Original Article

Prognostic Role of Optic Nerve Sheath Diameter in Stroke in Emergency Department, A Case Control Study

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Abstract

Background: Sonographic measurement of optic nerve sheath diameter (ONSD) can reflect intracranial pressure (ICP) indirectly and determine the neurology intensive care unit (NICU) requirement and mortality in acute ischemic stroke (AIS). **Aim:** To demonstrate the effectiveness of ONSD to determine mortality, morbidity, and NICU requirement on patients with the AIS. **Methods:** The sonographic ONSD measurements were performed on each patient with AIS, over 18 years old. All patients were categorized according to the Oxfordshire Community Stroke Project (OCSP) classification system. MRI images were examined for increased ICP, and the patients were categorized into two groups as increased ICP (i-ICP) and normal ICP. The ONSD results were evaluated in terms of classifications, outcomes, and prognosis of the patients. **Results:** One hundred and five patients were included and 31 (35.2%) were in the i-ICP group. The median ONSDs were 5.26 mm in the i-ICP group and 4.62 mm in the normal ICP group ($P < 0.001$). The median ONSDs were 5.13 mm in the NICU group and 4.69 mm in the neurology ward (NW) group ($P = 0.001$). The total anterior circulation infarction (TACI) subgroup had higher ONSDs than the others (TACI: 5.27 mm; PACI: 4.73 mm; POCI: 4.77 mm; and LACI: 4.64 mm, $P < 0.001$). The NICU requirements were higher in the TACI subgroup. The median ONSD was 5.42 mm in the deceased group (survived: 4.77 mm, $P < 0.001$). **Conclusion:** ONSD may be favorable for predicting the increased ICP and the NICU requirement in OCSP subgroups. Moreover, ONSD can be used to foresee the mortality of AIS.

Keywords: *Emergency department, optic nerve sheath diameter, outcome, Oxfordshire Community Stroke Project, stroke*

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Introduction

Stroke is ranked as the second leading cause of death and the main factor for long-term neurological disability in adults worldwide.[1] According to the WHO data, the emergency department (ED) admissions due to stroke reach 15 million per year.[2] The mortality rate of ischemic stroke is 5–10%.

The Oxfordshire Community Stroke Project (OCSP) classification presents a simple clinical pattern to subdivide acute strokes. In this classification, patients are classified into four subgroups according to the clinical criteria. The patients who display hemiparesis, higher cortical dysfunction (dysphasia, etc.), and homonymous hemianopia are categorized as total anterior circulation infarction (TACI). TACI usually occurs as a result of occlusion in the root or the major branch of middle cerebral artery (MCA).[3] A large hemispheric infarct which has occurred as a result of MCA root occlusion is called "Malignant MCA Infarction." The Malignant MCA Infarction is characterized by increased intracranial pressure (ICP).[4] Several different methods can be used to evaluate ICP. To measure the optic nerve sheath diameter (ONSD) sonographically is an accessible,

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repeatable, and non-invasive method among all methods which are used to detect increased ICP. A meta-analysis, published in 2010, compared the measurements of ICP with intra-parenchymal devices (gold standard) to sonographic ONSD measurements. There were not any significant differences between sensitivity, specificity, negative, or positive predictive value and diagnostic odds ratios of both groups.[5] In 2010, a systematic review showed that sonographic ONSD measurements had 90% sensitivity and 85% specificity on detecting increased ICP.[6] These patients who had increased ICP due to MCA occlusion required intensive care treatment and had high mortality.[4] In 2016, Yang *et al*.[7] showed that TACI subgroup displayed significantly higher 7-day and 3-month mortality rates (16,24%–26.9%) than the other OCSP subgroups ($P < 0.001$).

Among the OCSP subgroups, TACI is often associated with increased ICP. Increased ICP is an indicator of mortality. It is crucial to determine the relationship between increased ICP and mortality and the relationship between increased ICP and neurology intensive care unit (NICU) requirement. The present study aims to reveal the efficiency of ONSD in predicting the NICU requirement and the mortality of OCSP subgroups in the early period of ED admission.

Materials and Methods

This single center prospective case control study was conducted at an ED of a tertiary hospital between March 2015 and September 2015. G Power 3.1 package program was used for sample calculation. A power analysis in the one-way analysis of variance category for the study group consisting of four subgroups indicated that the minimum sample size to yield a statistical power of at least 0.95 with an alpha of 0.05 and effect size 0.45 is 91. Possible data loss was determined as 10%. In this case, it was aimed to include a minimum of 100 patients in the study. Patients with ICP findings were considered as "cases," and patients without ICP findings were considered as "controls".

Patients, over 18 years old, admitted to the ED with a pre-diagnosis of acute ischemic stroke (AIS) were included in the study. Patients with intracranial hemorrhage (ICH), intracranial mass, previous stroke, or surgical history in the health records and unsuitable conditions for the measurement of ONSD (optic nerve atrophy, enophthalmos, etc.) were excluded from the study. Ocular ultrasound (US) and magnetic resonance imaging (MRI) were performed on each patient. The NIH stroke scale (NIHSS) results were recorded.

The ONSD measurements were recorded in the first hour of admission. All sonographic measurements were performed by two chief EM residents who were unaware of the symptoms, neurological examinations, and the neuroimaging findings. The EM residents had passed a two-week US training course supervised by an EM attending and they scanned 30 healthy volunteers ONSD before the study. When a patient is admitted to the ED with a pre-diagnosis of AIS, the practitioners were informed by the emergency physicians. Practitioners reached the ED within an hour and one of them performed ocular US. Ocular US duration was not longer than 5 minutes in any patient. Optic nerve imaging was conducted through a high-frequency (>7.5 MHz) linear transducer with an insonation depth of 5–8 cm in the supine position. The eye bulbs and the retrobulbar structures were visualized transversely by sonography. In the eyeball, anechoic vitreous fluid and echogenic papilla in the posterior wall were detected, then echogenic fat tissue and hypoechoic optic nerve complex were visualized in the post-bulbar area. When the cursor was positioned on the outer edges of the optic nerve, measurement was taken at the 3 mm posterior to the papilla and perpendicularly to the cursor.[8]

National Institutes Health Stroke Scale (NIHSS) is a standard stroke impairment scale with proven validity and reliability.[9] In the present study, the NIHSS scores of all patients were also recorded.

The diagnosis of AIS was confirmed with MRI. The MRI sequences were assessed by radiologist unaware of the patients' information and sonographic ONSD measurements. The MRI sequences were evaluated primarily for the presence of brain edema. The posterior scleral flattening, prelaminar staining of optic nerves, vertical curvature of orbital optic nerves, swelling of perioptic subarachnoid space, midline shift, ventricular-sulcal effacement, and herniation were accepted as the signs of brain edema, and each of them was the references of the existence of ICP.[10]

The OCSP classification, which was originally designed for patients having their first stroke in a lifetime, presents a simple clinical pattern to subdivide acute stroke. The OCSP classification, based on clinical syndromes solely, can be used to estimate the site and dimensions of the infarct on CT in patients with AIS. The subgroups of OCSP are TACI, partial anterior circulation infarcts (PACI), posterior circulation infarcts (POCI), or lacunar infarcts (LACI). The classification is based upon bedside clinical features. Symptoms and signs can help to localize the infarction. TACI contains the triad of hemiparesis, higher cortical dysfunction, and homonymous hemianopia. It occurs due to large proximal MCA infarct or internal carotid artery. The PACI has isolated higher cortical dysfunction or limited

motor/sensory dysfunction due to smaller infarcts of MCA or anterior cerebral artery (ACA). Infarct in the posterior cerebral hemisphere, brain stem, or cerebellum cause the POCI. The LACI presents with pure motor, pure sensory, sensory-motor, or ataxic hemiparesis. It is a small deep infarct mainly in the regions of basal ganglia or pons.[3,11,12]

The patients were categorized into four subgroups according to the OSCP classification system. The patients were grouped as TACI, PACI, POCI, or LACI depending on the maximum neurological defects. The patients are divided into two subgroups according to their hospitalization as NICU or neurology ward (NW). The efficiency of the ONSD in predicting the NICU requirement and the 30-day mortality rate in each subgroup were studied. In accordance with this purpose, we tried to identify the optimum cutoff point of ONSD for i-ICP and NICU requirement.

Ethical consideration

Ethical approval of the study was granted by the University Ethics Committee with decision number 2015/04 GO 15/32-23 on the January 21st, 2015. Patients and/or their guardians were informed about the study and sonographic measurement, and their informed consent was obtained. The patient was included in the study after the informed consent form was signed.

Data analysis

Statistical analysis was performed using the IBM SPSS for Windows version 23.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (interquartile range [IQR]) for continuous variables and in number and frequency for categorical variables. The distribution of continuous variables was analyzed using the Shapiro–Wilk tests. For multiple group comparisons, the continuous variables were analyzed using the Kruskal–Wallis, and the categorical variables were analyzed using Pearson's Chi-square test and Fisher's exact test. The statistical analysis between two independent groups with non-normal distribution data was performed with Mann–Whitney U test. One-way Anova analysis was performed for the difference between more than two groups. In these groups whose variances are not equal, *post hoc* analysis was performed with Tamhane's T2 test. Receiver operating characteristic (ROC) analysis was used to demonstrate the accuracy of ONSD in admission to NICU and ICP increasing. Youden index was used to adjust the best cutoff point. The calculation of sensitivity and specificity was performed with the 95% confidence intervals (CIs). A *P* value of < 0.05 was considered statistically significant.

Results

In the present study, a total of 120 patients were included. Among those, 15 patients were excluded from the study (five patients withdrew their consents, the final diagnosis of the nine patients was ICH/mass, and one patient had optic atrophy). Finally, 105 patients were analyzed statistically [Figure 1].

The mean age of patients was 66.5 ± 14.3 years, and 52.4% of patients were male. The concomitant diseases were hypertension (60.9%), diabetes mellitus (24.7%), coronary artery diseases (23.8%), congestive heart failure (15.2%) and valvular heart diseases (5.7%), chronic obstructive pulmonary disease (3.8%), and carotid artery stenosis (3.8%) among study group. The twenty-one percent of patients were hospitalized in the NICU, and the mortality rate was 4.8%. Table 1 shows the descriptive statistics and clinical characteristics of the patients.

According to the MRI findings, the patients were divided into two groups as increased ICP (i-ICP) and normal ICP (n-ICP). The median ONSDs were 5.24 mm in the i-ICP group (n = 31 – 29.5%) and 4.61 mm in the n-ICP group (n = 74-70.5%) (*P* < 0.001).

Figure 2 shows the ROC curve diagram of mean ONSD for detecting ICP. Area under curve (AUC) was 0.978 (95%CI = 0.951 to 1.0). The cutoff value of ONSD for detecting increased ICP was 5.05 mm (sensitivity = 96.8%, specificity = 95.6%).

The patients were categorized into two groups according to the requirement of NICU (n = 21-20%) or NW (n = 84-80%). The median ONSDs were 5.13 mm in the NICU group and 4.69 mm in the NW group (*P* = 0.001).

The ROC curve diagram of mean ONSD for the need of NICU treatment is shown in Figure 3. The AUC was 0.807 (95% CI = 0.681 to 0.933), and the cutoff value of ONSD for the requirement of NICU treatment was

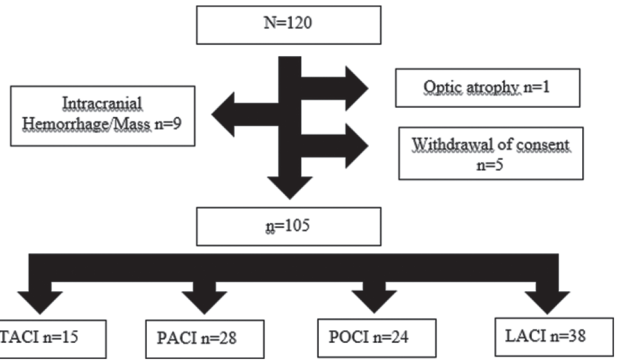

Figure 1: Flowchart of the study. LACI: Lacunar Infarct, PACI: Partial Anterior Circulation Infarct, POCI: Posterior Circulation Infarct, TACI: Total Anterior Circulation Infarct

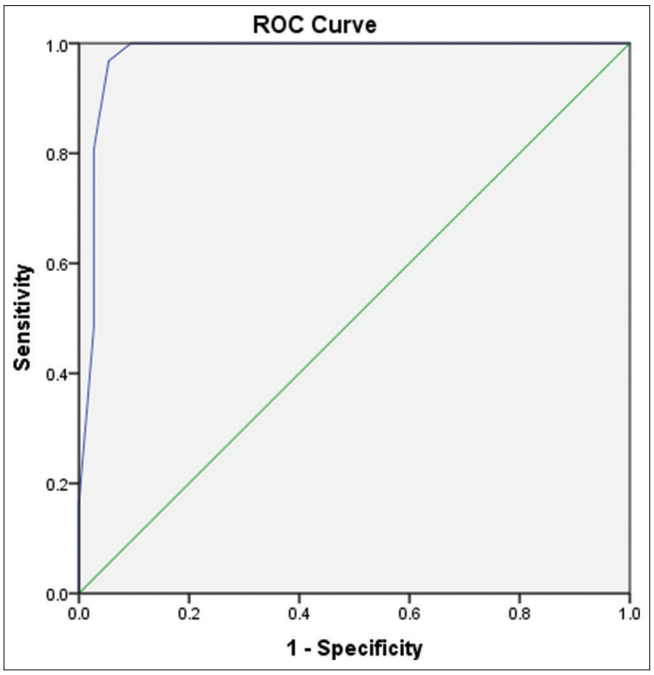

Figure 2: The ROC curve diagram of mean ONSD for detecting increased ICP

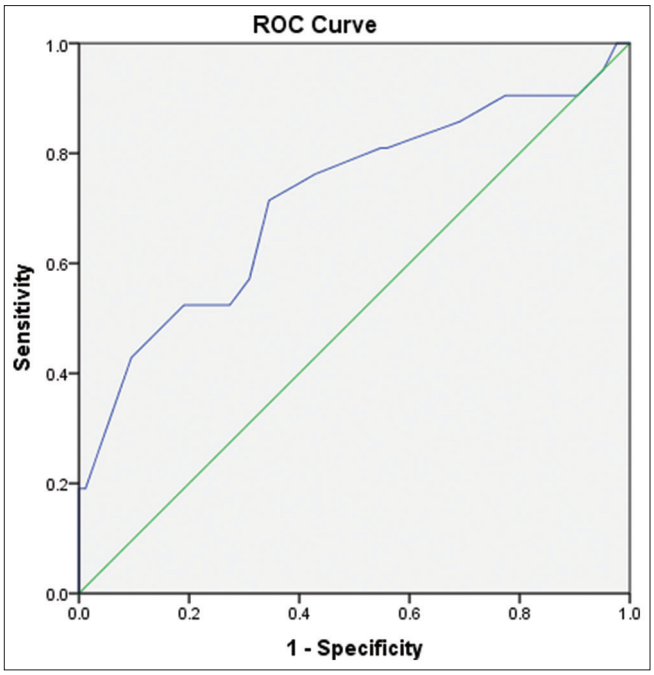

Figure 3: The ROC curve diagram of mean ONSD for the need of NICU treatment

Table 1: Demographic, clinical characteristics, and outcome of participants

Characteristics	n	%
Gender		
Male	55	52.4
Female	50	47.6
Most Frequent Concomitant Diseases		
Hypertension	64	60.9
Diabetes mellitus	26	24.7
Coronary artery disease	25	23.8
Congestive heart failure	16	15.2
Valvular heart disease	6	5.7
COPD	4	3.8
Carotid artery stenosis	4	3.8
Chronic kidney disease	3	2.8
Rheumatic disease	3	2.8
Hospitalization		
Neurology ward	84	80
Intensive care unit	21	20
Outcome		
Survived	100	95.2
Deceased	5	4.8

COPD: Chronic Obstructive Pulmonary Disease

Table 2: Comparison of NIHSS among OCSP subgroups

OCSP subgroups	NIHSS median (IQR)	*P**			
		TACI	PACI	POCI	LACI
TACI	21.5 (9)	-	<0.001	<0.001	<0.001
PACI	9 (6)	<0.001	-	<0.001	<0.001
POCI	5.5 (4)	<0.001	<0.001	-	0.016
LACI	3 (4)	<0.001	<0.001	0.016	-

*Mann–Whitney U test. Non-parametric analysis of more than two independent groups was performed with the Kruskal–Wallis test. Mann–Whitney *U* test was used in *post hoc* analysis.
OCSP: Oxfordshire Community Stroke Project, NIHSS: National Institutes of Health Stroke Scale, TACI: Total Anterior Circulation Infarct, PACI: Partial Anterior Circulation Infarct, POCI: Posterior Circulation Infarct, LACI: Lacunar Infarct

4.95 mm (sensitivity = 71.4%, specificity = 79.6%). The NICU requirement rate increased 9.3 times on the patients with ONSD greater than 4.95 mm (RR = 9.3).

The 30-day mortality of the patients included in the study was followed up. All deaths (n = 5) occurred in the NICU group. The median ONSDs were 5.42 mm in the deceased and 5.15 mm in survived patients in NICU group ($P = 0.019$), whereas 4.77 mm in survived patients among all groups ($P < 0.001$).

In the ROC curve diagram of mean ONSD for detecting decease, the AUC was 0.973 (95% CI = 0.932 to 1.000) and the cutoff value of ONSD for decease was 5.25 mm (sensitivity = 80%, specificity = 93%) [Figure 4]. The mortality rate increased 34.2 times on patients with ONSD greater than 5.25 mm (RR = 34.2).

The patient characteristics, median NIHSS scores, and median ONSD measurements considering to OCSP subgroups are shown in Table 2. The median NIHSS was higher in the TACI subgroup 21.5 (9). TACI-NIHSS

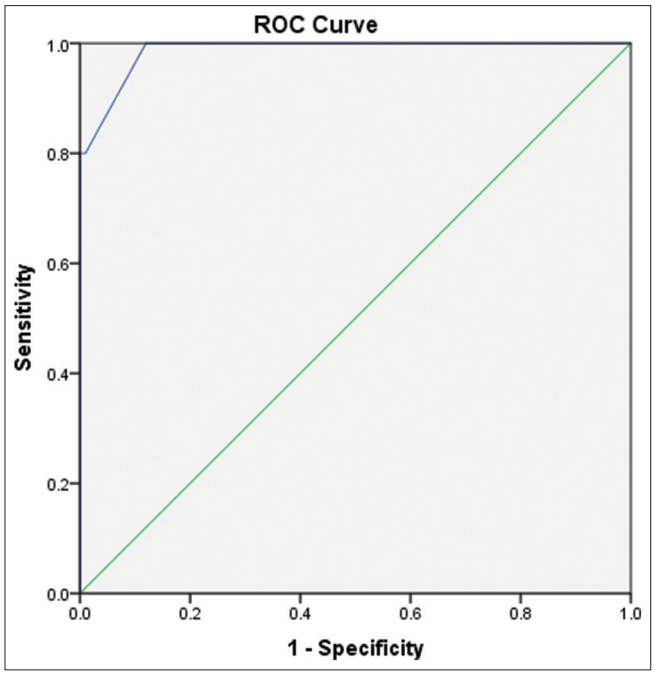

Figure 4: The ROC curve diagram of mean ONSD for detecting the mortality in the AIS

Table 3: Comparison of ONSD among OCSP subgroups

OCSP subgroups	ONSD (mm) median (IQR)	*P**			
		TACI	PACI	POCI	LACI
TACI	5.27 (0.40)	-	0.004	0.001	<0.001
PACI	4.87 (0.60)	0.004	-	0.568	0.126
POCI	4.67 (0.50)	0.001	0.568	-	0.337
LACI	4.80 (0.30)	<0.001	0.126	0.337	-

*Mann–Whitney U test. Non-parametric analysis of more than two independent groups was performed with the Kruskal–Wallis test. Mann–Whitney U test was used in *post hoc* analysis. OCSP: Oxfordshire Community Stroke Project, ONSD: Optic Nerve Sheath Diameter, TACI: Total Anterior Circulation Infarct, PACI: Partial Anterior Circulation Infarct, POCI: Posterior Circulation Infarct, LACI: Lacunar Infarct

Table 4: The median ONSDs in NICU and NW subgroups of all OCSP groups

OCSP subgroups	ONSD (mm)				*P**
	NW subgroup		NICU subgroup		
	n	Median (IQR)	*n*	Median (IQR)	
TACI	7	5.17 (0.40)	8	5.37 (0.30)	0.010
PACI	20	4.87 (0.50)	8	4.68 (0.40)	0.162
POCI	30	4.67 (0.50)	4	4.80 (0.30)	0.579
LACI	37	4.80 (0.50)	1	4.68	0.102

*Mann–Whitney U test LACI: Lacunar Infarct, NICU: Neurology Intensive Care Unit, NW: Neurology Ward OCSP: Oxfordshire Community Stroke Project, ONSD: Optic Nerve Sheath Diameter, PACI: Partial Anterior Circulation Infarct, POCI: Posterior Circulation Infarct, TACI: Total Anterior Circulation Infarct

score was higher than other groups in paired group analysis ($P < 0.001$). The median PACI-NIHSS score

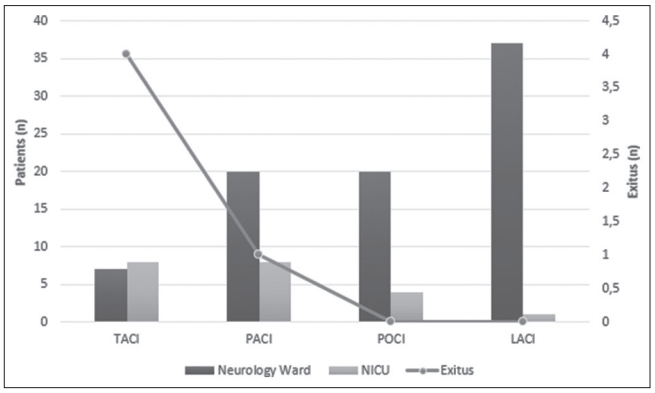

Figure 5: Outcomes of the patients and hospitalization requirements according to OCSP. LACI: Lacunar Infarct, NICU: Neurology Intensive Care Unit, PACI: Partial Anterior Circulation Infarct, POCI: Posterior Circulation Infarct, TACI: Total Anterior Circulation Infarct

9 (6) was higher than median POCI-NIHSS 5.5 (4) and LACI-NIHSS 3 (4) scores ($P < 0.001$).

The median ONSD was higher in the TACI subgroup than in the others. The median ONSD in TACI was 5.27 mm, whereas the median ONSDs in PACI, POCI, and LOCI were 4.87 mm, 4.67 mm, and 4.80 mm, respectively ($P < 0.001$) [Table 3]. *Post hoc* analysis results were evaluated. There was a significant difference between the TACI subgroup and all other groups ($P < 0.001$). No significant difference was detected between the other groups (PACI and POCI ($P = 0.568$); PACI and LACI ($P = 0.126$); and POCI and LACI ($P = 0.337$)).

All OCSP subgroups were divided into two subgroups as patients treated in NICU and in NW. The median ONSD of NICU and NW subgroups was shown in Table 4. The median ONSD of TACI-NICU was 5.37 mm, and TACI-NW was 5.17 mm ($P = 0.010$).

The subgroups were evaluated in terms of outcomes. The TACI subgroup had higher NICU requirement (53.3%) than the others (PACI = 28.57%, POCI = 16.67%, LACI = 2.63%, $P < 0.001$). In addition, four of the patients who died (n = 5) were in the TACI subgroup and one of them was in the PACI subgroup [Figure 5].

Discussion

In recent years, many novel methods have been described for detecting increased ICP in AIS indirectly. The sonographic ONSD measurement is one of these methods and plays an important role in detecting increased ICP. This study discusses the effectiveness of sonographic ONSD measurement in predicting the clinical severity, the NICU requirement, and the mortality on AIS.

The acute stroke usually followed by delayed clinical deterioration due to the edema of the infarcted tissue.[9]

Persistent increased ICP may cause severe neurological damage or death due to the pressure and the herniation. On the first days of AIS, the treatments should be done to reduce the risk of edema and to prevent the development of malignant brain edema. These groups of patients should be evaluated in the early period by the neurosurgeon (Class I C-LD). In unilateral MCA infarcts, in which clinical deterioration continues despite medical treatment within 48 hours, early decompression may reduce the mortality close to 50% (Class IIa). Assessment of increased ICP in the early period may lead to effective results on mortality and morbidity.[9] Jeon *et al*.[4] compared the medical treatment to the early decompression in massive ischemic stroke in terms of neurology recovery rate. They showed that early decompression increased the neurologic recovery rate 2 to 3 times in one year. In a meta-analysis study published in 2018, researchers observed that the median time from the onset of symptoms to decompressive craniotomy (DC) was 41 hours and showed that DC reduced the mortality rate in these patients.[13] These studies in the literatures indicates that detecting increased ICP in the early period of AIS is crucial in changing the treatment strategy and decreasing mortality.

Invasive ICP monitoring techniques like intra-parenchymal probes and intraventricular catheters are associated with complications such as infection and hemorrhage.[14] But the non-invasive techniques like MRI, computerized tomography, ophthalmodynamometer, electroencephalogram, and ocular ultrasound are safer than invasive methods. Recently, non-invasive techniques have been widely used in spotting the increased ICP. In particular, the evaluation of ONSD by ocular US which is an accessible, repeatable, and non-invasive technique has an important place among these techniques. Kimberly *et al*.[15] studied on the patients presented to the emergency service with traumatic brain injury or with ICH. They tried to obtain exact results of ICP using intra-parenchymal devices and compared these results with sonographic ONSD measurements. They reported the upper limit of the ONSD as 5.0 mm, and the sensitivity and specificity for this value were 88% and 93%, respectively. Moretti and Pizzi reviewed six studies which were compared the measurement of ICP by interventional devices to sonographic ONSD.[16] In this review, it was determined that the upper limit of ONSD was 5.0 mm, the sensitivity was 88.71%, the specificity was 79.74%, the PPV was 72.94%, and the NPV was 90.5%. In addition, Toscano *et al*.[17] reported a strong correlation between increased ONSD and high ICP. MRI is one of the most useful noninvasive techniques that reveal the increased ICP objectively.[18] MRI findings are posterior scleral flattening, prelaminar staining of optic nerves, vertical curvature of orbital optic nerves and swelling of perioptic subarachnoid space, midline shift and ventricular-sulcal effacement and herniation. These could be used as an indicator of increased ICP with the sensitivity 90% and specificity 100%.[19-21] In our study, when these MRI findings were accepted as a reference, the most appropriate cutoff of ONSD for increased ICP was found 5.05 mm (sensitivity = 96.8%, specificity = 95.6%). The cutoff value of ONSD, its sensitivity, and specificity was similar to the literature for the detection of increased ICP.

The ONSD measurements can provide predictions about hospitalization and mortality rate. We could not find any studies which clarified the relationship between ONSD and NICU requirements in the literature. We showed that the ONSD could predict the NICU requirement in the early stage of admission. In the present study, the median ONSD of the NICU group was higher than the NW group (5.13 mm vs 4.69 mm) and the patients with ONSD over 4.95 mm required 9.3 times more NICU treatment. The higher ONSD values could predict the mortality in AIS.[22-24] Seyedhosseini *et al*.[25] and Robba *et al*.[26] determined the relationship between higher ONSD and mortality in AIS. Robba *et al*.[27] demonstrated a strong association between mortality and ONSD. Sekhon *et al*.[28] reported that 1 mm increase in ONSD eventuates a twofold increase in hospital mortality. Legrand *et al*.[29] indicated that the higher ONSD was associated with mortality in an independent way, and they found the ONSD cutoff for mortality as 7.3 mm (sensitivity = 86.4%, specificity = 74.6%). In our study, the median ONSD of deceased group was higher than the survived group (5.42 mm vs 4.77 mm) and the patients with ONSD over 5.25 mm had 34.2 times more mortality rate.

The simple clinical classification method of OCSP relies on clinical findings to classify the stroke according to the brain territory involved. It is used to predict mortality and functional recovery in stroke and can be completed in the ED. Similarly, NIHSS is used to measure stroke severity and long-term outcome.[30] TACI subgroup had higher NIHSS scores than other OCSP groups in the current study. Sung *et al*.[31] found that the NIHSS scores in the TACI subgroup were higher than in the other OCSP groups. Some studies show the TACI subgroup is associated with poor outcome and high mortality rate. Gökcen *et al*.[32] displayed that the highest ONSD was in TACI subgroup (6.2 mm). Paci *et al*.[23] analyzed 8773 patients in a systematic review in 2011. They found that TACI subgroup had poor outcome and higher mortality rate compared to the other subgroups. Cheung *et al*.[24] described the mortality rates of TACI,

PACI, POCI, and LACI were 52.4%, 9.6%, 7.9%, and 1.9%, respectively. In the study of Kortazar-Zubizarreta *et al*.[22], the researchers worked on predictors of in-hospital mortality in AIS and demonstrated that the mortality rate in AIS was higher in TACI subgroup than the others. In our study, the TACI subgroup had higher ONSD (5.27 mm), higher NICU requirement (53.3%), and higher 30-day mortality rate (26.6%) than the other subgroups. In addition, when the TACI subgroup was divided into two subgroups as patients treated in the NICU and NW, the median ONSD of the NICU subgroup (5.37 mm) was found to be higher than the median ONSD of NW (4.77 mm) ($P < 0.001$). In the light of this information, when the OCSP classification system and ONSD measurement are integrated, it can be useful in estimating the need for NICU treatment and mortality at admission.

The main limitation of the current study is being single-centered study. Multicenter studies with more individuals may provide more generalizable results. Although 30-day mortality rates were recorded, a detailed information about the outcome could be given by monitoring the neurological healing rate and time of the patients.

Conclusion

In the current study, a significant relationship was found between ONSD values and mortality and NICU requirement. The study showed that ONSD values were higher on patients with poor outcome sonographic ONSD measurements may be useful for predicting the increased ICP, the intensive care unit requirement, and the mortality in AIS. The higher values of ONSD can be an indicator of poor prognosis in AIS. Considering the OCSP subgroups, the TACI subgroup has higher mortality risk and needs to be treated in NICU. The clinical course of the patient with ONSD measurements should be followed closely in the TACI subgroup to provide accurate treatment strategy and to predict possible morbidity or mortality at an early stage.

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Conflicts of interest

There are no conflicts of interest.

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