mm and 5.63 ± 1.85 mm, respectively. The required sample size was calculated as 90 participants (effect size: 0.53, a-error: 0.05, power: 0.8); finally, considering a 10% drop-out rate, 99 participants were required.

2.5 Statistical analysis

Continuous and categorical variables were reported as the median with interquartile range (IQR) and number with percentages, respectively. Normally distributed variables were analyzed using the Mann-Whitney U-test and Wilcoxon rank-sum test while non-normally distributed variables were analyzed using the Shapiro-Wilk test. Chi-square tests or Fisher's exact test were used to analyze categorical variables. Statistical significance was set at $P < 0.05$. Multivariable analysis with logistic regression was used to determine the risk factors for poor neurologic outcomes with adjustment for confounding variables found significant on univariate analysis. Variables with $p < 0.2$ on univariate analysis with the rate of ONSD change were included in the multivariable analysis. Further, the Hosmer-Lemeshow test was used to confirm the logistic model calibrations. The predictive performance of the main outcome was assessed using the area under the receiver operating characteristic curve ([ROC] AUC) of the sensitivity over 1 − specificity. Results were obtained using the Youden index and presented as a 95% confidence interval (CI) of AUC with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). ROC analysis was performed using MedCalc Statistical Software (version 17.2, MedCalc Software, Ostend, Belgium) while the other statistical analyses were performed using SPSS software (version 25.0, IBM, Armonk, NY).

3. Results

3.1 Baseline characteristics

Among 145 post-CA survivors who underwent brain CT before and after CA, 49 patients were excluded as follows: 40 patients who were transferred to another hospital, seven patients with intracranial or subarachnoid hemorrhage, one patient with a brain tumor, and one patient aged ≤ 18 years. Finally, we enrolled 96 patients and allocated them to the GNO (n = 25, 26.0%) and PNO groups (n = 71, 74.0%) (Figure 1).

Table 1 summarizes the demographic and clinical characteristics. The median age of the included patients was 70 (IQR: 58–79) years with 56.3% being male. The GNO group

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was significantly younger than the PNO group. Moreover, the GNO group showed a significantly higher frequency of cardiac etiology and shockable rhythm, as well as a shorter no-flow and low-flow time, than the PNO group. Contrastingly, out-of-hospital cardiac arrest was more frequent in the PNO group.

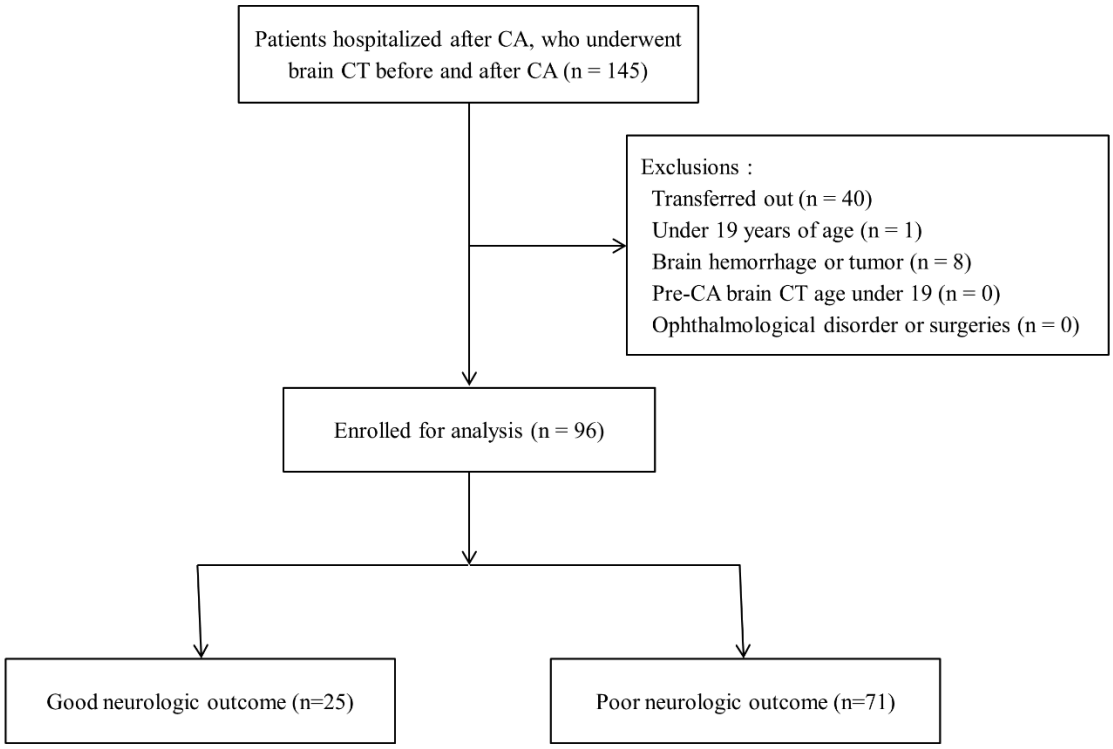

Figure 1. Flow chart of the study process.

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Table 1. Baseline characteristics of enrolled patients.

	Total (n = 96)	GNO (n = 25)	PNO (n = 71)	*p*-value
Demographics				
Age, year	70 (58-79)	60 (52-67)	75 (61-80)	< 0.001
Gender, male	54 (56.3)	15 (60.0)	39 (54.9)	0.660
Comorbidities				
HTN	52 (54.2)	14 (56.0)	38 (53.5)	0.831
DM	37 (38.5)	6 (24.0)	31 (43.7)	0.082
MI	16 (16.7)	4 (16.0)	12 (16.9)	1.000
Etiology				
Cardiac	23 (24.0)	14 (56.0)	9 (12.7)	< 0.001
Respiratory	40 (41.7)	8 (32.0)	32 (45.1)	0.254
Others	33 (34.4)	3 (12.0)	30 (42.3)	0.006
Resuscitation				
Location of arrest, OHCA	76 (79.2)	16 (64.0)	60 (84.5)	0.030
Witnessed	72 (75.0)	19 (76.0)	53 (74.6)	0.893
Bystander CPR	61 (63.5)	18 (72.0)	43 (60.6)	0.307
Shockable rhythm	11 (11.5)	8 (32.0)	3 (4.2)	0.001
No-flow time, min	10 (0-21)	4 (0-9)	11 (2-25)	0.003
Low-flow time, min	10 (6-16)	6 (3-10)	11 (8-18)	0.004
TTM	6 (6.3)	3 (12.0)	3 (4.2)	0.180
CT to ROSC interval*, month	27 (6-55)	40 (6-55)	23 (6-53)	0.780
ROSC to CT interval†, min	104 (51-171)	60 (33-118)	113 (60-200)	0.017

Abbreviations: GNO = good neurologic outcome; PNO = poor neurologic outcome; HTN = hypertension; DM = diabetes mellitus; MI = myocardial infarction; OHCA = out-of-hospital cardiac arrest; CPR = cardiopulmonary resuscitation; TTM = targeted temperature management; CT = computed Tomography; ROSC = return of spontaneous circulation.

* The interval between the latest pre-CA brain CT and ROSC.

† The interval between ROSC and post-CA brain CT.

3.2 Comparison of pre-CA and post-CA ONSDs

In both groups, the post-CA ONSD was significantly higher than the pre-CA ONSD (Figure 2). The pre-CA ONSD and post-CA ONSD were 5.06 and 5.50 mm, respectively (p < 0.001) in the GNO group and 5.07 and 5.72 mm, respectively, (p = 0.001) in the PNO group (Supplemental Table 1).

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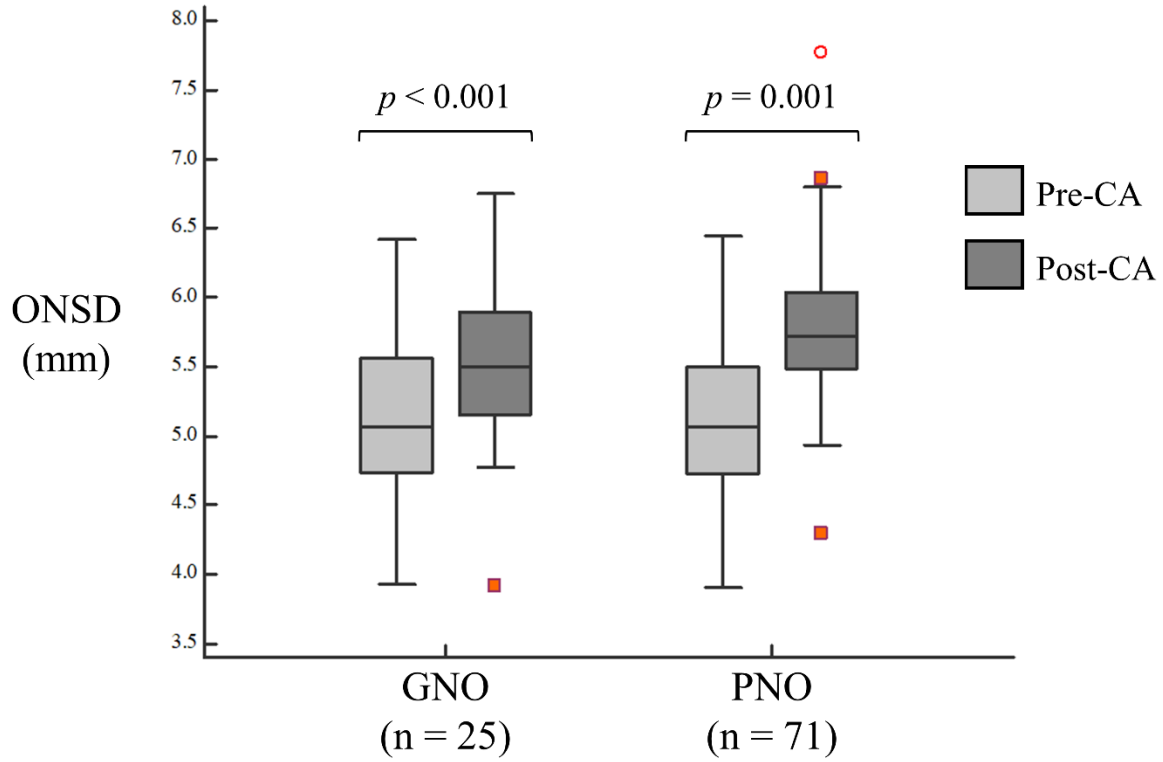

Figure 2. Comparison of the optic nerve sheath diameter between pre-cardiac arrest and post-cardiac arrest in good and poor neurologic outcome group.

3.3 The association between ONSD changes and neurologic outcomes

Table 2 presents the between-group comparisons of the amount and rate of ONSD changes. There were no significant between-group differences in pre-CA ONSD (5.06 vs. 5.07 mm, $p = 0.967$) and post-CA ONSD (5.50 vs. 5.72 mm, $p = 0.075$). However, the amount of ONSD change in the GNO group was significantly lower than that in the PNO group (0.30 vs. 0.63 mm, $p = 0.030$). Additionally, the rate of ONSD change in the GNO group was significantly lower than that in the PNO group (5.26 vs. 12.29 %, $p = 0.041$). Multivariable analysis revealed no independent association between the rate of ONSD change and poor neurologic outcome (OR = 1.075; 95% CI = 0.990-1.167; $p = 0.084$) (Table 3).

Table 2. The comparisons of the amount and rate of ONSD changes between good and poor neurologic outcome.

	Total (n = 96)	GNO (n = 25)	PNO (n = 71)	p-value
Optic nerve sheath diameter				
Pre-CA, mm	5.07 (4.73 - 5.52)	5.06 (4.76-5.53)	5.07 (4.73-5.52)	0.967
Post-CA, mm	5.66 (5.41-6.01)	5.50 (5.16-5.88)	5.72 (5.49-6.04)	0.075
Optic nerve sheath diameter changes between pre-CA and post-CA				
Amount of change, mm	0.57 (0.25-0.84)	0.30 (0.18-0.65)	0.63 (0.32-0.87)	0.030
Rate of change, %	11.10 (4.70-17.21)	5.26 (3.85-14.15)	12.29 (5.83-18.74)	0.041

Abbreviations: GNO = good neurologic outcome; PNO = poor neurologic outcome; CA = cardiac arrest.

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Table 3. Multivariable logistic regression analysis for poor neurologic outcome with baseline variables and rate of optic nerve sheath diameter change.

Variables	Adjusted OR (95% CI)	p-value
Age, year	1.115 (1.031-1.206)	0.006
DM	3.358 (0.636-17.733)	0.154
Shockable rhythm	0.084 (0.008-0.911)	0.042
No-flow time, min	1.113 (1.003-1.235)	0.043
Low-flow time, min	1.123 (1.024-1.231)	0.013
TTM	0.119 (0.008-1.794)	0.124
Location of arrest, OHCA	0.833 (0.115-6.014)	0.856
ROSC to CT interval*, min	0.999 (0.999-1.000)	0.086
Etiology, cardiac	0.080 (0.012-0.558)	0.011
Rate of change, %	1.075 (0.990-1.167)	0.084

Abbreviations: OR = odds ratio; DM = diabetes mellitus; TTM = targeted temperature management; OHCA = out-of-hospital cardiac arrest; ROSC = return of spontaneous circulation; CT = computed tomography.

* The interval between ROSC and post-CA brain CT.

3.4 Diagnostic value of ONSD changes for predicting the neurologic outcome

The AUC for predicting PNO was 0.64 (95% CI = 0.53–0.73; $p = 0.04$) in the ROC curve for the rate of ONSD change (Figure 3). Patients with a rate of ONSD change > 27.2% had PNO with a specificity and PPV of 100%. GNO could be predicted using a cut-off value of ≤ 5.83% in the ROC curve for the rate of ONSD change, with a sensitivity and specificity of 60.0% and 76.06%, respectively; the PPV and NPV were 46.9% and 84.4%, respectively (Table 4).

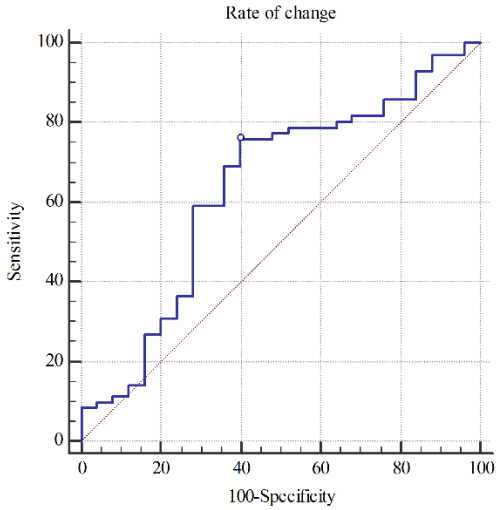

Figure 3. Receiver operator curve for predicting poor neurologic outcome using rate of optic nerve sheath diameter change. AUC = 0.64 (95% Confidence interval = 0.53-0.73)

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Table 4. Cut-off and diagnostic value of optic nerve sheath diameter change for predicting good and poor neurologic outcome.

	Cut-off, %*	Sensitivity	Specificity	PPV	NPV
Rate of change for predicting PNO	> 27.2	0.085	1.000	1.000	0.278
Rate of change for predicting GNO	≤ 5.83	0.600	0.761	0.469	0.844

Abbreviations: PPV = positive predictive value; NPV = negative predictive value; PNO = poor neurologic outcome; GNO = good neurologic outcome.

4. Discussion

This study found that the amount and rate of ONSD change were significantly associated with neurologic outcomes. However, there was no significant between-group difference in the post-CA ONSD and no independent association of the rate of ONSD change with neurologic outcomes after adjusting for confounding variables. Together with other established predictors, the rate of ONSD change may be useful for predicting neurologic outcomes. To the best of our knowledge, this is the first study to investigate individual differences in ONSD changes among post-CA survivors.

Previous studies have reported an association of neurologic outcomes in critically ill patients, including post-CA survivors, with increased ICP values [3,4,21,22]. The optic nerve sheath enclosing the optic nerve is comprised of a subarachnoid space layer, which is filled with cerebrospinal fluid (CSF) [23]; hence, ICP is positively correlated with the CSF pressure and ONSD [23,24]. ONSD is a potential non-invasive ICP estimator and could be useful for assessing intracranial hypertension [24]. In patients with post-CA hypoxic cerebral injury, increased ICP is associated with the neurologic outcome [3,21,22].

Several studies have reported that ONSD can predict neurologic outcomes in post-CA survivors. A retrospective cohort study from Korea reported an association of higher ONSD values on initial brain CT with poor neurologic outcome [15]. Chelly et al. demonstrated the potential role of ONSD as an early prediction tool for outcomes in post-CA patients treated with TTM administration [19]. Other studies have applied ONSD in combination with other predictors, including GWR or albumin levels, to enhance the predictive value [14,20,21]. Moreover, a recent meta-analysis reported the potential use of ONSD in predicting neurologic outcome [20]. A registry-based multicenter study showed inconsistency with these previous findings as it reported no correlation between ONSD on early unenhanced brain CT and neurologic outcome in post-CA survivors managed with TTM administration [25]. Furthermore, previous study have shown a limited and insufficient role of post-CA ONSD alone in predicting neurologic outcomes in post-CA survivors [26].

ONSD can provide non-invasive ICP measurement and could serve as a surrogate marker for increased ICP [17,18]. However, in healthy adults, there are differences in the baseline ONSD according to individual characteristics, including sex, body mass index (BMI), race, or eyeball size [27,28]. Most studies performed on healthy volunteers have reported that the mean ONSD ranges from about 3 mm to 5 mm; furthermore, the reported mean or median ONSD values have varied across study cohorts depending on the race or measurement tools [27-30]. Ultrasonographic evaluation of healthy Asians revealed a higher ONSD value in males and individuals with high BMI [27,28]. Therefore, these individual differences could confound the interpretation of post-CA ONSD; furthermore, considering the baseline ONSD may help in improving the prognostic value. Therefore, ONSD changes are potential useful markers for ICP measurement changes. A prospective observational study on ONSD changes in patients with hydrocephalus reported a significant reduction in ONSD after ventriculoperitoneal shunt operation [31]. In our study, ONSD changes were more reliable than the ONSD itself in predicting neurologic outcomes in patients with post-CA.

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A recent meta-analysis reported that in comparison to CT and MRI (magnetic resonance imaging), sonographic measurement provided more accurate prediction of neurologic outcome in patients with post-CA [20]. However, obtaining and comparing pre-CA and post-CA ONSD using ultrasound has limitations in clinical settings. Moreover, determining the pre-CA ONSD using brain MRI also has limitations given its specific modality. Recent studies have indicated that the axial proton density/T2-weighted turbo spin-echo fat-suppressed sequence is required for ONSD measurements using MRI. However, in most post-CA patients, the T2-TSE (turbo spin exho) image is not included in the diffusion-weighted MRI [32,33]. Additionally, there is a strong association of ONSD with eyeball transverse diameter (ETD) and ONSD/ETD ratio in healthy adults [34]. Furthermore, there is a need for further studies on the association between ONSD/ETD ratio and neurologic outcome in post-CA patients.

This study has several limitations. First, this was a single-center study with a limited sample size that led to an insufficient statistical power; however, we calculated the sample size, which was relatively large compared with that of other studies. Second, this retrospective study included patients who underwent both pre- and post-CA brain CT, which could lead to selection bias affecting the results. Third, although we attempted to extensively collect variables, there could be hidden confounders. Fourth, there could have been minor measurement errors given the very small size of the ONSD in brain CT. However, to minimize these errors, two blinded emergency physicians performed measurements using a standardized method showing consensus. Fifth, current guidelines recommend neurologic outcome assessment at 3 months after discharge. However, we measured the neurologic outcome at discharge and did not determine the long-term outcome. This was a retrospective study and the clinical utility of the predictive value for prognosis remains unclear. Hence, there is a need for large-scale prospective studies to confirm our findings.

5. Conclusions

The rate and amount of ONSD changes on brain CT were significantly associated with neurologic outcome in patients with post-CA. ONSD changes may be useful to predict neurologic outcome in patients with post-CA.

Supplementary Materials: The following are available online at www.mdpi.com/xxx/s1, Table S1: Comparison of the optic nerve sheath diameter between pre-cardiac arrest and post-cardiac arrest in good neurologic outcome and poor neurologic outcome group.

Author Contributions:

Conceptualization, H.S; methodology, H.S. and H.L.; software, H.L. and J.L.; validation, C.K., H.J.C. and B.S.K.; formal analysis, H.S. and H.L.; investigation, H.S. and H.L.; data curation, C.K., H.J.C. and B.S.K.; writing—original draft preparation, H.L. and J.L.; writing—review and editing, H.S. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was approved by the Institutional Review Board of Hanyang University Guri Hospital (IRB No. GURI 2020-12-008). , which waived the requirement of informed consent.

Informed Consent Statement: This retrospective medical recored review study was waived the requirement of informed consent.

Data Availability Statement: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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Abbreviations: ONSD, optic nerve sheath diameter; CA, cardiac arrest; CT, computed tomography; GNO, good neurologic outcome; PNO, poor neurologic outcome; ICP, intracranial pressure; ROSC, return of spontaneous circulation; GWR, grey-to white matter ratio; CPR, cardiopulmonary resuscitation; TTM, targeted temperature management; CPC, Cerebral Performance Categories; PACS, picture archiving and communication system; IQR, interquartile range; AUC, area under curve; ROC, the receiver operating characteristic; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; CSF, cerebrospinal fluid; BMI, body mass index; ETD, eyeball transverse diameter.

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Figure legends

1. Figure 1. Flow chart of the study process.
2. Figure 2. Comparison of the optic nerve sheath diameter between pre-cardiac arrest and post-cardiac arrest in good and poor neurologic outcome group.
3. Figure 3. Receiver operator curve for predicting poor neurologic outcome using rate of optic nerve sheath diameter change. AUC = 0.64 (95% Confidence interval = 0.53-0.73)

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Supplemental table 1. Comparison of the optic nerve sheath diameter between pre-cardiac arrest and post-cardiac arrest in good neurologic outcome and poor neurologic outcome group.

	GNO (n = 25)			PNO (n=71)		
	Pre-CA	Post-CA	*p*-value	Pre-CA	Post-CA	*p*-value
Right eye, mm	5.04 (4.76-5.62)	5.39 (5.13-5.96)	0.001	5.22 (4.65-5.51)	5.79 (5.53-6.19)	<0.001
Left eye, mm	5.09 (4.76-5.68)	5.57 (5.10-5.88)	<0.001	5.05 (4.73-5.39)	5.70 (5.40-5.99)	<0.001
Average*, mm	5.06 (4.71-5.60)	5.50 (5.16-5.91)	<0.001	5.07 (4.73-5.52)	5.72 (5.49-6.04)	0.001

Abbreviations: GNO, good neurologic outcome; PNO, poor neurologic outcome; CA, cardiac arrest

*Average optic nerve sheath diameter of right and left eyes