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# The Relationship between Optic Nerve Sheath Diameter, Optic Disc Edema, and Mortality in Patients with Septic Encephalopathy: A Prospective Observational Study

**Muhammed Akay, Nazire Belgin Akıllı, Ramazan Köylü**

Konya City Hospital, Clinic of Emergency Medicine, Konya, Türkiye

## Abstract

**Aim:** Our objective was to examine ocular ultrasonography findings in sepsis-related encephalopathy and assess its relationship with mortality.

**Materials and Methods:** Male and female patients over the age of 18 who were diagnosed with septic encephalopathy and whose relatives or self-consent were given to participate in the study were included in the study. Healthy adult patients over 18 years of age were included in the control group. Demographic and laboratory data, glasgow coma scale, Sequential Organ Failure Assessment (SOFA), quick SOFA, APACHE II scores, ocular ultrasonographic results and death status were noted.

**Results:** 100 patients and 30 control groups were included in the study. While the right optic nerve sheath diameter (ONSD) values were 0.49±0.006 cm in the patient group and 0.40±0.02 cm in the control group, the left ONSD values were 0.48±0.006 cm in the patient group and 0.41±0.02 cm in the control group. While the right optic disc elevation (ODE) values were 0.009±0.03 cm in the patient group and 0.00±0 cm in the control group, the left ODE values were 0.005±0.01 cm in the patient group and 0.00±0 cm in the control group ($p<0.05$). Sensitivity for left ONSD >0.48: 72.2 (46.5-90.3), specificity: 74.3 (63.6-83.4), positive predictive value: 38.2 (28-49.7), negative predictive value: 92.4 (85.1-96.3) (area under the curve 0.75 and p: 0,0003).

**Conclusion:** ONSD and ODE are enlarged in patients with septic encephalopathy compared to healthy controls. Inpatients with septic encephalopathy, ONSD and ODE measurement can give preliminary information about intracranial pressure, clinical course and mortality.

**Keywords:** Septic encephalopathy, optic nerve sheath diameter, optic disc elevation, pocus

## Introduction

Sepsis is a life-threatening clinical condition accompanied by organ dysfunction, resulting from inadequate and inappropriate host response to infection (1). It is a serious condition that affects millions of people worldwide every year and results in the death of one in four patients (2). The mortality attributed to sepsis varies based on patient-related and independent risk factors, the size of the healthcare facility, early diagnosis of the condition, and prompt initiation of treatment for patients with delayed diagnosis and treatment, even in cases of eventual recovery, a significant decline is observed in the quality of life after the disease (3,4). The development of a systemic inflammatory response in sepsis induces hemostatic changes, leading to subsequent organ dysfunction (5). One of these is sepsis-associated encephalopathy (SAE), a common but poorly understood neurological complication of sepsis. It is characterized by generalized brain dysfunction associated with an infection in another part of the body, in the absence of any sedation, analgesics, or benzodiazepines, and without an overt central nervous system infection. The pathophysiology of SAE is complex and multifactorial, involving a number of interconnected mechanisms, including vascular injury, endothelial activation, blood–brain barrier disruption, altered brain signaling, brain inflammation, and apoptosis. Clinical manifestations of SAE can range from mild symptoms, such as weakness and lack of concentration, to deep coma. The lack of any specific research or biomarkers and the widespread use of sedation in critically ill patients make the assessment of

**Corresponding Author:** Muhammed Akay PhD, Konya City Hospital, Clinic of Emergency Medicine, Konya, Türkiye
**E-mail:** makay686@gmail.com **ORCID ID:** orcid.org/0000-0002-6371-1518
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cognitive dysfunction difficult (6). When accompanying sepsis, this condition, known as septic encephalopathy, can increase mortality rates from 26% to 49% (7). It is important to recognize SAE because of its high mortality rate. SAE can manifest in the initial stages of sepsis, even preceding the fulfillment of diagnostic criteria for sepsis (6).

Increased intracranial pressure (ICP) is a condition that arises from cerebral edema and can result from either traumatic or metabolic factors. Cerebral edema and increased ICP may occur during the course of sepsis. Intracranial catheters are used as an invasive method for measuring ICP, whereas computed tomography, transcranial Doppler sonography, ophthalmoscopy, and ultrasonography (USG) measurement of optic nerve sheath diameter (ONSD) serve as noninvasive techniques for ICP measurement. These diagnostic methods have both advantages and disadvantages when compared to each other (8). Studies indicate that USG measurement of ONSD demonstrates high sensitivity and specificity in detecting increased ICP (9). Compared to other methods, USG assessment of ICP is faster, simpler, reproducible, noninvasive, and can be conducted at the bedside.

In this study, our objective was to examine ocular USG findings in sepsis-related encephalopathy and assess its relationship with mortality.

## Materials and Methods

This study was conducted as a prospective cohort study at the Emergency Department of Konya City Hospital from October 2021 to June 2022. Ethics committee approval for the study was obtained from the Necmettin Erbakan University Non-Drug and Non-Medical Device Research Ethics Committee (decision no: 2021/3413(7074), date: 17.09.2021) conducted in accordance with the principles outlined in the Declaration of Helsinki. The study included 100 men and women patients aged over 18 diagnosed with septic encephalopathy, all of whom provided consent either personally or through their relatives. A control group comprising 30 healthy adults aged over 18 was included in the study. Electronic and written documentation were used to record data from both the groups.

No formal a priori sample size calculation was performed before patient enrollment. After completion of the study, a sample size adequacy assessment was conducted for the primary comparison of ONSD between patients with SAE and healthy controls. Assuming a two-sided alpha level of 0.05, 80% power, an allocation ratio of approximately 3:1, and an anticipated moderate-to-large standardized effect size of 0.60 for the difference in ONSD, at least 89 patients and 30 controls were required. The final study population of 100 patients and 30 controls was therefore considered adequate for the primary between-group comparison. Analyses comparing survivors and non-survivors were considered exploratory because of the relatively small number of non-survivors.

We excluded patients under 18 years old, those with traumatic injuries, anatomical eye defects, optic neuritis, as well as individuals with an unassessable glasgow coma scale (GCS) score due to Alzheimer's disease and dementia. Patients with structural central nervous system disorders, such as intracranial mass, hemorrhage, or infarction, those with sepsis due to meningitis or encephalitis, acute renal failure, hyponatremia, hypernatremia, diabetic ketoacidosis, hyperosmolar nonketotic coma, hypoglycemia, Wernicke's encephalopathy, toxic drug overdose, hepatic encephalopathy, or suspected encephalopathy from metabolic or toxic abnormalities, pregnant patients, and those who declined to provide consent were also excluded.

Sepsis was diagnosed based on the current guideline criteria, identifying it as an inappropriate host response to the existing infection, subsequently causing organ dysfunction (10). The diagnosis of infection was confirmed by culture results.

Septic encephalopathy was defined as a GCS score below 15 or the presence of delirium symptoms (inattention, disorientation, altered thinking, decreased psychomotor activity, and/or agitation), accompanied by cognitive and neuropsychiatric impairment identified by healthcare personnel (physicians, nurses) or the relatives of a patient in a sepsis clinic (11).

Age, gender, systolic and diastolic blood pressures, pulse rate, saturation levels, GCS scores, Sequential Organ Failure Assessment (SOFA) scores, quick SOFA (qSOFA) scores, APACHE II scores, hematologic and biochemical markers, site and source of infection, ocular USG findings, duration of hospitalization, and in-hospital mortality were recorded.

Optic USG was performed after the patient was diagnosed with septic encephalopathy in the emergency department. The practitioner was trained and experienced in ocular USG and had 4 years of experience in ocular USG. All examinations were performed using a Mindray DC-80 ultrasound system with a linear probe (5-12 MHz). The procedure was conducted in a blinded manner, ensuring that participant information (patient and control) remained undisclosed. During the examination, patients were in the supine position with the head in a neutral position. Ocular USG was used to measure both the ONSD and the optic disc height (Figure 1 and 2). Using a closed-eye technique, a linear probe was placed directly onto the eyelid where gel was applied, and the eyeball was visualized in the transverse plane. ONSD was measured transversely, positioned

0.3 cm behind the papilla in the eyeball. To measure optic disc height, ultrasound imaging was used to determine the distance between the anterior apex of the optic disc and its intersection with the posterior surface of the globe. The measurements were performed three times for each eye, and the average value was calculated. The ocular USG findings were compared between the groups with septic encephalopathy and the healthy controls. Based on the acquired findings, the association between ocular USG findings and mortality was investigated.

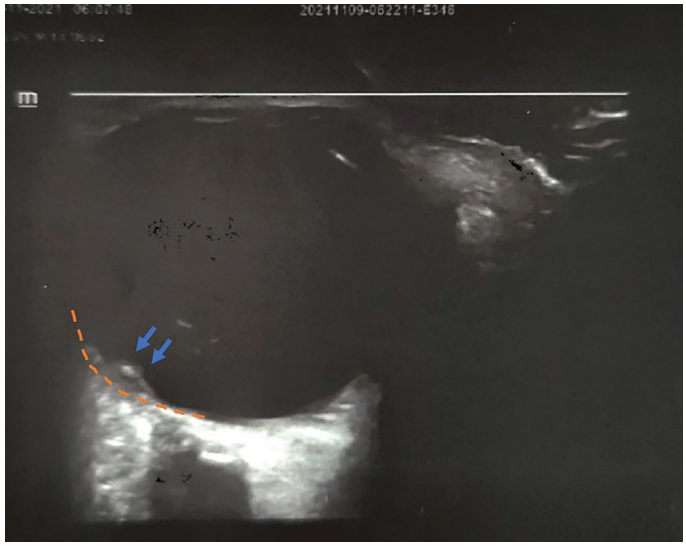

**Figure 1.** Ultrasonographic appearance of optic disc edema. Representative ocular ultrasonography image demonstrating optic disc elevation consistent with optic disc edema. The area protruding from the optical disk boundary, indicated by two blue arrows and orange dashed lines, is the optical disk elevation

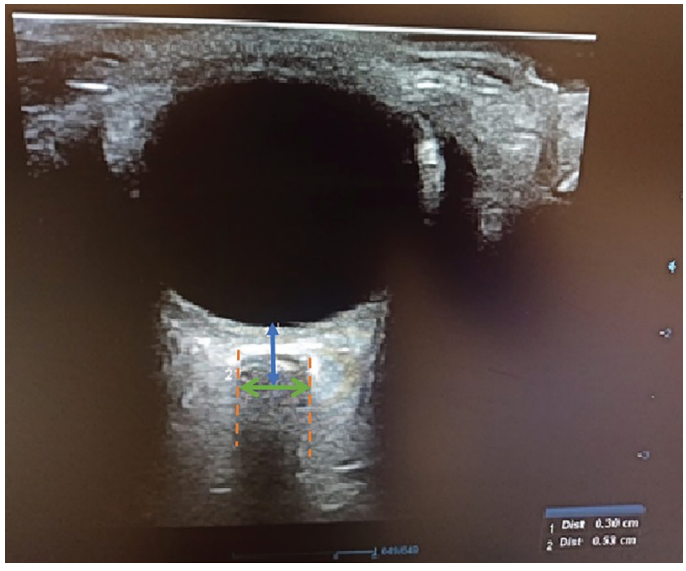

**Figure 2.** Ultrasonographic measurement of optic nerve sheath diameter. Representative ocular ultrasonography image showing the measurement of optic nerve sheath diameter, performed 3 mm posterior to the optic disc. The blue line indicates a distance of 3 mm from the optic disc. The dashed orange line indicates the boundaries of the optic nerve. The horizontal green line indicates the diameter of the optic nerve sheath

The data were entered into the SPSS 20 database for statistical analysis. The conformity of the variables to normal distribution was examined both visually (histogram and probability graphs) and analytically (Kolmogorov-Smirnov and Shapiro-Wilk tests). Descriptive statistics were reported as mean ± standard deviation (SD) for normally distributed variables, median [interquartile range (IQR)] for non-normally distributed variables, and n (%) for categorical variables. The Student's t-test was applied for normally distributed variables, the Mann-Whitney U test for non-normally distributed variables, and the Fisher's exact test (instead of the chi-square test) for categorical variables in comparisons between two independent groups. ROC curve analysis was performed to evaluate the discriminatory performance of ONSD measurements for mortality. The area under the curve (AUC) with 95% confidence intervals was calculated. The optimal cut-off values were determined using the Youden index method, and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratios were calculated. A p value <0.05 was considered statistically significant.

## Results

When analyzing the demographic characteristics of the study groups, the mean age was 70.07±15.9 years in the patient group and 69.2±12.7 years in the control group. There was no statistically significant difference between the groups in terms of age (p>0.05). In the patient group, 44% (n=44) were women, whereas 56% (n=56) were men. In the control group, the gender distribution was 50% women (n=15) and 50% men (n=15). When comparing the patient and control groups based on gender, no significant difference was observed (p>0.05). Demographic characteristics are presented in Table 1.

In our study, the source of infection was unidentified in 42 (42%) cases of pneumonia, 43 (43%) cases of urinary tract infection, 3 (3%) cases of acute gastroenteritis, and 5 (5%) cases.

Of the patients with infection, the source of infection was not found in 66 (66%). *E. coli* was the source in 13 (13%) patients, *Klebsiella pneumonia* in 5 (5%) patients, and Gram-positive *cocci* in 3 (3%) patients. The cause of infection was unidentified in 66 (66%) cases. Sources and causes of infection are shown in Table 2.

Out of the 100 patients included in the study, 18 did not survive, while 82 were discharged with recovery.

The mean right ONSD was 0.49±0.006 cm in the patient group and 0.40±0.02 cm in the control group. The mean left ONSD was

| Table 1. Demographic characteristics of study population | | | | |
|---|---|---|---|---|
| **Feature** | **Subgroup** | **Case group (n:100)** | **Control group (n:30)** | **p value** |
| Age (year) mean ± SD | | 70.07±15.9 | 69.2±12.7 | 0.77 |
| Gender %(n) | Male | 56% (n=56) | 50% (n=15) | 0.56 |
| | Woman | 44% (n=44) | 50% (n=15) | |
| Vital signs | SBP mmHg mean ± SD | 82.45±0.87 | | |
| | DBP mmHg mean ± SD | 49.9±0.93 | | |
| | Pulse/min. mean ± SD | 97.56±1.32 | | |
| Laboratory | WBC $0^3$/µL median (IQR) | 15.05 (9.43) | | |
| | HGB g/Dl median (IQR) | 12.7 (2.8) | | |
| | PLT $10^3$/µL median (IQR) | 239.5 (156.25) | | |
| | Glucose mg/dL median (IQR) | 133 (68.5) | | |
| | BUN mg/dL median (IQR) | 22 (12.5) | | |
| | Creatine mg/dL median (IQR) | 1.2 (0.58) | | |
| | Sodium mmol/L mean ± SD | 136.46±0.58 | | |
| | Potasıum mmol/L mean ± SD | 4.46±0.065 | | |
| | CRP mg/L mean ± SD | 223.29±9.49 | | |
| | Procalsitonin µg/L median (IQR) | 1.62 (9.42) | | |
| Scoring | GCS median (IQR) | 13 (2) | | |
| | qSOFA median (IQR) | 2 (1) | | |
| | SOFA median (IQR) | 6 (2) | | |
| | APACHE median (IQR) | 14 (10) | | |
| Losıng period (day) median (IQR) | | 9.5 (8) | | |
| ONSD | ONSD right (cm) mean ± SD | 0.49±0,006 | 0.40±0,02 | 0.00 |
| | ONSD left (cm) mean ± SD | 0.48±0.006 | 0.41±0.02 | 0.00 |
| ODE | ODE right (cm) mean ± SD | 0.009 ±0.03 | 0.00±0 | 0.01 |
| | ODE left (cm) mean ± SD | 0.005±0.01 | 0.00±0 | 0.006 |
| Mortality %(n) | | 18% (n=18) | | |

SD: Standard deviation, IQR: Interquartile range, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GCS: Glasgow coma score, WBC: White blood cell, HBG: Hemoglobin, PLT: Platelet, BUN: Blood urea nitrogen, CRP: C-reactive protein, USG: Ultrasonography, qSOFA: quick Sepsis Related Organ Failure Assessment, SOFA: Sequential Organ Failure Assessment, ONSD: Optic nerve sheath diameter, ODE: Optic disc elevation

| Table 2. Causes of infection sources | |
|---|---|
| **Escherichia coli** | **13** |
| *Enterococcus* | 2 |
| *Klebsiella pneumoniae* | 5 |
| *Staphylococcus aureus* | 1 |
| *Staphylococcus capitis* | 1 |
| *Leucocytes in sputum* | 2 |
| *Acinetobacter baumannii* | 1 |
| *Gram-positive cocci* | 3 |
| *Enterococcus faecium* | 1 |
| *Morganella morganii* | 1 |
| Coagulase-negative *Staphylococcus* | 1 |
| Group A beta-hemolytic *Streptococcus* | 2 |
| Gram-negative bacilli | 1 |
| Undiagnosed | 66 |

0.48±0.006 cm in the patients group and 0.41±0.02 cm in the control group. There was a significant difference between the patient and control groups in both right and left ONSD values (p<0.05). Among the other ocular USG parameters, the mean right optic disc elevation (ODE) measured 0.009±0.03 cm in the patient group and 0.00±0 cm in the control group. The mean left ODE was 0.05±0.1 cm in the patient group and 0.00±0 cm in the control group. Statistically significant differences were observed in both right and left ODE between the case and control groups (p<0.05).

In the comparison of survivors and non-survivors, the median (IQR) age of the 18 non-survivors was 77 (14) years, whereas the median (IQR) age of the 82 survivors was 73 (16) years (p=0.17). Among the non-survivors, 66.7% (12/18) were male, compared with 53.6% (44/82) of survivors (p=0.31). The median right ONSD was 0.52 (0.12) cm in non-survivors and 0.46 (0.06) cm in survivors, showing a difference close to statistical significance (p=0.06). The median left ONSD was significantly higher in non-survivors than in survivors [0.52 (0.11) cm vs. 0.46 (0.06) cm, respectively; p=0.01]. No significant differences were observed in right-eye ODE [0 (0.025) vs. 0 (0), p=0.08] or left-eye ODE [0 (0) vs. 0 (0), p=0.95]. A comparison of vital signs and laboratory parameters between survivors and non-survivors is presented in Table 3.

Sensitivity for right ONSD > 0.5 cm: 55.5 (30.8-78.5), specificity: 81.7 (71.6-89.4), PPV: 40 (26.5-55.3), NPV: 83.3 (83.2-93.4). (AUC is 0.70 and p: 0.003).

Sensitivity for left ONSD > 0.48 cm: 72.2 (46.5-90.3), specificity: 74.3 (63.6-83.4), PPV: 38.2 (28-49.7), NPV: 92.4 (85.1-96.3). (AUC 0.75 and p: 0.0003) (Figure 3). Table 4 presents the performance of ONSD in predicting mortality.

## Discussion

Our study is a prospective observational study investigating the diagnostic and prognostic significance of ONSD and ODE in

**Table 3. Comparison of dead and living patients**

| | Death n=18 | Live n=82 | p |
|---|---|---|---|
| Age year median (IQR) | 77 (14) | 73 (16) | 0.17 |
| Gender n (%) | %66.7 (12) | %53.6 (44) | 0.31 |
| Pulse min (%) | 115 (16.3) | 90 (10) | 0.00 |
| $SO_2$ %median (IQR) | 87.5 (6) | 90 (5) | 0.00 |
| SBP mmHG median (IQR) | 80 (10) | 90 (10) | **0.00** |
| DBP MmHG median n (IQR) | 40 (10) | 50 (20) | **0.001** |
| $WBC0^3/\mu L$ median (IQR) | 12.6 (10.5) | 15.65 (9.8) | 0.64 |
| HGB g/Dl median (IQR) | 10.9 (4.3) | 12.7 (2.3) | 0.038 |
| PLT $10^3/\mu L$ median (IQR) | 99.5 (224) | 250 (145.8) | **0.01** |
| Glucose mg/Dl median (IQR) | 141.5 (52.5) | 131.5 (86) | 0.8 |
| BUN mg/Dl median (IQR) | 21.5 (10.7) | 23.5 (13.25) | 0.78 |
| Creatine mg/Dl median (IQR) | 1.3 (0.6) | 1.1 (0.5) | 0.19 |
| Sodium mmol/ median (IQR) | 135 (9) | 137 (6) | 0.35 |
| Potasium mmol/L median (IQR) | 4.5 (0.9) | 4.4 (0.8) | 0.52 |
| CRP mg/L median (IQR) | 205 (195) | 232 (140.8) | 0.55 |
| Procalsitonin µg/L median (IQR) | 1.59 (50.3) | 1.67 (8) | 0.28 |
| APACHE median (IQR) | 27 (12) | 12 (7) | **0.00** |
| GCS median (IQR) | 12 (3) | 13 (1) | **0.00** |
| qSOFA median (IQR) | 3 (0) | 2 (0) | **0.00** |
| SOFA median (IQR) | 12.5 (3) | 5 (3) | **0.00** |
| ONSD rıght (cm) median (IQR) | 0.52 (0.12) | 0.46 (0.006) | 0.06 |
| ONSF left (cm) median (IQR) | 0.52 (0.11) | 0.46 (0.006) | **0.01** |
| ODE right (cm) median (IQR) | 0 (0.025) | 0 (0) | 0.08 |
| ODE left (cm) median (IQR) | 0 (0) | 0 (0) | 0.95 |

SD: Standard deviation, IQR: Interquartile range, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, GCS: Glasgow coma score, WBC: White blood cell, HBG: Hemoglobin, PLT: Platelet, BUN: Blood urea nitrogen, CRP: C-reactive protein, USG: Ultrasonography, qSOFA: quick Sepsis Related Organ Failure Assessment, SOFA: Sequential Organ Failure Assessment, ONSD: Optic nerve sheath diameter, ODE: Optic disc elevation

patients admitted to the emergency department with sepsis-related encephalopathy. Based on our study findings, patients diagnosed with septic encephalopathy exhibited enlarged ONSD and ODE in comparison to the healthy control group. Among patients diagnosed with SAE, both eyes showed higher ONSD measurements in non-survivors when compared to survivors. Although not statistically significant, mortality was numerically higher among patients with SAE who developed ODE compared with those without ODE (35% vs. 15%, p=0.06).

In sepsis, almost every organ can be affected or fail. In the respiratory system, sepsis can induce acute respiratory distress syndrome, whereas in the gastrointestinal tract, the effects can range from edema and inflammation on the bowel wall to ulcer, ileus, and hemorrhage. Hypovolemia, hypotension, and renal vasoconstriction can cause acute tubular necrosis and acute kidney failure. SAE is a severe neurological syndrome characterized by extensive brain dysfunction resulting from the body's abnormal response to infection (12,13).

Septic encephalopathy is one of the main manifestations of organ dysfunction caused by sepsis, excluding clinical or laboratory evidence of central nervous system infection, structural abnormality, or other forms of encephalopathy, such as hepatic encephalopathy or uremic encephalopathy. Septic encephalopathy refers to extensive brain dysfunction caused by sepsis and mainly manifests as delirium, cognitive impairment, reduced learning and memory abilities, and coma (14,15). Patients with septic encephalopathy may have any degree of disorientation and cognitive impairment, ranging from mild disturbance of consciousness to deep coma (12,16). In delirium due to sepsis, there is hypoactivity rather than hyperactivity (17).

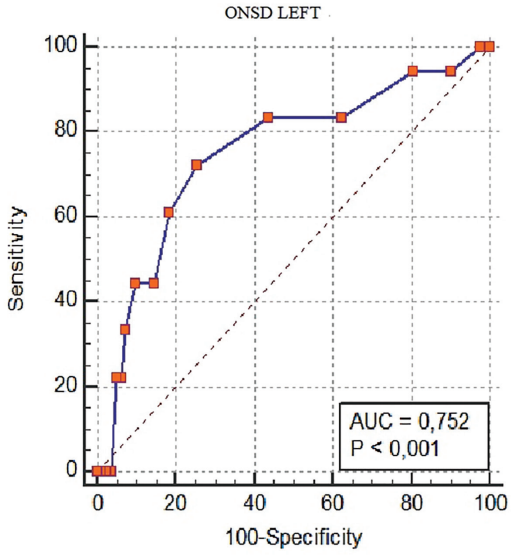


**Figure 3.** ROC curve analysis of left optic nerve sheath diameter (ONSD) for mortality. ROC curve demonstrating the discriminatory performance of left ONSD for mortality among patients with septic encephalopathy

AUC: Area under the curve

The underlying mechanism might be cerebral microvascular cell dysfunction, compromised integrity of the blood–brain barrier, mitochondrial malfunction, activation of microglia and astrocytes, and subsequent neuronal death (18,19). These mechanisms are not uniform throughout the brain, leading to varied clinical presentations based on the affected areas (20,21). No specific biomarker or radiological imaging method exists for the definitive diagnosis of septic encephalopathy. There are several biomarkers that indicate brain damage (22-24). These biomarkers have low sensitivity and specificity and have little clinical relevance (25). The use of blood biomarkers for diagnosing SAE faces challenges due to undefined optimal assessment timing, uncertainty about the exact onset of SAE, inconclusive findings on prognostic utility and precise thresholds, and limited accessibility to specific biomarkers, hindering their routine clinical application (26). In 20% of patients with septic encephalopathy, electroencephalography (EEG) reveals changes similar to those observed in nonconvulsive status epilepticus (27). At the same time, different wave activities can be monitored. However, sedative drugs, such as benzodiazepines, barbiturates and propofol, may cause similar abnormalities in EEG. Furthermore, EEG lacks specificity in assessing SAE, as similar abnormalities might manifest in various forms of encephalopathy (26). Radiological imaging studies rarely reveal lesions. In 30% of patients with septic shock, magnetic resonance imaging scans might display hyperintensity in the white matter, a finding suggestive of ischemia (28,29). While there have been multiple studies on the use of evoked potentials, their application is constrained by several factors, limited availability of devices in the intensive care setting, challenges in interpretation, and their moderate prognostic value within the sepsis population (26).

**Table 4. Performance characteristics of ONSD in predicting mortality**

| | Sensitivity (%95 CI) | Specificity (%95 CI) | +LR (%95 CI) | -LR (%95 CI) | +PV (%95 CI) | -PV (%95 CI) | AUC (%95 CI) | p |
|---|---|---|---|---|---|---|---|---|
| Right ONSD >0.5 | 55.5 (30.8-78.5) | 81.7 (71.6-89.4) | 3.04 (1.6-5.6 | 0.54 (0.3-0.9) | 40 (26.5-55.3) | 83.3 (83.2-93.4) | 0.70 (0.58-0.79) | 0.003 |
| Left ONSD >0.48 | 72.2 (46.5-90.3) | 74.3 (63.6-83.4) | 2.82 (1.8-4.5) | 0.37 (0.2-0.8) | 38.2 (28-49.7) | 92.4 (85.1-96.3) | 0.75 (0.69-0.86) | 0.0003 |

ONSD: Optic nerve sheath diameter, CI: Confidence İnterval, LR: Likelihood Ratio, PV: Predictive Value, AUC: Area under the curve

The diagnostic criteria and potential risk factors for septic encephalopathy remain poorly understood, lacking a reliable tool for the clinical assessment of neurological dysfunction associated with sepsis (30). As in many other organ dysfunctions, sepsis induces cerebral damage, resulting in cerebral edema. Cerebral edema secondary to SAE is recognized as one of the leading causes of complications and death in patients with sepsis, and early detection of intracranial hypertension is of great importance for timely intervention and improved prognosis (31). There are invasive and noninvasive diagnostic methods to detect brain edema.

Ocular USG, an inexpensive and easily conducted noninvasive bedside technique, has previously demonstrated its utility as an advantageous tool for clinicians in evaluating disease severity and clinical progression. In the initial studies conducted by Hansen et al. (32) in 1994 and later studies by Ohle (9) an association was established between the increase in ONSD and increased ICP, demonstrating high sensitivity and specificity. In a study conducting ultrasonographic evaluation of the optic nerve in patients with severe traumatic brain injury, those with ICP exceeding 22 mmHg exhibited significantly higher ONSD and ODE values. It was found that an ONSD greater than 0.72 demonstrated a sensitivity of 82% (48%-98%) and a specificity of 79% (70%-86%). An ODE greater than 0.04 cm demonstrated a sensitivity of 90% (56%-100%) and a specificity of 71% (61%-79%) (33). In another study in which USG ODE evaluation was performed by emergency physicians, maximum disc height greater than 0.6 cm predicted the presence of ODE noted on fundoscopic examination with a sensitivity of 82% (48%-98%) and a specificity of 76% (50%-93%) (34).

Only one study was identified that examined the relationship between SAE and ocular USG. In the study conducted by Yang et al. (31), ultrasound examination of the ONSD was conducted on 142 patients with sepsis. These patients were categorized into three groups: those who did not develop SAE, those who developed SAE, and those who developed SAE but eventually recovered. The median ONSD was 0.51 (0.475-0.54) cm, 0.59 (0.56-0.625) cm, respectively) and 0.535 (0.5075-0.55) cm across the respective patient groups. In their study, measurements were obtained with the patient's head elevated at a 30-degree angle. Patients with SAE had a significantly wider ONSD than patients without SAE ($p<0.001$) and patients with recovered SAE. Their study did not examine the association of ODE and ocular USG findings with mortality.

In our study, upon comparing the patient group with the control group, the mean right ONSD was $0.49\pm0.006$ in the patient group and $0.40\pm0.02$ in the control group, while the mean left ONSD measured $0.48\pm0.006$ in the patient group and $0.41\pm0.02$ in the control group. Additionally, 16% of the patients exhibited ODE. Among the patients with ODE, 35% did not survive, whereas 15% of those without USG ODE died ($p=0.06$). Hence, it is plausible that the ONSD might be enlarged in patients with sepsis-related encephalopathy. Our findings suggest that optic USG may represent a promising bedside tool for the assessment of patients with septic encephalopathy, although further validation studies are required. The increase in ONSD and the presence of ODE may be associated with adverse outcomes; however, further studies with larger sample sizes are needed to clarify their prognostic value. Specifically, the left ONSD demonstrates acceptable predictive capability for mortality, with an AUC of 0.75. It may also be useful in detecting low-risk patients with a NPV of 92.4%. Regarding cerebral resuscitation in patients exhibiting enlarged ONSD or ODE, directing interventions toward preventing fever, regulating blood pressure and ventilation, maintaining euglycemia, preventing electrolyte imbalances, and administering anti-edema therapy could potentially enhance mortality outcomes. In fact, Sonneville et al. (26) highlights the importance of preventing secondary damage in SAE and emphasize that precautions should be taken just like post-resuscitation care and neurocritical care guidelines, although they are not mentioned in sepsis guidelines. Laboratory tests including EEG and sensory evoked potentials used in the diagnosis of septic encephalopathy are both more expensive and not always easy to perform under intensive care conditions. Interpretation also requires expertise. USG represents an accessible, inexpensive diagnostic and monitoring modality, readily applicable by clinicians at the bedside. Its ease of training and widespread utilization in daily practice by intensive care and emergency medicine specialists underscore its significance. Considering various factors contributing to encephalopathy, including the use of sedatives and neurotoxic antibiotics, particularly during the intensive care unit management of sepsis patients, neurological assessments can be complex. We believe that patient monitoring through USG could serve as a valuable aid for clinicians in navigating these challenges.

### Study Limitations

Our study is one of the first studies investigating ocular USG findings in patients with septic encephalopathy. However, it also has some limitations. Firstly, this is the single-center design of our study and small sample size. Secondly, the diagnosis of septic encephalopathy relied on an exclusionary diagnostic approach, considering patient complaints, clinical findings, and investigations, a method commonly employed in similar studies. EEG and sensory evoked potentials were not performed because of the cost and the fact that these examinations can be performed in the electrophysiology laboratory of our hospital. A third limitation involves the

selection of the control group from healthy volunteers. In fact, it would have been better if the control group consisted of patients with sepsis without encephalopathy. However, studies have shown that EEG can reveal brain abnormalities in 50% of patients with laboratory evidence of bacteremia but no evidence of clinical encephalopathy on physical examination (with relatively preserved cognition) (35). Brain dysfunction is one of the earliest forms of organ dysfunction in sepsis, and sepsis-induced delirium occurs in as high as 70% of patients (36). The encephalopathy clinic may also occur later in the course of sepsis. The fact that we used qSOFA in the inclusion criteria according to the guidelines at that time and that this score includes those with low GCS made it difficult for us to take the control group from patients with sepsis without encephalopathy. Recognizing the potential bias arising from these factors, we composed the control group using healthy individuals. Multicenter and more comprehensive studies are needed. Another limitation of our study is that all ocular USG measurements were performed by a single experienced operator. Therefore, inter-rater reliability could not be assessed, and intra-rater reproducibility was not evaluated with repeated measurements. Future studies including multiple trained operators and repeated measurements are needed to further assess the reproducibility and clinical applicability of ocular USG-based ONSD measurements.

## Conclusion

In patients with SAE, the ONSD is wider than in healthy individuals and ODE may develop. An expanded ONSD can be used to predict mortality with an AUC of 0.75. There is currently no standard biochemical, radiological or electrophysiologic test for the diagnosis of SAE. Studies with USG are needed in this field and optical USG is promising in this respect. Moreover, we believe that further studies are needed to investigate the effect of interventions aiming to improve cerebral resuscitation on sepsis-related mortality in patients with enlarged ONSD and ODE.

### Ethics

**Ethics Committee Approval:** Ethics committee approval for the study was obtained from the Necmettin Erbakan University Non-Drug and Non-Medical Device Research Ethics Committee (decision no: 2021/3413(7074), date: 17.09.2021).

**Informed Consent:** This study was conducted as a prospective cohort study.

**Data availability:** The collected data sets are available from the corresponding author upon reasonable request in anonymized form.

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### Footnotes

### Authorship Contributions

Surgical and Medical Practices: M.A., N.B.A., R.K., Concept: M.A., R.K., Design: M.A., N.B.A., R.K., Data Collection or Processing: M.A., N.B.A., Analysis or Interpretation: M.A., R.K., Literature Search: M.A., N.B.A., R.K., Writing: M.A., N.B.A.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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