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ORIGINAL RESEARCH

Optic nerve sheath diameter as a predictor of altered mental status in drug intoxication patients

Keon Kim[1], Seong Jin Bae[2], Seong Jong Yun[3], Sun Hwa Lee[4,*]

[1]Department of Emergency Medicine, Ewha Womans University, Seoul Hospital, 07804 Seoul, Republic of Korea
[2]Department of Emergency Medicine, Chung-Ang University Hospital, 06973 Seoul, Republic of Korea
[3]Department of Radiology, G SAM Hospital, 15839 Gyeonggi, Republic of Korea
[4]Department of Emergency Medicine, Ewha Womans University, Mok-Dong Hospital, 07985 Seoul, Republic of Korea

***Correspondence**
sunhwa9@hanmail.net
(Sun Hwa Lee)

Abstract

Objectives: As far as we know, proposed the predictive performance of optic nerve sheath diameter measured (ONSD) from brain computed tomography to predict poor prognosis in drug intoxication patients. The aim of our study was to evaluate the predictive performance of ONSD for predicting mortality and admission in patients with altered mental status among drug intoxication patients.

Method: We retrospectively enrolled patients with drug intoxication patients who underwent brain computed tomography due to altered mental status between January 2018 and December 2019.

Two emergency physicians independently measured ONSD at 3 mm behind the globe in each patients. Statistical analysis including multivariate logistic regression analysis were yielded to estimate predictive performance.

Results: A total of 18 patients (8.7%) were death and 57 patients (24%) were admitted out of 206 patients. ONSD was independently predictive factors for predicting mortality and admission. ONSD (cut-off = 4.35) had 69.05% sensitivity and 53.33% specificity with area under the receiver operating characteristic curve of 0.824 (95% CI = 0.803–0.927) for predicting mortality among drug intoxication patients while the ONSD (cut-off = 3.96) had 100% sensitivity and 51.5% specificity with area under the receiver operating characteristic curve of 0.824 (95% CI, 0.722–0.927) for predicting admission among patients. There were excellent inter- and intra-observer agreements for measuring ONSD on brain CT.

Conclusion: ONSD was demonstrated as feasible predictive marker for predicting admission and mortality among drug intoxication patients with altered mental status. This information can help decision making for emergency physicians to provide prompt treatment in drug intoxication patients.

Keywords

Drug overdose; Computed tomograhy; Mortality; Outcome; Prognostic marker

1. Introduction

Drug intoxication (DI) become considerable health problem among physicians, patients and health care system due to increasing frequency, morbidity and mortality. Since 2008, DI has been the leading cause of injury-related fatality in the U.S about 50,000 death per year [1, 2]. According to this increasing incidence and interest, as emergency physician, determining prognosis and providing prompt timely treatment are essential to DI patients. Delayed diagnosis and inappropriate prognosification of DI can incur critical effects to patients including permanent sequelae and death.

However, the prognosification of DI is challenging since the patient's ability to provide a reliable history is often impaired because of drug's effect or patient's altered consciousness [3]. It is reported that toxicologic causes include variety of drugs and toxins, and accounts for from 20% to 25% of altered mental status (AMS) in ED. Brain computed tomography (CT) is greatly useful in discriminating neurologic causes and DI [4].

Accordingly, diagnosis of DI and differential diagnosis require thorough history taking, physical examination, electrocardiography, radiologic studies and laboratory studies yet limited. Several studies have reported electrocardiography, serum lactate level and GCS as prognostic tools in acute drug intoxication [5–8]. However, no study were done to show how predictive the finding is in radiologic exams.

Optic nerve sheath diameter (ONSD) has been identified as alternative tool of intracranial pressure (ICP) recently [9]. ONSD has been used to predict prognosis and mortality after brain traumatic injury, hemorrhagic/ischemic stroke and post-cardiac arrest [10, 11].

To the best our knowledge, there are no study has investigated the ability of ONSD as prognostic value in DI patients with AMS. In this study, we hypothesized high ONSD would

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be useful for predicting hospital length in such patients. Therefore, we aimed to evaluate the association between ONSD and the hospital length of DI patients presenting with AMS in ED.

2. Methods

2.1 Study design

This study was a single-centre, retrospective design using the electronic medical records (EMRs) of patients who presented in the ED with suspected DI patients who underwent brain CT. The study was approved by the Institutional Review Board, and the requirement for written informed consent was waived (IRB approval number: EUMC 2020-02-013).

2.2 Study setting and population

This study included patients who visited authors' hospital emergency department in tertiary teaching hospital visits from January 2018 through December 2019. The inclusion criteria were (1) patients aged 18 years old or older who visited the ED complaining of DI (within 24 hours of exposure); (2) confirmed DI by laboratory results or patients' statement of overdose during clinical process; (3) patients whose brain CT was performed simultaneously in the ED due to altered mentality.

The criteria of exclusion were (1) patients with an ophthalmologic disease, such as glaucoma, that could influence ONSD results; (2) patients with brain pathology such as stroke, hemorrhage, or brain tumor; (3) patients who had undergone brain surgery; (4) patients who had traumatic injury on head and (5) patients for whom there was insufficient EMR data.

2.3 Data collection and outcome measurement

The data was collected from EMRs that were stored in a picture archiving and communication system (PACS) (Infinitt PACS, Infinitt, Seoul, Republic of Korea). The data included patients' demographic characteristics including sex; age; laboratory findings; clinical manifestation including initial vital sign, and clinical outcomes such as admission, hospital length and mortality.

2.4 Image acquisition and ONSD measurement

In the authors' hospital, brain CT examinations was performed using a 320-slice multidetector CT scanner (Aquilion ONE Dynamic Volume CT, Toshiba Medical Systems Corporation, Otawara, Japan). Brain CTs were reconstructed with a series of 5 mm thicknesses parallel to the tuberculum sellae-occipital protuberance line.

All images were retrospectively and independently evaluated by two board-certified emergency physicians (9 years of experience and 7 years of experience) who were not involved in patient selection and who were blinded to the final diagnosis and outcome. They performed their evaluations in random order with respect to patient numeric code and radiographic image. ONSD was measured at a distance of 3 mm (ONSD3) behind the eyeball immediately below the sclera of a patient's left and right eyes using axial planes of brain CT images obtained with PACS in stack mode (Fig. 1). The ONSDs obtained for a patient's left and right eyes were averaged. Window parameters were spine window, middle third; window width: 60; window length: 360; accuracy: 1 pixel with 200% enlarged plane. All measurements were made using the same window, contrast, and brightness. Both reviewers agreed to measurement points and methods prior to image review.

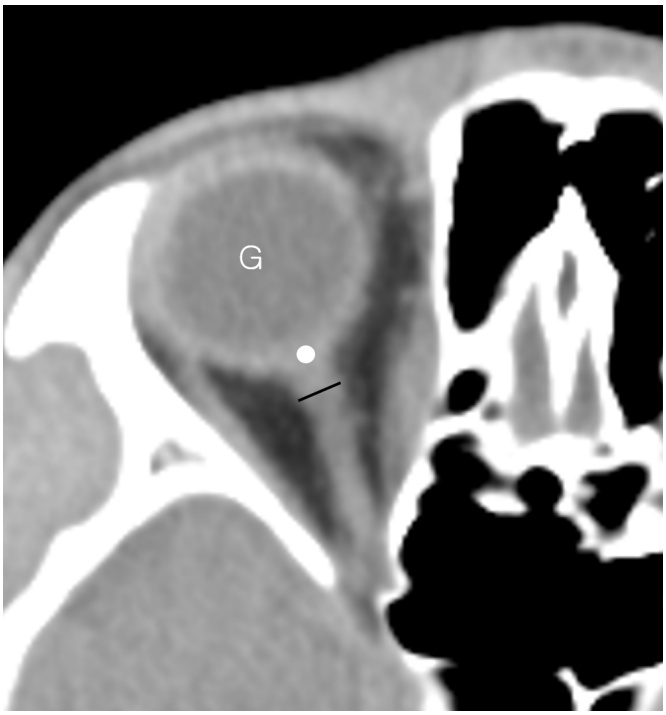

FIGURE 1. Use of axial non-contrast computed tomography to measure the optic nerve sheath diameter (ONSD). G, globe.

ONSD (solid line) was defined as the transverse diameter of 3 mm behind the globe (white point).

2.5 Statistical analysis

First, continuous variables are presented as means with SD (standard deviations) and ranges while categorical variables are presented as count (percent). We performed the statistical analysis which was evaluated normally distribution. Baseline clinical and demographic characteristics were summarized using the independent *t*-test was performed for continuous variables, and Pearson's chi-squared test was performed for numerical variables.

Second, to evaluate the independent factors for the prognosis of DI patients by mortality and admission, multivariate logistic regression analysis was applied to determine independent factors of prediction of prognosis using data from reviewer 1 (senior emergency physician). Multivariate logistic regression analysis was conducted. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were generated from multivariate analyses. Third, a receiver operating characteristic (ROC) curve analysis [including cut-off values for optimal area under the curve (AUC), sensitivity, and specificity] was performed to identify diagnostic performance of ONSD for predictive power

of prognosis of DI patients (mortality, admission). An optimal cut-off value was defined followed by Youden's index [12]. Fourth, intraclass correlation coefficients (ICCs) with 95% CIs were calculated to determine agreement between reviewers. Significance was set at $P < 0.05$. Statistical analyses were conducted using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1 Baseline characteristics

From January 2018 through December 2019, a total of 206 patients were finally enrolled in this study. The baseline characteristics are demonstrated in Table 1. The mean age of enrolled patients was 55.6 years and 56.1% of patients were female. The enrolled patients' mental status was predominantly verbal response (55.7%) and the most common overdosed drug classes was sleeping drugs (44.3%) following by cardiovascular drug (18%). Among them, 18 (8.7%) were death during clinical process.

3.2 Clinical factors associated with the prognosis of DI patients

Association between death and clinical, laboratory variables are presented in Table 2. In the univariate analysis, body temperature, leukocyte, BUN, creatinine, ONSD, hospital length were significantly higher in patients who died in clinical progress than in surviving patients. In the multivariate logistic regression analysis, ONSD was the only independent variable for prediction of mortality among DI patients.

A comparison analysis between admission and clinical factors are presented in Table 3. Univariate analysis was presented that pulse rate, respiratory rate, decreased alertness, leukocyte, BUN, Creatinine, ONSD, mortality were significant higher in admission group than in discharge group. On the other hand, systolic blood pressure, diastolic blood pressure were significantly low in admission group. In multivariate logistic regression analysis, leukocyte, ONSD, in hospital death were considered independent variables for prediction of admission in ED.

In addition, a comparison analysis mortality and clinical, laboratory variables was conducted among the patients whose level of consciousness below stupor presented in Table 4. In univariate analysis, leukocyte, BUN and ONSD were significantly higher in patients who died in clinical progress and glucose was lower than in surviving patients. In the multivariate logistic regression analysis, glucose and ONSD showed independent variables for prediction of mortality among DI patients.

3.3 Predictive value of ONSD in DI patients

The ROC curves of significant factors for the prediction of death are shown in Fig. 1. The AUC of ONSD for the prediction of death was 0.824 (95% CI, 0.803–0.927) and the cut-off value was 4.35 (Fig. 2). When we set cut-off value 4.35, the sensitivity was 69.05% and the specificity was 53.33% for predictive power of ONSD for prediction death in DI patients

TABLE 1. Demographic characteristics and clinical information of 206 patients.

Characteristic	
Age (years)	55.6 (19.6)
Sex	
Men (%)	73 (30.8)
Women (%)	133 (56.1)
Body mass index	23.9 (13.8)
Systolic blood pressure (mmHg)	128.0 (29.5)
Diastolic blood pressure (mmHg)	73.8 (16.9)
Pulse rate (/min)	88.5 (19.9)
Respiratory rate (/min)	20.3 (2.8)
Body temperature (°C)	36.4 (0.9)
Initial mental status	
Alert (%)	0 (0)
Verbal resoponse (%)	132 (55.7)
Painful response (%)	72 (30.4)
Unresponsiveness (%)	2 (0.8)
Type of ingested drug	
Sleeping drug (%)	105 (44.3)
Cardiovascular drug (%)	43 (18.1)
Neurologic or psychiatric drug (%)	30 (12.7)
Pesticide or herbicide (%)	7 (3)
Pain reducing drug (%)	10 (4.2)
Endocrine drug or insulin injection (%)	11 (4.6)
Leukocyte (10^9/L)	8.890 (4.3)
Hemoglobin (g/dL)	13.5 (1.9)
Platelet (10^9/L)	244.3 (72.8)
Aspartate aminotransferase (IU/L)	40.9 (85.4)
Alanine aminotransferase (IU/L)	23.2 (35.1)
C-reactive protein (mg/dL)	0.9 (2.5)
Glucose (mg/dL)	127.7 (71.6)
Blood urea nitrogen (mg/dL)	15.7 (9.9)
Creatinine (mg/dL)	0.86 (4.8)
Optic nerve sheath diameter, averaged (mm)*	4.0 (0.3)
Optic nerve sheath diameter, averaged (mm)†	3.97 (0.32)
Hospital day (days)	2.9 (7.7)
ICU stay (days)	1.8 (3.5)
Admission	
Discharge (%)	149 (62.9)
Admission (%)	57 (24)
Survival	
Alive (%)	188 (91.3)
Death (%)	18 (8.7)

Data are mean (standard deviation) or number (%).
** The average of ONSD result of first reviewer which has 9 years of experience.*
† The average of ONSD result of second reviewer which has 7 years of experience.

TABLE 2. Associations between death and clinical variables.

	Univariate analysis[a]		*P*	Multivariable logistic regression OR[†]	B	*P*
	Alive (n = 188)	Death (n = 18)				
Age (years)	54.9 (19.1)	62.1 (23.2)	0.48			
Sex			0.61			
Men	68 (36.2)	5 (27.8)				
Women	120 (63.8)	13 (72.2)				
Body mass index	23.9 (14.5)	24.1 (2.7)	0.97			
Systolic blood pressure (mmHg)	128.7 (28.9)	121.5 (35.4)	0.33			
Diastolic blood pressure (mmHg)	74.3 (16.9)	69.2 (17.8)	0.23			
Pulse rate (/min)	88.6 (19.4)	87.1 (25.3)	0.76			
Respiratory rate (/min)	20.0 (2.8)	20.4 (2.8)	0.81			
Body temperature (°C)	36.5 (0.6)	37.0 (1.2)	**0.03**	1.70 (0.9, 3.2)	0.5	0.09
Initial mental status			0.858			
Alert	0 (0)	0 (0)				
Verbal response	121 (64.4)	11 (61.1)				
Painful response	65 (34.6)	7 (38.8)				
Unresponsiveness	2 (1.1)	0 (0)				
Type of ingested drug			0.675			
Sleeping drug	97 (51.6)	8 (44.5)				
Cardiovascular drug	40 (21.3)	3 (16.7)				
Neurologic or psychiatric drug	27 (14.4)	3 (16.7)				
Pesticide or herbicide	4 (2.1)	3 (16.7)				
Pain reducing drug	9 (4.8)	1 (5.6)				
Endocrine drug or insulin injection	11 (5.9)	0 (0)				
Leukocyte (10^9/L)	8.7 (4.2)	10.9 (6.7)	**0.04**	1.0 (1.0, 1.0)	0	0.38
Hemoglobin (g/dL)	13.6 (1.9)	12.8 (2.3)	0.14			
Platelet (10^9/L)	243.7 (74.0)	249.9 (59.6)	0.73			
pH	7.39 (0.06)	7.36 (0.12)	0.116			
pCO_2	41.2 (8.19)	44.47 (17.5)	0.249			
pO_2	84.4 (23.4)	98.1 (48.3)	0.444			
AST (IU/L)	41.5 (89.2)	34.9 (15.5)	0.76			
ALT (IU/L)	23.5 (36.4)	20.1 (15.9)	0.69			
C-reactive protein (mg/dL)	0.9 (2.5)	1.0 (3.0)	0.79			
Glucose (mg/dL)	128.3 (73.3)	121.3 (52.2)	0.33			
BUN (mg/dL)	14.9 (8.8)	23.4 (15.9)	**0.01**	0.9 (0.9, 1.1)	-0.01	0.99
Creatinine (mg/dL)	0.8 (0.3)	1.3 (0.8)	**0.01**	0.3 (0.1, 1.1)	-1.2	0.06
ONSD	3.9 (0.3)	4.4 (0.3)	< **0.001**	**0.7 (0.01, 0.4)**	**-2.9**	**0.003**
Hospital length (days)	2.2 (6.4)	9.5 (15.6)	**0.01**	1.0 (0.9, 1.1)	0.02	0.56
Results			< **0.001**			
Discharge	146 (77.7)	3 (16.7)				
Admission	42 (22.3)	15 (83.3)		0.3 (0.04, 2.2)	-1.2	0.23

Boldface type indicates statistical significance (P < 0.05).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; B, regression coefficient; BP, blood pressure; BUN, blood urea nitrogen; ICU, intensive care unit; ONSD, optic nerve sheath diameter; OR, odds ratio.

[a] Data are mean (standard deviation) or number (%).

† Data in parentheses are 95% confidence intervals, conducted on variables with a P value of < 0.1 on univariate analysis.

TABLE 3. Association between admission and clinical variables.

	Univariate analysis[a]		*P*	Multivariable logistic regression OR[†]	B	*P*
	Admission (n = 57)	Discharge (n = 149)				
Age (years)	58.7 (20.2)	54.4 (19.2)	0.16			
Sex			0.06			
Men	26 (45.6)	47 (31.5)				
Women	31 (54.4)	102 (68.5)				
Body mass index	23.1 (3.2)	24.3 (16.2)	0.47			
Systolic blood pressure (mmHg)	124.1 (33.8)	129.6 (27.6)	**0.05**	1.0 (0.96, 1.01)	-0.01	0.44
Diastolic blood pressure (mmHg)	71.3 (18.7)	74.8 (16.2)	**0.04**	1.03 (0.99, 1.1)	0.03	0.19
Pulse rate (/min)	94.7 (24.1)	86.1 (17.6)	**0.02**	0.99 (0.96, 1.01)	-0.01	0.34
Respiratory rate (/min)	20.6 (4.1)	20.3 (2.2)	**0.01**	0.90 (0.77, 1.01)	-0.1	0.19
Body temperature (°C)	36.3 (0.8)	36.4 (0.9)	0.98			
Initial mental status			**0.001**			0.40
Alert	0	0				
Verbal response	39 (68.4)	93 (62.4)				
Painful response	17 (29.8)	55 (36.9)		1.37 (0.51, 3.7)	0.3	0.54
Unresponsiveness	1 (1.8)	1 (0.7)		0.14 (0.01, 3.8)	-1.9	0.24
Type of ingested drug			0.07			
Sleeping drug	24 (42.1)	81 (54.4)				
Cardiovascular drug	6 (10.5)	37 (24.8)				
Neurologic or psychiatric drug	13 (22.8)	17 (11.4)				
Pesticide or herbicide	6 (10.5)	1 (0.7)				
Pain	5 (8.8)	5 (3.4)				
Endocrine drug or insulin injection	3 (5.3)	8 (5.4)				
Leukocyte (10^9/L)	11.4 (5.5)	7.9 (3.4)	**0.01**	1.0 (1.0, 1.0)	0	**0.007**
Hemoglobin (g/dL)	13.8 (2.1)	13.4 (1.9)	0.12			
Platelet (10^9/L)	260.4 (65.9)	238.1 (74.5)	0.43			
pH	7.37 (0.12)	7.4 (0.1)	0.23			
pCO_2	93.5 (49.6)	87.5 (13.5)	0.65			
pO_2	43.2 (15.9)	37.1 (8.2)	0.07			
AST (IU/L)	41.5 (31.1)	40.7 (98.6)	0.61			
ALT (IU/L)	26.2 (26.9)	22.1 (37.8)	0.41			
C-reactive protein (mg/dL)	1.1 (2.5)	0.8 (2.5)	0.11			
Glucose (mg/dL)	136.8 (47.6)	124.2 (78.7)	0.98			
BUN (mg/dL)	19.4 (12.2)	14.2 (8.5)	**0.006**	1.01 (0.95, 1.1)	0.01	0.67
Creatinine (mg/dL)	1.1 (0.5)	0.8 (0.3)	**0.003**	0.75 (0.18, 3.13)	-0.3	0.69
ONSD	4.3 (0.4)	3.9 (0.2)	**0.03**	0.2 (0.0, 0.2)	-5.9	**0.01**
Mortality			**0.01**	0.2 (0.03, 0.91)	-1.8	**0.04**
Survival	42 (73.7)	146 (2.0)				
Death	15 (26.3)	3 (98.0)				

Boldface type indicates statistical significance ($P < 0.05$).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; B, regression coefficient; BP, blood pressure; BUN, blood urea nitrogen; GW, general ward; ICU, intensive care unit; OR, odds ratio.

[a] *Data are mean (standard deviation) or number (%).*

TABLE 4. Associations between death and clinical variables among level of consciousness bellows stupor.

	Univariate analysis[a]		*P*	Multivariable logistic regression OR†	B	*P*
	Alive (n = 67)	Death (n = 7)				
Age (years)	56.0 (18.9)	54.1 (21.0)	0.80			
Sex			0.41			
Men	24 (32.4)	1 (1.4)				
Women	43 (58.1)	6 (8.1)				
Body mass index	23.1 (3.1)	24.4 (2.3)	0.29			
Systolic blood pressure (mmHg)	124.7 (27.9)	124.1 (40.8)	0.97			
Diastolic blood pressure (mmHg)	70.4 (13.9)	71.0 (21.8)	0.92			
Pulse rate (/min)	89.2 (18.7)	88.7 (34.5)	0.96			
Respiratory rate (/min)	20.3 (2.7)	20.7 (3.6)	0.73			
Body temperature (°C)	36.3 (0.9)	36.1 (0.8)	0.48			
Initial mental status			0.82			
Painful response	65 (87.8)	7 (9.5)				
Unresponsiveness	2 (2.7)	0 (0)				
Type of ingested drug			0.49			
Sleeping drug	35 (47.3)	3 (4.1)				
Cardiovascular drug	17 (22.9)	2 (2.7)				
Neurologic or psychiatric drug	10 (13.5)	1 (1.4)				
Pesticide or herbicide	1 (1.4)	1 (1.4)				
Pain reducing drug	2 (2.7)	0 (0)				
Endocrine drug or insulin injection	2 (2.7)	0 (0)				
Leukocyte (10^9/L)	8.6 (3.2)	13.0 (5.7)	**0.09**	1.0 (1.0, 1.0)	0	0.08
Hemoglobin (g/dL)	13.6 (1.9)	14.2 (1.9)	0.47			
Platelet (10^9/L)	239.9 (74.4)	256.0 (45.0)	0.58			
AST (IU/L)	39.3 (39.1)	40.4 (16.8)	0.89			
ALT (IU/L)	23.4 (24.3)	23.1 (8.7)	0.95			
C-reactive protein (mg/dL)	0.6 (1.1)	2.1 (4.8)	0.45			
Glucose (mg/dL)	138.8 (108.0)	84.6 (42.4)	**0.02**	**1.0 (1.0, 1.1)**	**0.04**	**0.02**
BUN (mg/dL)	14.5 (6.6)	20.6 (6.6)	**0.02**	0.9 (0.8, 1.0)	-0.1	0.08
Creatinine (mg/dL)	0.8 (0.3)	1.3 (0.6)	0.05			
ONSD	3.9 (0.4)	4.3 (0.4)	**0.03**	**0.02 (0, 0.9)**	**-4.1**	**0.04**
Hospital length (days)	2.6 (7.9)	5.7 (7.6)	0.31			

Boldface type indicates statistical significance ($P < 0.05$).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; B, regression coefficient; BP, blood pressure; BUN, blood urea nitrogen; ICU, intensive care unit; ONSD, optic nerve sheath diameter; OR, odds ratio.
[a] Data are mean (standard deviation) or number (%).
† Data in parentheses are 95% confidence intervals, conducted on variables with a P value of < 0.1 on univariate analysis.

($P = 0.001$).

The AUC of ONSD for the prediction of death among patients whose level of consciousness below stupor was 0.734 (95% CI, 0.532–0.939) and the cut-off value was 4.4. When we set cut-off value 4.4, the sensitivity was 90.9% and the specificity was 57.1% for predictive power of ONSD for prediction death in DI patients ($P = 0.03$).

Prediction of admission for DI patients in ED using ONSD are presented in Fig. 2. The AUC of ONSD for the prediction of death was 0.824 (95% CI, 0.722–0.927) and the cut-off value was 3.96 (Fig. 3). When we set cut-off value 3.96, the sensitivity was 100% and the specificity was 51.5% for predictive power of ONSD for prediction admission in DI patients ($P = 0.001$).

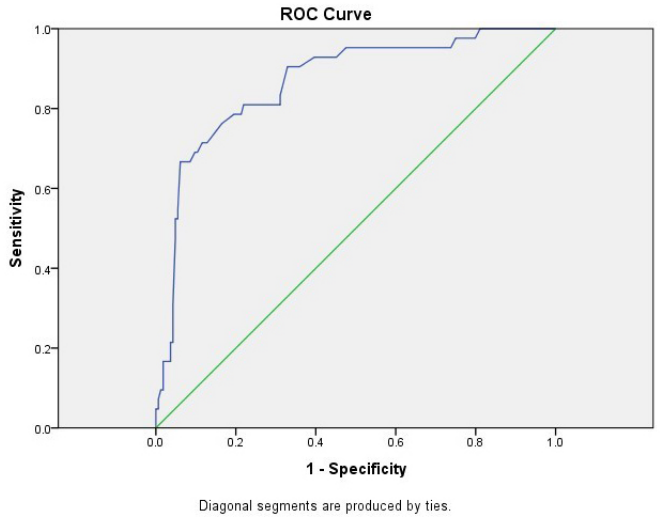

FIGURE 2. Receiver-operating characteristics (ROC) curves for predicting death in DI patients. AUC, area under the ROC curve; CI, confidence interval; DI, drug intoxication.

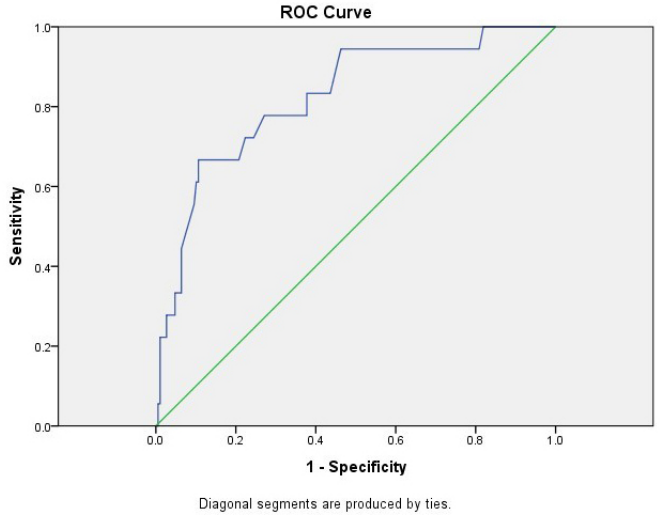

FIGURE 3. Receiver-operating characteristics (ROC) curves for predicting admission in DI patients. AUC, area under the ROC curve; CI, confidence interval; DI, drug intoxication.

4. Discussion

Our study found that ONSD values was independent poor prognosis predictor of DI patients presenting AMS in the ED. ONSD showed feasibility with 69.05% sensitivity and 53.33% specificity for predicting mortality and 100% sensitivity for predicting admission. Therefore, we speculate ONSD value can predict mortality and assist ED physicians determining admission.

Traditionally, measuring ICP needs invasive procedures such as lumbar puncture and ventricular catheterization. The optic nerve sheath is surrounded by cerebrospinal fluid (CSF). Increased ICP is transmitted to subarachnoid space surrounding the optic nerve, causing optic nerve sheath expansion. Through measuring ONSD on brain CT, we can predict ICP without invasive procedures [9].

Acute drug intoxication is related to cerebral edema and increased ICP. Previous studies suggest several pathophysiological mechanisms of increased ICP after DI. Many drugs can trigger acute hypoxia by CNS depression (eg. opiates, barbituates, ethanol, methanol), impairing oxygen diffusion (eg. opiates, salicylates, hydrocarbons, paraquat, smoke), paralysis of the ventilator muscles (eg. NM blockers, tetanus toxin, organophosphate), displace oxygen in the lungs (eg. methane, propane, nitrogen) and cellular asphyxiantes (eg. CO, cyanide, methemoglobinemia) [13–15].

Acute hypoxia brakes the balance of cerebral oxygen supply and use. As cerebral oxygen supply decreases, adenosine triphosphate production also decreases, causing cessation of energy-dependent ion channel function. It causes influx of sodium and water into ischemic cells and cytotoxic edema. Consequently, endothelial cells loss their function, it leads to porous blood-brain barrier, formation of vasogenic cerebral edema follows [16]. Parenchymal bulk from cerebral edema cause intracranial hypertension because of fixed intracranial volume consisted by cranial bone [17].

Additionally, disturbing respiratory drive, acute drug intoxication can cause hypocapnia or hypercapnia. Sustained hypocapnia decreases cerebral blood flow and induces ischemic brain damage by increasing cerebral oxygen extraction. Hypercapnia is a cerebrovascular vasodilator, it causes hyperemia and exacerbates ICP [16].

Some drugs can cause cerebral edema after indigestion. The exact mechanisms is unclear, but these drugs can cause cerebral edema during their metabolism [14, 15] (eg. methamphetamine, opioids, valproic acids).

There is no standard method for measuring ONSD. Previous study suggested that measuring ONSD 3 mm behind the globe was useful for predicting elevated ICP. Based on previous study, we selected distances of 3 mm behind the globe for measuring ONSD on brain CT [18]. In a different way, we can measure ONSD on ultrasound, but this technique have a higher risk of bias related to patient position, compliance and the different observer [19].

In previous study, ED physicians predict prognosis of DI patients based on physical examination, electrocardiogram and laboratory data. Yet, not every drugs mechanism of action and metabolism are the same, ED physicians may consider various ways to predict prognosis of DI patients. ONSD measurement on brain CT takes just few minutes, we expect ONSD may be a highly useful tool for predicting mortality and determining admission in DI patients.

This study has several limitations. First, the result from our study is limited to generalize since the study was retrospective and designed for single hospital. Furthermore, the study retrospectively evaluated EMR and differences in patient management of different physicians who had varying experience managing DI patients. Second, only DI patient presenting AMS took brain CT scan. Most DI patients who were presenting alert mental status did not take brain CT, and therefore, there should be careful to interpret and generalize our result. Furthermore, prospective and multi-center studies are required to generalize contexts. Despite of these limitations, we suggest that ONSD is useful and reliable predictor for managing DI patients presenting AMS.

5. Conclusions

In conclusion, ONSD measurement is a predictive tool for drug intoxication in patients with altered mental status. ONSD larger than 4.23 mm showed good sensitivity and specificity for predicting patients' mortality and ONSD larger than 3.96 mm showed feasible sensitivity and specificity for predicting patients' admission. ONSD measurement can assist emergency physicians with decision to more intensive care in drug intoxication patients with altered mental status.

AUTHOR CONTRIBUTIONS

Conception and design: KK. Acquisition, analysis, and interpretation of data: SJB, SHL. Drafting the manuscript for intellectual content: SJB, SJY. Statistical analysis: SJB, SHL. All authors reviewed: revised: and approved the manuscript for submissions. Study supervision: SHL.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board, and the requirement for written informed consent was waived (IRB approval number: EUMC 2020-02-013).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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