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ORIGINAL RESEARCH

Association between the neurological pupil index and the cause of altered level of consciousness in the emergency department: a cross-sectional observational study

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Abstract

Altered level of consciousness (ALC) is a common chief complaint during emergency department (ED) visits, with a broad spectrum of disease causes. The neurological pupil index (NPI) is an objective method for assessing the pupillary light reflex (PLR) by measuring pupil-related indices in patients with ALC. This study hypothesized that NPI values would differ according to the cause of ALC and aimed to determine the association between NPI values and the cause of ALC in patients admitted to the ED. Patients with a chief complaint of ALC or those who presented with signs of ALC as perceived by healthcare providers in the ED were enrolled. The main exposure was the NPI value measured in the ED at either the arrival time or when ALC was first detected and 1 hour after the initial NPI check. The primary outcome was ALC etiology, which included non-brain and brain causes. Multivariable logistic regression analysis was performed to test the association between the NPI value and cause of ALC. A total of 607 patients were analyzed. The proportions of non-brain *vs.* brain causes in the initial NPI <3 and initial NPI ≥ 3 groups were 52.4% *vs.* 36.1% and 66.4% *vs.* 17.2%, respectively. The proportions of non-brain *vs.* brain causes in the 1-hour NPI <3 and 1-hour NPI ≥ 3 groups were 46.2% *vs.* 41.8% and 68.4% *vs.* 15.6%, respectively. In the multivariable logistic regression analysis, the adjusted odds ratio (AOR) of initial NPI ≥ 3 was 2.28 and 0.27 for non-brain and brain causes. The AORs of 1-hour NPI ≥ 3 for non-brain and brain causes were 2.75 and 0.21, respectively. If the initial and 1-hour NPIs are <3, the ALC is likely caused by brain-related issues. Conversely, if the initial and 1-hour NPIs are ≥ 3, the ALC is likely caused by non-brain-related issues.

Keywords

Neurological pupil index; Consciousness; Etiology; Emergency department

1. Introduction

Altered level of consciousness (ALC) refers to any change or deterioration in a patient's mental status [1]. ALC can cause a wide range of diseases, including central nervous system and metabolic disorders, adverse reactions to prescribed drugs, and infections. ALC is a common chief complaint during emergency department (ED) visits, occurring in approximately 40% of the older patients [2, 3]. Furthermore, the terms "loss of consciousness", "altered mental status", and "disorders of consciousness" are synonyms of ALC and have obscured the etiologies of ALC [4–6].

Severe etiologies such as systemic infection, metabolic causes, stroke, drug intoxication (DI), cardiovascular issues, seizures, psychiatric disorders, and traumatic brain injury can cause ALC [4, 7, 8]. Making a correct diagnosis in the ED is challenging due to limited resources, time constraints, and the dynamically changing disease characteristics [7]. However, it is crucial to identify the etiology of ALC in the ED, as different etiologies require different approaches, such as physical examinations, laboratory and radiologic evaluations, and treatment plans [1, 9].

There are several ways to evaluate ALC, such as using the Glasgow Coma Scale (GCS) or alert, voice, pain, unresponsive (AVPU) scale. The GCS was introduced in 1974 as the first objective grading scale to determine a patient's level of consciousness [10]. The AVPU scale is another widely used tool for evaluating the level of consciousness owing to its simplicity (four grades instead of the 15 grades of the GCS) [6, 11]. The AVPU scale is often preferred to the GCS in prehospital settings because the GCS is complicated evaluation tool. Although these are the most widely used evaluation tools,

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grading scales have an inherent interrater discrepancy [12].

The NPI is a proprietary algorithm combined with a pupillometer to detect the pupillary light reflex (PLR) and record pupil size, constriction velocity, dilation velocity, and latency [13]. An NPI value <3 is considered an abnormal PLR, indirectly indicating ALC dysfunction [14, 15]. In a previous study, the NPI value showed a strong correlation with GCS among patients in critical care units [16]. Thus, the NPI can be used as an objective tool to evaluate ALC, supplementing the GCS or AVPU evaluation. We hypothesized that NPI values would differ according to the cause of ALC. Therefore, this study aimed to determine the association between NPI score changes and the cause of ALC in patients with ALC who visited the ED.

2. Methods

2.1 Study design and setting

This retrospective, observational, cross-sectional study used the Workup on Awakeness for Koma Evaluation, Unicenter registry (WAKE-Up). The registry data were collected from a tertiary teaching hospital in Gyeonggi Province, South Korea, between January 2022 and December 2023. The hospital is a regional level I emergency center with an annual ED volume of approximately 70,000 patients.

2.2 Data source and collection

Patients with a chief complaint of ALC or who presented with signs of ALC as perceived by healthcare providers in the ED were enrolled in the WAKE-Up registry. Patients with Do-Not-Resuscitation (DNR) and ALC after the return of spontaneous circulation during cardiac arrest were not included in the registry. When patients were enrolled, trained healthcare providers reviewed their medical records and checked the diagnostic results, laboratory findings and hospital disposition. For patients with ALC, NPI was measured in both the left and right eyes upon arrival at the ED and at 1, 3, 6 and 24 hours in routine clinical practice.

2.3 Study population

This study included adult patients aged ≥18 years; patients who presented with new-onset ALC compared to their baseline consciousness; patients with baseline cerebral performance category (CPC) of 1, 2 or 3; and patients with ED direct visits were included. The CPC is a five-point scale used to categorize neurological status after cardiac arrest. CPC 1 and 2 are generally considered good outcomes, whereas 3 and 4 are considered poor outcomes. A CPC of 5 indicates death. Patients with missing NPI values at the initial visit or 1 hour in the ED and those with missing outcomes were excluded.

2.4 Variables

The main exposure was NPI values measured in the ED at either the time of arrival or when ALC was first detected as well as 1 hour after the initial NPI check. The NPI values were dichotomized in the following manner: The combination of the initial and 1-hour NPI values was determined by grouping participants as follows: Group 1 (initial NPI <3 and 1-hour NPI <3), Group 2 (initial NPI ≥3 and 1-hour NPI <3), Group 3 (initial NPI <3 and 1-hour NPI ≥3) and Group 4 (initial NPI ≥3 and 1-hour NPI ≥3). When the NPI was measured in both eyes, the smaller value was set as the representative value. Demographic data including age, sex, comorbidities (hypertension, diabetes mellitus, liver cirrhosis, psychosis, ischemic stroke, and brain hemorrhage), and hospital information, including oxygen saturation (SpO_2), initial GCS, and 1-hour GCS were collected.

2.5 Outcome measures

The primary outcome was ALC etiology, namely non-brain (metabolic and DI) and brain (ischemic stroke and hemorrhage) causes. Metabolic causes include electrolyte imbalances, such as acute kidney injury (AKI), hyponatremia, and hyperammonemia as well as hepatic encephalopathy, diabetic ketoacidosis (DKA), and systemic infections such as pneumonia, cholangitis, and pyelonephritis. Drug intoxication encompasses an overdose of prescribed medications. An ischemic stroke comprises any type of arterial occlusion that leads to brain injury. Brain hemorrhages included intracerebral hemorrhage (ICH), subdural hemorrhage (SDH), subarachnoid hemorrhage (SAH), epidural hemorrhage (EDH), and intraventricular hemorrhage (IVH).

2.6 Statistical analysis

Patient demographics and factors related to ALC, such as age, sex, comorbidities, SpO_2, and GCS findings, were compared according to exposures and outcomes. Categorical variables were described using counts and proportions and compared using the chi-squared test. Continuous variables were presented as the median and interquartile range (IQR) using the Kruskal-Wallis test. Multivariable logistic regression analysis was performed to test the association between the NPI group and the cause of ALC. The potential factors that could influence the results, such as age, sex, comorbidities, SpO_2, and GCS findings, were taken into account and adjusted for. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the outcomes. All analyses were performed using the R software package, version 4.1.3 (R Foundation for Statistical Computing). A two-tailed p-value < 0.05 was considered statistically significant.

3. Results

Of the 788 eligible patients with ALC, 607 were analyzed, excluding patients with unknown outcomes (n = 6), unknown exposures (n = 67), pediatric patients aged <18 years (n = 5), baseline CPC >3 (n = 48), and those transferred from other facilities (n = 55) (Fig. 1).

In Table 1, the patients were analyzed according to the initial and 1-hour NPI values. The numbers (%) of patients with initial NPI <3 and initial NPI ≥3 were 166 (27.3%) and 441 (72.7%), respectively. The proportion of males was 57.2% in the initial NPI <3 group. The median SpO_2 values in the initial NPI <3 and initial NPI ≥3 groups were 98% (95–100%) and 98% (96–99%), respectively. The proportions of non-brain

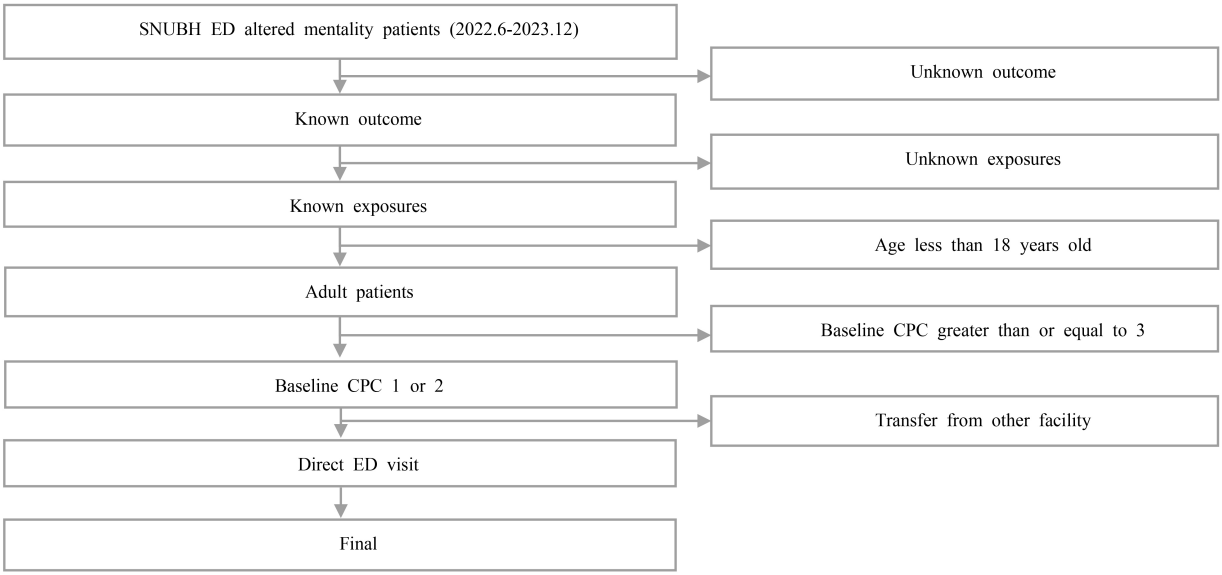


FIGURE 1. Study flow chart. CPC: Cerebral Performance Category; ED: Emergency Department.

causes in the initial NPI <3 and initial NPI ≥3 groups were 52.4% and 66.4%, respectively, and the proportions of brain causes were 36.1% and 17.2%, respectively. The numbers (%) of patients with 1-hour NPI <3 and 1-hour NPI ≥3 were 158 (26.0%) and 449 (74.0%), respectively. The median SpO_2 values in the 1-hour NPI <3 and 1-hour NPI ≥3 groups were 97% (95–99%) and 98% (96–99%), respectively. The proportions of non-brain causes in the 1-hour NPI <3 and 1-hour NPI ≥3 groups were 46.2% and 68.4%, respectively, and the proportions of brain causes were 41.8% and 15.6%, respectively (Table 1).

In the multivariable logistic regression analysis, the AOR (95% CIs) of non-brain cause in the initial NPI ≥3 group was 2.28 (1.51–3.44). The AOR of brain cause in the initial NPI ≥3 group was 0.27 (0.17–0.43). The AOR of brain hemorrhage in the initial NPI ≥3 group was 0.21 (0.13–0.34) (Table 2).

In multivariable logistic regression analysis, the AORs of the 1-hour NPI ≥3 group for the non-brain cause was 2.75 (1.81–4.16) compared to the 1-hour NPI <3 group. For metabolic cause, the AORs of the 1-hour NPI ≥3 group was 1.84 (1.16–2.94) compared to the 1-hour NPI <3 group. The AORs of the 1-hour NPI ≥3 group for brain cause was 0.21 (0.13–0.34) compared to the 1-hour NPI <3 group. For brain hemorrhage, the AORs of the 1-hour NPI ≥3 group was 0.16 (0.10–0.27) compared to the 1-hour NPI <3 group (Table 3).

Of the 607 patients included, the numbers (percentages) of patients in each exposure group were as follows: 127 (20.9%) in Group 1, 31 (5.1%) in Group 2, 39 (6.4%) in Group 3 and 410 (67.5%) in Group 4. The median ages (IQR) of Groups 1, 2, 3 and 4 were 67 (55–81), 63 (47–71), 71 (51–82) and 73 (55–83), respectively. The proportions of males in Groups 1, 2, 3 and 4 were 56.7%, 51.6%, 59.0% and 46.1%, respectively. The median (IQR) of initial and 1-hour GCS were the highest in Group 4, at 9 (7–12) and 10 (7–13), and the lowest in Group 1, at 7 (4–9) and 5 (3–8). The proportions of non-brain and brain cause in Groups 1, 2, 3 and 4 were 46.5%, 45.2%, 71.8% and 68.0% and 44.1%, 32.3%, 10.3% and 16.1%, respectively (Table 4).

Table 5 shows the association between the NPI combination group and outcomes. In the multivariable logistic regression analysis, the AORs (95% CIs) for non-brain cause were 1.03 (0.43–2.47) for Group 2, 1.92 (0.82–4.48) for Group 3 and 2.86 (1.81–4.50) for Group 4. The AORs for brain cause for Groups 2, 3 and 4 were 0.62 (0.24–1.61), 0.23 (0.07–0.72) and 0.19 (0.11–0.32), respectively. The AORs for brain hemorrhage cause for Groups 2, 3 and 4 for were 0.56 (0.21–1.48), 0.19 (0.05–0.68) and 0.14 (0.08–0.25), respectively (Table 5).

4. Discussion

The NPI was calculated using an automated pupillometer. The NPI measures baseline pupil size, maximum constriction size, pupil latency, pupil constriction rate, and pupil redilation and combines these individual measurements into a single score that reflects the overall function of the PLR pathway [17]. A registry study analyzing single-center retrospective data from a regional level I emergency center found that patients who visited the emergency room with ALC and had NPI values ≥3 initially and 1 hour later were more likely to have metabolic causes or DI than those with values <3 at both time frames. The probability of hemorrhage was low. The results of this study are expected to help establish the direction of ED treatment in clinical settings.

To our knowledge, no previous studies have examined the association between NPI values and ALC etiology in patients in the ED. The PLR is a series of reactions that constrict the pupils in response to light stimulation. This reflex pathway involves the following structures: retinal ganglion cells, optic nerve (cranial nerve II), optic chiasm, pretectal nucleus (anterior to the superior colliculus), oculomotor Edinger-Westphal nuclei, oculomotor nerve (cranial nerve III), short ciliary nerves, and sphincter muscle of the pupil [18, 19]. Depending on the mechanism of PLR and the location of the lesion in the brain, there may be a difference in the PLR of the two eyes. This study also showed that when the NPI was <3, the possibility of ALC caused by brain damage was high.

TABLE 1. Demographic findings according to the initial and 1-hour NPI.

		All		Initial NPI <3		Initial NPI ≥3		*p*-value	All		1-hour NPI <3		1-hour NPI ≥3		*p*-value
		N	%	N	%	N	%		N	%	N	%	N	%	
Variables		607	100.0	166	27.3	441	72.7		607	100.0	158	26.0	449	74.0	
Age															
	<65	245	40.4	76	45.8	169	38.3	0.095	245	40.4	78	49.4	167	37.2	0.007
	≥65	362	59.6	90	54.2	272	61.7		362	59.6	80	50.6	282	62.8	
Median (IQR)		71 (54–82)		67 (54–81)		72 (54–82)		0.290	71 (54–82)		65 (52–80)		72 (55–83)		0.028
Sex	Male	300	49.4	95	57.2	205	46.5	0.018	300	49.4	88	55.7	212	47.2	0.067
Past Medical Hx															
	HTN	238	60.8	103	62.0	266	60.3	0.697	238	60.8	96	60.8	273	60.8	0.993
	DM	184	30.3	53	31.9	131	29.7	0.595	184	30.3	48	30.4	136	30.3	0.983
	LC	51	8.4	22	13.3	29	6.6	0.008	51	8.4	15	9.5	36	8.0	0.565
	Psychosis	184	30.3	46	27.7	138	31.3	0.392	184	30.3	39	24.7	145	32.3	0.073
	Ischemic stroke	79	13.0	22	13.3	57	12.9	0.915	79	13.0	25	15.8	54	12.0	0.222
	Brain hemorrhage	39	6.4	11	6.6	28	6.3	0.901	39	6.4	12	7.6	27	6.0	0.486
SpO_2 (%)															
	<80	47	7.7	16	9.6	31	7.0		47	7.7	16	10.1	31	6.9	
	≥80–<94	50	8.2	16	9.6	34	7.7	0.386	50	8.2	12	7.6	38	8.5	0.417
	≥94	510	84.0	134	80.7	376	83.3		510	84.0	130	82.3	380	84.6	
Median (IQR)		98 (95–99)		98 (95–100)		98 (96–99)		0.626	98 (95–99)		97 (95–99)		98 (96–99)		0.148
Initial GCS	Median (IQR)	8 (6–11)		7 (4–10)		9 (7–12)		<0.001	8 (6–11)		7 (4–10)		9 (7–12)		<0.001
1-hour GCS	Median (IQR)	9 (6–12)		6 (3–10)		9 (7–13)		<0.001	9 (6–12)		6 (3–9)		10 (7–13)		<0.001
Non-brain cause	Yes	380	62.6	87	52.4	293	66.4	<0.001	380	62.6	73	46.2	307	68.4	<0.001
Metabolic	Yes	258	42.5	68	41.0	190	43.1	0.637	258	42.5	54	34.2	204	45.4	0.014
DI	Yes	122	20.1	19	11.4	103	23.4	<0.001	122	20.1	19	12.0	103	22.9	<0.001
Brain cause	Yes	136	22.4	60	36.1	76	17.2	<0.001	136	22.4	66	41.8	70	15.6	<0.001
Ischemic stroke	Yes	31	5.1	6	3.6	25	5.7	0.305	31	5.1	6	3.8	25	5.6	0.385
Brain hemorrhage	Yes	105	17.3	54	32.5	51	11.6	<0.001	105	17.3	60	38.0	45	10.0	<0.001

NPI: Neurological pupil index; IQR: Interquartile range; HTN: Hypertension; DM: Diabetes mellitus; LC: Liver cirrhosis; SpO_2: Oxygen saturation; GCS: Glasgow coma scale; DI: Drug intoxication.

TABLE 2. Association analysis between the initial NPI and the cause of the altered level of consciousness.

Outcomes						
Non-brain cause						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Initial NPI <3	Reference			Reference		
Initial NPI ≥3	1.80	1.25	2.59	2.28	1.51	3.44
Metabolic						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Initial NPI <3	Reference			Reference		
Initial NPI ≥3	1.09	0.76	1.57	1.49	0.95	2.34
DI						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Initial NPI <3	Reference			Reference		
Initial NPI ≥3	2.36	1.39	3.99	2.31	1.24	4.32
Brain cause						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Initial NPI <3	Reference			Reference		
Initial NPI ≥3	0.37	0.25	0.55	0.27	0.17	0.43
Ischemic stroke						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Initial NPI <3	Reference			Reference		
Initial NPI ≥3	1.60	0.65	3.98	1.22	0.47	3.15
Hemorrhage						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Initial NPI <3	Reference			Reference		
Initial NPI ≥3	0.27	0.18	0.42	0.21	0.13	0.34

NPI: neurological pupil index; OR: odds ratio; CI: confidence interval; DI: drug intoxication.

TABLE 3. Association analysis between the 1-hour NPI and the cause of the altered level of consciousness.

Outcomes						
Non-brain cause						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
1-hour NPI <3	Reference			Reference		
1-hour NPI ≥3	2.52	1.74	3.65	2.75	1.81	4.16
Metabolic						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
1-hour NPI <3	Reference			Reference		
1-hour NPI ≥3	1.60	1.10	2.34	1.84	1.16	2.94
DI						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
1-hour NPI <3	Reference			Reference		
1-hour NPI ≥3	2.18	1.29	3.69	2.20	1.18	4.10
Brain cause						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
1-hour NPI <3	Reference			Reference		
1-hour NPI ≥3	0.26	0.17	0.39	0.21	0.13	0.34

TABLE 3. Continued.

Outcomes						
Ischemic stroke						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
1-hour NPI <3	Reference			Reference		
1-hour NPI ≥3	1.49	0.60	3.71	1.17	0.45	3.05
Hemorrhage						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
1-hour NPI <3	Reference			Reference		
1-hour NPI ≥3	0.18	0.12	0.28	0.16	0.10	0.27

NPI: neurological pupil index; OR: odds ratio; CI: confidence interval; DI: drug intoxication.

TABLE 4. Demographic findings according to the initial and 1-hour NPI combination.

		NPI combination										*p*-value
		All		Group 1		Group 2		Group 3		Group 4		
		N	%	N	%	N	%	N	%	N	%	
Variables		607	100.0	127	20.9	31	5.1	39	6.4	410	67.5	
Age												
	<65	245	40.4	59	46.5	19	61.3	17	43.6	150	36.6	0.017
	≥65	362	59.6	68	53.5	12	38.7	22	56.4	260	63.4	
Median (IQR)		71 (54–82)		67 (55–81)		63 (47–71)		71 (51–82)		73 (55–83)		0.017
Sex	Male	300	49.4	72	56.7	16	51.6	23	59.0	189	46.1	0.113
Past Medical Hx												
	HTN	238	60.8	76	59.8	20	64.5	27	69.2	246	60.0	0.682
	DM	184	30.3	42	33.1	6	19.4	11	28.2	125	30.5	0.511
	LC	51	8.4	13	10.2	2	6.5	9	23.1	27	6.6	0.004
	Psychosis	184	30.3	31	24.4	8	25.8	15	38.5	130	31.7	0.262
	Stroke	79	13.0	22	17.3	3	9.7	0	0.0	54	13.2	0.042
	Hemorrhage	39	6.4	10	7.9	2	6.5	1	2.6	26	6.3	0.702
SpO_2 (%)												
	<80	47	7.7	13	10.2	3	9.7	3	7.7	28	6.8	
	≥80–<94	50	8.2	8	6.3	4	12.9	8	20.5	30	7.3	0.072
	≥94	510	84.0	106	83.5	24	77.4	28	71.8	352	85.9	
Median (IQR)		98 (95–99)		98 (95–99)		96 (95–98)		98 (93–100)		98 (96–99)		0.252
Initial GCS	Median (IQR)	8 (6–11)		7 (4–9)		9 (5–12)		9 (5–11)		9 (7–12)		<0.001
1-hour GCS	Median (IQR)	9 (6–12)		5 (3–8)		8 (4–11)		9 (6–13)		10 (7–13)		<0.001
Non-brain cause	Yes	380	62.6	59	46.5	14	45.2	28	71.8	279	68.0	<0.001
Metabolic	Yes	258	42.5	47	37.0	7	22.6	21	53.8	183	44.6	0.024
DI	Yes	122	20.1	12	9.4	7	22.6	7	17.9	96	23.4	0.007
Brain cause	Yes	136	22.4	56	44.1	10	32.3	4	10.3	66	16.1	<0.001
Ischemic stroke	Yes	31	5.1	5	3.9	1	3.2	1	2.6	24	5.9	0.665
Brain hemorrhage	Yes	105	17.3	51	40.2	9	29.0	3	7.7	42	10.2	<0.001

NPI: Neurological pupil index; IQR: Interquartile range; HTN: Hypertension; DM: Diabetes mellitus; LC: Liver cirrhosis; SpO_2: Oxygen saturation; GCS: Glasgow coma scale; DI: Drug intoxication.

TABLE 5. Association analysis between the NPI combinations and the cause of the altered level of consciousness.

Outcomes						
Non-brain cause						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Group 1		Reference			Reference	
Group 2	0.95	0.43	2.09	1.03	0.43	2.47
Group 3	2.93	1.35	6.40	1.92	0.82	4.48
Group 4	2.46	1.64	3.68	2.86	1.81	4.5
Metabolic						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Group 1		Reference			Reference	
Group 2	0.50	0.20	1.24	0.60	0.18	1.94
Group 3	1.99	0.96	4.10	1.49	0.60	3.72
Group 4	1.37	0.91	2.07	1.74	1.10	2.86
DI						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Group 1		Reference			Reference	
Group 2	2.80	1.00	7.83	1.82	0.47	7.12
Group 3	2.10	0.76	5.76	2.54	0.65	9.99
Group 4	2.93	1.55	5.54	2.34	1.03	5.33
Brain cause						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Group 1		Reference			Reference	
Group 2	0.60	0.26	1.39	0.62	0.24	1.61
Group 3	0.15	0.05	0.43	0.23	0.07	0.72
Group 4	0.24	0.16	0.38	0.19	0.11	0.32
Ischemic stroke						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Group 1		Reference			Reference	
Group 2	0.81	0.09	7.22	1.33	0.14	12.76
Group 3	0.64	0.07	5.67	1.07	0.11	10.29
Group 4	1.52	0.57	4.06	1.22	0.44	3.44
Hemorrhage						
NPI	Unadjusted OR	95% CI		Adjusted OR	95% CI	
Group 1		Reference			Reference	
Group 2	0.61	0.26	1.43	0.56	0.21	1.48
Group 3	0.12	0.04	0.43	0.19	0.05	0.68
Group 4	0.17	0.11	0.27	0.14	0.08	0.25

NPI: neurological pupil index; OR: odds ratio; CI: confidence interval; DI: drug intoxication.

In particular, in the case of hemorrhage, it was confirmed that the NPI was <3 in the initial and 1-hour measurements. Therefore, by observing the NPI, it was possible to confirm indirectly whether there is a problem with the PLR. According to McKay *et al*. [20], opioids can affect pupillary oscillatory motion. Kongsgaard *et al*. [21] also reported that pupillary size, velocity, and latency differed among patients with cancer taking high-dose opioids. However, little is known about the effect of intoxication with sedatives or antidepressants, which affect the level of consciousness and are commonly encountered in the ED on PLR. Additionally, no study has investigated the effects of metabolic causes or how drug effects change over time on PLR in patients with ALC. The results of this study showed that if the NPI is >3 in both the initial and 1-hour measurements, the possibility of metabolic causes or DI is high. This may indirectly suggest that metabolic causes or DI have little effect on the PLR pathway. However, further research is needed to determine which specific causes or drugs have an impact and to what extent.

In this study, the outcomes were categorized into non-brain and brain causes. It would be ideal to analyze the causes of ALC in detail in the ED and establish a treatment plan; however, in resource-limited ED settings, setting the overall direction of treatment rather than making a definitive diagnosis is more appropriate. Therefore, this outcome was assigned to a large category. As shown in Tables 2,3,5, the results of this study suggest that the initial and 1-hour NPI values and their changes can be used to determine whether the cause of ALC is brain related or non-brain related. However, the initial and 1-hour NPI values alone were insufficient to distinguish between metabolic and DI causes of non-brain-related ALC. If ALC is confirmed to be of a non-brain-related cause, further testing, such as intoxication and electrolyte laboratory tests, is needed. Because the specific treatment methods for metabolic causes and DI differ depending on the underlying cause, such as electrolyte imbalance correction and antibiotics and antidote administration, further analysis is needed to distinguish between the two causes. Brain imaging is suggested for brain-related ALC if the initial NPI score is <3. If imaging cannot be performed immediately, it is recommended to determine the follow-up NPI after 1 hour. If the NPI remains <3, brain hemorrhage can be suspected.

Kim *et al*. [7] previously analyzed the etiology of ALC in patients admitted to the ED and defined stroke as both ischemic and hemorrhagic types. Therefore, this study also included both hemorrhage and ischemic stroke as causes of brain-related ALC. However, the treatment approaches differed significantly: ischemic stroke requires reperfusion therapy, whereas hemorrhage treatment depends on the specific type, potentially involving decompression surgery or coil embolization. Ischemic stroke is rarely known to cause clinical ALC [22, 23]. In this study, more patients had hemorrhage than ischemic stroke (105 *vs.* 31 patients). Therefore, the influence of ischemic stroke on the NPI group analysis could not be determined (Table 5). Alternatively, the small number of patients with ischemic stroke in this registry, which enrolled patients with ALC in the ED, may have been due to the low likelihood of ischemic stroke causing ALC. PLR can reflect intracranial pressure changes caused by brain swelling, suggesting a possible association with a large ischemic stroke [15]. However, this study was limited by its inability to analyze the size of the ischemic stroke. Additionally, the specific type of brain hemorrhage could not be determined. Future studies are needed to investigate the relationship of ischemic stroke lesions, size of the affected region, and brain hemorrhage type with ALC.

The difference between the previous and current studies is that the current study used an objective NPI to verify the cause of ALC. We measured the initial and 1-hour NPI and confirmed the change in NPI, a process similar to measuring vital signs. We hypothesized that the NPI value would differ depending on the cause of ALC. However, the analysis combining the initial and 1-hour NPIs confirmed the expected results between each group (Table 4). For Group 1, where all NPI scores were <3, the PLR was impaired, suggesting a high probability of hemorrhage. In Group 4, the probability of metabolic causes, which had little effect on the PLR, was statistically higher. Group 2 also had a higher proportion of brain causes (32.3%) than Groups 3 and 4 (10.3% and 16.1%, respectively). These results suggest that the deterioration of consciousness over time was due to brain hemorrhage. However, Group 3 showed unexpected results. Although there were a few cases in which the level of consciousness improved from the initial to the 1-hour measurement, brain-related causes were observed. This suggests that brain-related causes cannot be ruled out, even if the NPI improves in the ED. However, considering that all groups had a mixture of non-brain- and brain-related causes, NPI alone cannot be used to definitively identify the cause but can be helpful in determining the most likely cause. Further studies involving additional analyses, such as vital signs and physical examination items, along with the NPI, are needed to improve the accuracy of cause identification.

This study has some limitations. First, the NPI value with the lowest score was used as the representative value. The NPI values of the left and right eyes may have differed because of other factors, such as the location of the brain lesion or light intensity. However, selection bias was introduced when we used the smaller value as the representative value. Second, the NPI uses a proprietary algorithm that measures pupil size, constriction velocity, dilation velocity and latency. The lack of transparency regarding the specific components of the NPI algorithm hinders researchers from interpreting the results fully and drawing additional insights. Third, the NPI value may vary depending on the examiner, meaning measurement bias cannot be ignored. Fourth, this study did not describe precise results, such as drug levels or computed tomography findings, that are crucial for diagnosing DI or ICH. Fifth, the evaluation, treatment, and management of patients with ALC can vary across EDs, limiting the generalizability of the results.

5. Conclusions

In cases where both the initial and 1-hour NPIs in the ED were ≥3, the probability of the cause of the ALC being metabolic or DI was higher than in cases where both NPIs were <3. Compared to when both NPIs were ≥3, when both the initial and 1-hour NPIs in the ED were <3, the cause of the ALC was

likely to be brain related. When the initial and 1-hour NPI at the ED change based on a threshold of 3, it was difficult to identify the etiology of ALC. Further research is required to determine the association between the specific cause of ALC and NPI values in the ED.

AVAILABILITY OF DATA AND MATERIALS

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

DKK, SMP and SK—designed the research study. DSP and DKK—performed the formal analysis and wrote the manuscript. DKL, YHJ, YJK and HEK—performed the data curation, validation and methodology. SMP and SK—were responsible for the project administration and manuscript editing. All of the authors contributed to editorial changes in the manuscript and read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Institutional Review Board of Seoul National University Bundang Hospital approved this study (No. B-2205-757-303) and waived the requirement for informed consent.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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