Original Research Article

Use of Automated Infrared Pupillometry to Predict Delirium in the Intensive Care Unit: A Prospective Observational Study

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Abstract

Introduction: Delirium is an acute state of brain dysfunction prevalent among critically ill patients. Disturbances in the sympathetic neurons, including cholinergic neurons, have been reported to cause delirium by upsetting the balance of neurotransmitter synthesis, release, and inactivation. The cholinergic system mediates pupillary constriction as a response to light stimulation, and this reflex can be measured using automated infrared pupillometry (AIP). The relationship between delirium and AIP parameters has been examined. The Confusion Assessment Method for the Intensive Care Unit (CAM ICU) and the Intensive Care Unit Delirium Screening Checklist (ICDSC) are used for assessing delirium. However, that between the ICDSC score and AIP parameters remains unclear.

Objective: To examine the relationship between AIP parameters and the various categories of delirium as defined by the ICDSC score (delirium, subsyndromal delirium, no delirium).

Methods: This prospective observational study included patients aged ≥18 years admitted to the intensive care unit (ICU) from May 2018 to September 2018. ICU patients were classified into delirium, subsyndromal delirium, and no delirium groups according to the ICDSC score during ICU stay. The pupillary light reflex was assessed in both eyes immediately after admission using AIP with a portable infrared pupillometer. Logistic regression analyses were used to estimate the odds ratio to examine the relationship between the severity of delirium as assessed by the ICDSC score and the AIP parameters.

Results: In total 133 patients were included in the study. Based on the ICDSC scores, 41.4% of patients had no delirium, 40.6% had subsyndromal delirium, and 18% had delirium. Dilation velocity (DV) measured by AIP was significantly different among the delirium, subsyndromal delirium, and no delirium groups. Post-hoc comparisons showed that DV was significantly slower in the delirium group than in the no delirium group but was not significantly different between the subsyndromal delirium and no delirium groups. After adjusting for patients' sex and age at enrollment, DV was shown to be independently associated with delirium.

Conclusion: This study suggests that the use of AIP at ICU admission may improve the identification of patients at a high risk of developing delirium.

Keywords

automated infrared pupillometry, delirium, dilation velocity, intensive care delirium screening checklist, subsyndromal delirium

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Introduction

Delirium is an acute state of brain dysfunction prevalent among critically ill patients. It is characterized by altered consciousness, in addition to impaired concentration, persistence, and attention. Moreover, it develops rapidly and fluctuates over the course of the day. Numerous studies have reported that delirium is associated with prolonged stays in intensive care units (ICUs) and hospitals and increased mortality and health care costs (Stollings et al., 2021). One meta-analysis estimated the prevalence of delirium to be 30%, suggesting that it is a common symptom

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among patients in the ICU, and identifying several approaches that have been developed and validated to diagnose delirium (Krewulak et al., 2018). Therefore, prevention, early detection, treatment, and care of delirium in the intensive care setting are important.

Neuroinflammation caused by pro-inflammatory cytokines during systemic disease can also affect the sympathetic nervous system, including cholinergic neurons. This leads to an imbalance in the synthesis, release, and inactivation of neurotransmitters, especially acetylcholine and dopamine, which is considered to cause delirium (Maldonado, 2018). The cholinergic system mediates pupillary constriction as a response to light stimulation, and this reflex can be measured using automated infrared pupillometry (AIP). The quantitative measurement of the pupillary light reflex by AIP represents an attractive tool for evaluating cholinergic activity in a clinical setting (Bower et al., 2021). In recent years, AIP has been suggested as an effective method for the early detection of delirium (Favre et al., 2020; Yang et al., 2018). Therefore, we hypothesized that AIP at ICU admission could predict the severity of delirium during the ICU stay.

Review of Literature

Delirium is an acute syndrome of impaired attention, fluctuating mental status, and impaired consciousness. One possible cause of delirium is transiently decreased brain cell activity due to systemic inflammatory changes occurring during sepsis and surgery (Zaal & Slooter, 2012). Brainstem dysfunction due to neuroinflammation, in particular, is believed to be associated with the development of delirium (Benghanem et al., 2020). The brainstem regulates the sleep–wake cycle and vital functions through the ascending reticular activating system and the autonomic nervous system, respectively. Neuroinflammation, including the sympathetic nervous system, leads to an imbalance in the synthesis, release, and inactivation of neurotransmitters, especially those of acetylcholine and dopamine; this is believed to cause delirium (Maldonado, 2018).

Delirium during ICU stay has been reported to be an independent risk factor for long-term cognitive decline (Goldberg et al., 2020). Practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disturbances in ICU adult patients recommend that ICU nurses assess for delirium using delirium screening tools for early detection (Devlin et al., 2018). Several approaches have been developed and validated to diagnose delirium in ICU patients, including the Confusion Assessment Method for the Intensive Care Unit (CAM ICU) (Ely et al., 2001) and the Intensive Care Unit Delirium Screening Checklist (ICDSC) (Bergeron et al., 2001), which are the most frequently used tools for critically ill patients. However, the CAM-ICU cannot assess the severity of delirium. In contrast, the ICDSC score can be used to assess the severity of delirium, including diagnosing subsyndromal delirium (Sakuramoto et al., 2015).

A decline in brainstem function or brainstem injury is manifested in the pupillary light reflex. The quantitative measurement of the pupillary light reflex by AIP presents an attractive tool for evaluating cholinergic activity in a clinical setting (Bower et al., 2021) and can provide insights into the imbalance between the sympathetic and parasympathetic nervous systems that may contribute to delirium. The use of AIP for evaluating patients in both psychiatric and neurological settings extensively studied and has been used to predict outcomes after subarachnoid hemorrhage or cardiac arrest (Natzeder et al., 2019; Riker et al., 2020; Tamura et al., 2020). Recent studies have examined the relationship between CAM ICU scores and AIP indices (Favre et al., 2020; Yang et al., 2018). However, no study has investigated the relationship between the ICDSC score and AIP parameters.

At the time of ICU admission, it is important to predict whether the patient will develop delirium during the ICU stay. Predicting delirium may enable identification of targets for focused preventive intervention, and early intervention may prevent its onset. Predictive models have been developed to determine the likelihood of developing delirium. Prediction of Delirium in ICU patients (PRE-DELIRIC) is a routine screening tool for predicting delirium in ICU patients based on current guidelines. Although this model showed good predictive power (Ho et al., 2020), it is not a simple assessment tool. In contrast, AIP is measured by a highly reliable portable device that objectively quantifies pupil diameter based on the counter-optical reflection of the pupil. AIP is a simple evaluation tool that can measure various parameters related to pupillary light reflection within 5 s and a more rapid and reliable method that does not require score calculation.

This study aimed to examine the relationship between AIP parameters and the various categories of delirium as defined by the ICDSC score (delirium, subsyndromal delirium, no delirium).

Methods

Design

This prospective observational study was conducted in the medical and surgical ICU of a university hospital between May 2018 and September 2018.

Patients were carefully screened and assessed by a research nurse before enrollment. On ICU admission, the eligible patients' demographic and baseline characteristic data, including age, sex, Sequential Organ Failure Assessment score, type of medical condition, and indication for ICU admission, general anesthesia, and tracheal intubation, were collected. General anesthesia included cases where the patient had surgery before ICU admission and cases where endotracheal intubation was required after ICU admission. The patients were followed up for a maximum of 7 days. The ICDSC scores during ICU stay (up to 7 days) were used to assess the presence and severity of delirium. The

pupillary light reflex was measured using a NeurOptics PLR-200TM portable infrared pupillometer (NeurOptics, Irvine, CA, USA). All patients were evaluated in both eyes using AIP immediately after ICU admission.

Sample

All participants in this study were patients aged ≥18 years who were admitted to the medical and surgical ICU.

Exclusion Criteria

The exclusion criteria were as follows: admission to the pediatric, neurosurgery, or neurology wards of our hospital; patients who required cardiopulmonary resuscitation; and diagnoses of psychiatric disorders or dementia.

Delirium Assessment in ICU Patients

The ICDSC score consists of eight items, including altered level of consciousness, inattention, disorientation, hallucination/delusions/psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbance, and symptom fluctuation. One point is added for each of the eight items if the relevant criteria are clearly met. In the absence of symptoms or in cases where scoring is not possible, a score of 0 is provided. The ICDSC scores during ICU stay (up to 7 days) were used to assess the presence and severity of delirium. The maximum score was 8, with a score of ≥4 indicating delirium, 1–3 indicating the presence of subsyndromal delirium, and <1 indicating no delirium (Bergeron et al., 2001). The ICDSC showed good diagnostic accuracy with an area under the curve of 0.843, sensitivity of 81.0%, specificity of 87.7%, positive predictive value of 53.1%, and negative predictive value of 96.4% (Detroyer et al., 2020).

Pupillary Light Reflex on ICU Admission

The pupillary light reflex was measured using a NeurOptics PLR-200^{TM} portable infrared pupillometer (NeurOptics). The AIP parameters extracted from the pupillary light reflex and recorded on the instrument were as follows: maximum pupil diameter (MAX, mm), minimum pupil diameter (MIN, mm), contraction rate (CH, %), latency (LAT, ms), mean contraction velocity (CV, mm/s), maximum contraction velocity (MCV, mm/s), and mean dilation velocity (DV, mm/s). The pupillometer also calculates the neurological pupil index (NPi), a unique scalar index with values ranging from 0 to 5, and the time it takes for the pupil to recover to 75% of its initial resting size (T75). The NPi was derived from the aforementioned seven indices, and the numerical value indicates the disease severity. If the NPi is < 3, the patient has an abnormal contrast reflex; if the NPi is ≥ 3, the patient is in the healthy range.

All patients were evaluated using AIP in both eyes immediately after ICU admission. The mean results of both eyes were used in the analysis.

Ethical Considerations

The study protocol was approved by a suitably constituted Research Ethics Committee of the affiliated university hospital and conformed to the provisions of the Declaration of Helsinki. The opt-out method of informed consent was used. A waiver of consent was granted because non-invasive pupillometry is part of the standard care. Before the study, the patients or their families reviewed a comprehensive brochure that explained the purpose of the study and the data collection methods, including a review of the medical records and interview with patients' nurses.

Statistical Analysis

Patient characteristics are presented as means and standard deviations or interquartile range and proportions. Patients' baseline demographics, clinical variables, and AIP parameters were assessed using one-way analysis for continuous variables; the χ^2 test or Fisher's exact test was used to compare proportions among the three groups. Bonferroni's multiple comparison test was performed to determine the statistical significance between the individual groups. Univariate and multivariate logistic regression analyses were used to estimate the odds ratio (OR) to examine the relationship between the severity of delirium as assessed by the ICDSC score and AIP parameters. Multivariate logistic regression analysis was used to assess the association between groups after adjusting for two covariates (age at enrollment and sex). All data analyses were performed using SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p \leq .05$.

Results

Sample Characteristics

During the study period, 397 patients were admitted to the ICU and screened for eligibility. In total 133 patients were included in the study (Figure 1). The baseline demographics of patients are shown in Table 1. Based on the ICDSC, 55 patients (41.4%) had no delirium, 54 (40.6%) had subsyndromal delirium, and 24 (18%) had delirium. There were significant between-group differences in the severity of illness (as measured by the Sequential Organ Failure Assessment score on ICU admission), mechanical ventilation, ICU stay duration, and number of days spent on ventilatory support.

Between-Group Differences in AIP Parameters

Figure 2 shows the mean scores and standard deviations of the CH, CV, MCV, LAT, DV, and NPi AIP parameters for

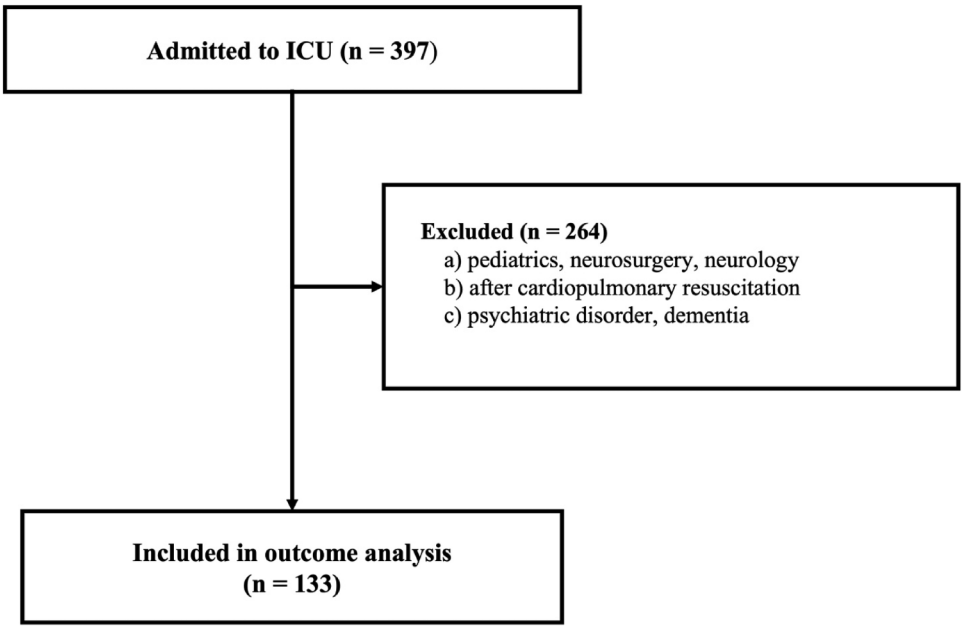

Figure 1. Flowchart of the Patient Selection Process in the Study.

Table 1. Patient Characteristics.

		ICDSC			
	All patients 133	No delirium 55 (41.4)	Subsyndromal delirium 54 (40.6)	Delirium 24 (18.0)	*p* value
Age, mean ± SD; years	67.9 ± 12	66.4 ± 13.4	68.8 ± 11.2	69.2 ± 10.4	.500
Males, *n* (%)	87 (63.5)	39 (70.9)	32 (59.3)	16 (66.7)	.430
SOFA score at ICU admission, mean ± SD	6 ± 0.3	4.7 ± 2.5	6.2 ± 3.1	8.2 ± 2.8	<.001*
Unscheduled ICU admission, *n* (%)	51 (37.2)	20 (36.4)	18 (33.3)	13 (54.2)	.201
General anesthesia, *n* (%)	99 (72.3)	39 (70.9)	43 (79.6)	17 (70.8)	.530
Mechanical ventilation, *n* (%)	37 (27)	4 (7.3)	20 (37)	13 (54.2)	<.001*
ICU stay, mean ± SD; days	3.6 ± 0.2	2.7 ± 1.7	3.54 ± 2.1	6.1 ± 2.8	<.001*
Ventilator days, median (IQR); days	0 (0,11)	0 (0,11)	0 (0,3)	1 (0,10)	<.001*

Note. ICU = intensive care unit; ICDSC = Intensive Care Delirium Screening Checklists; SOFA = Sequential Organ Failure Assessment; IQR = interquartile range. Proportions; $\chi 2$ tests, Fisher exact tests, continuous variables; one-way analysis of variance for no delirium versus subsyndromal delirium versus delirium.
*$p \leq .05$.

each group. DV was significantly different among the delirium (0.5 ± 0.35 mm/s), subsyndromal delirium (0.59 ± 0.34 mm/s), and no delirium (0.7 ± 0.36 mm/s) groups. Post-hoc comparisons showed that DV was significantly slower in the group with delirium than in the group without delirium ($p = .038$). No significant between-group differences were found in the CH, CV, MCV, LAT, or NPi.

Multivariate Analysis of Risk Factors for ICU Delirium

Univariate and multivariate logistic regression analyses were used to examine the relationship between the ICDSC score (delirium severity) and AIP parameters, and the results are presented in Table 2. In the univariate analysis, there was a significant difference in DV between the delirium and non-delirium groups (OR: 0.16, 95% confidence interval [CI]: 0.03–0.74). However, there were no differences in other AIP parameters. After adjusting for patients' sex and age at enrollment, the multivariate analysis showed that DV was independently associated with delirium (OR: 0.17, 95% CI: 0.35–0.81).

Discussion

We demonstrated that patients with delirium had a significantly slower DV than patients without delirium. After adjusting for patients' sex and age at enrollment, the multivariate analysis revealed that DV at ICU admission was independently associated with delirium during ICU stay.

The present study showed that the slower the DV, the stronger the association with delirium, indicating that the

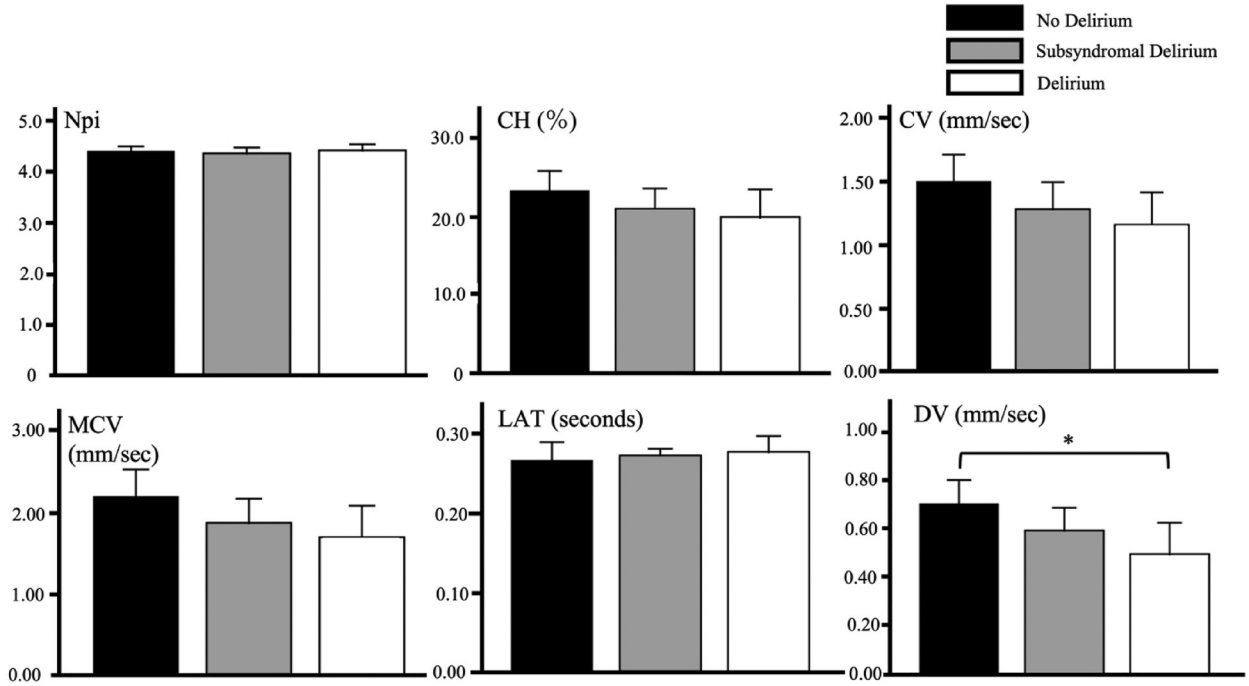

Figure 2. Comparison of the AIP parameter and delirium. One-way analysis of variance for no delirium versus subsyndromal delirium versus delirium.
Note. AIP = automated infrared pupillometry; Npi = Neurological Pupil Index; CH = percent constriction; CV = average constriction velocity; MCV = maximal constriction velocity; LAT = latency; DV = average dilation velocity.
*$p < .05$ (Bonferroni's multiple comparison test).

Table 2. Results of Logistic Regression of Variables Related to AIP Parameters.

		Univariate analysis		Multivariate analysis	
	ICDSC	Odds	95% CI	Adjusted odds	95% CI
NPi	No delirium	ref		ref	
	Subsyndromal delirium	0.731	0.26–2.02	0.82	0.29–2.34
	Delirium	1.17	0.27–4.75	1.25	0.32–5.17
CH	No delirium	ref		ref	
	Subsyndromal delirium	0.98	0.93–1.01	0.98	0.93–1.02
	Delirium	0.96	0.91–1.01	0.96	0.91–1.02
CV	No delirium	ref		ref	
	Subsyndromal delirium	0.69	0.41–1.14	0.72	0.43–1.21
	Delirium	0.52	0.26–1.08	0.55	0.26–1.14
MCV	No delirium	ref		ref	
	Subsyndromal delirium	0.78	0.55–1.1	0.79	0.56–1.23
	Delirium	0.65	0.40–1.06	0.67	0.41–1.09
LAT	No delirium	ref		ref	
	Subsyndromal delirium	7.04	0.01–88889.06	4.99	0.004–6644.76
	Delirium	18.6	0.01–52330.91	9.79	0.003–30169.08
DV	No delirium	ref		ref	
	Subsyndromal delirium	0.4	0.13–1.21	0.45	0.15–1.39
	Delirium	0.16	0.03–0.74	0.17	0.35–0.81

Note. CI = confidence interval; ICDSC = Intensive Care Delirium Screening Checklist; NPi = Neurological Pupil Index; CH = percent constriction; CV = average constriction velocity; MCV = maximal constriction velocity; LAT = latency; DV = average dilation velocity.
Adjustment for age at enrollment, and sex.

ICDSC score of ICU patients may correspond to the quantitative measure of DV. However, there was no significant difference in DV between the subsyndromal delirium and no delirium groups, although DV became slower with increasing delirium severity. This may be due to the small sample size and lack of statistical power for multigroup comparisons. Nonetheless, these data are consistent with those of a previous report showing that postoperative delirium assessed by the CAM-ICU was associated with ICU AIP parameters (Yang et al., 2018). In that study, CH and DV, when assessed in the post-anesthesia care unit, showed excellent predictive performance for delirium. Our results showed that patients with delirium in the ICU had significantly slower DV. Thus, we confirmed that development of delirium can be identified via DV measurements. Our results suggest that during episodes of severe illness, the imbalance in the synthesis, release, and inactivation of several neurotransmitters may predispose individuals to delirium. In contrast to the results of a previous study (Yang et al., 2018), our results showed no significant difference in the CH between the groups. This finding was anticipated; as previously suggested, this could be due to the effect of opioids and other agents affecting the central nervous system. Another study demonstrated that fentanyl reduced the CH but did not change the NPi (Shirozu et al., 2017). Therefore, the CH may be reduced under conditions such as sedative or opioid use, painful stimuli, emotional states, and room light levels (Ong et al., 2019). Likely, many of the ICU patients in this study were administered sedatives. We did not adjust for variables related to sedatives, room light levels, opiates, painful stimuli, or emotional states. Therefore, it is possible that there was no statistically significant difference in the CH.

In addition to using screening tools to evaluate the severity of delirium, PRE-DELIRIC has been used to predict delirium in ICU patients. Initial screening using this tool, which is based on 10 readily available indicators, has to be carried out within the first 24 h in the ICU. Although this model has good predictive power (Ho et al., 2020), it is not a simple assessment tool. In contrast, the AIP is a simple assessment tool that can determine various parameters related to the pupillary light reflex within 5 s. Furthermore, AIP provides an objective measurement of the pupil, which may reduce observer bias. The use of automated pupillometry can be adopted for standard practice when there is a need to accurate assess pupil size and reactivity (Zhao et al., 2016). The present study showed that DV at ICU admission is an independent predictor of the development of delirium in the ICU. Our findings provide the potential clinical application of quantitative pupillometry for the neurological monitoring of ICU patients at a high risk of delirium.

Limitations

The strength of this study was that it was the first to evaluate the association between the severity of delirium during the ICU stay as determined by the ICDSC and AIP parameters at ICU admission.

This study had some limitations. First, the present study only investigated the relationship between delirium and AIP parameters. Additionally, the observational nature of this study implies that we cannot assume a causal relationship between delirium and the AIP parameters. However, previous studies have found that AIP parameters reflect brain dysfunction (Olson et al., 2016). Therefore, AIP parameters at ICU admission may be an important factor in predicting ICU delirium. Second, this study was based on a small sample size and was performed in only one academic tertiary care center in Japan. Further investigations should include a multicenter study with a larger sample size. AIP parameters should be interpreted while considering the effect of medications (Bower et al., 2021), which was not done in the present study. Delirium is a clinical syndrome with complex pathophysiological mechanisms; hence, various types of critically ill patients should be examined in the future, including those with neurological complications at baseline.

Implications for Practice

We demonstrated that patients with delirium had a significantly slower DV than those without delirium. Therefore, AIP may be a useful tool to predict patients at a high risk of developing delirium in the ICU in a faster and more reliable way, as it does not require score calculations. Future studies should focus on improving the accuracy of predicting the onset of delirium using AIP parameters at ICU admission. AIP may also serve as valid research tool to investigate sympathetic nervous system dysfunction in critically ill patients and those with delirium.

Conclusions

This study showed that a slow DV measured by AIP on admission to the ICU was independently associated with the onset of delirium as determined by the ICDSC during ICU stay. However, no similar association was found between DV and subsyndromal delirium; therefore, there may be no association between the AIP parameters and the severity of delirium as determined by the ICDSC. The use of AIP at ICU admission is a reliable, simple, and rapid way to identify patients who are at a high risk of developing delirium.

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Ethical Statement

This study was approved by the Institutional Review Board of the Ethnic Board of the University of Nara Medical University Hospital Research Ethics Review Committee (approval no.: 1835).

Availability of Data and Materials

The datasets used and/or analyzed in this study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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References

Benghanem, S., Mazeraud, A., Azabou, E., Chhor, V., Righy Shinotsuka, C., Claassen, J., Rohaut, B., & Sharshar, T. (2020). Brainstem dysfunction in critically ill patients. *Critical Care*, *24*(1), 5. https://doi.org/10.1186/s13054-019-2718-9

Bergeron, N., Dubois, M. J., Dumont, M., Dial, S., & Skrobik, Y. (2001). Intensive care delirium screening checklist: Evaluation of a new screening tool. *Intensive Care Medicine*, *27*(5), 859–864. https://doi.org/10.1007/s001340100909

Bower, M. M., Sweidan, A. J., Xu, J. C., Stern-Neze, S., Yu, W., & Groysman, L. I. (2021). Quantitative pupillometry in the intensive care unit. *Journal of Intensive Care Medicine*, *36*(4), 383–391. https://doi.org/10.1177/0885066619881124

Detroyer, E., Timmermans, A., Segers, D., Meyfroidt, G., Dubois, J., Assche, A. van, Joosten, E., & Milisen, K. (2020). Psychometric properties of the intensive care delirium screening checklist when used by bedside nurses in clinical practice: A prospective descriptive study. *BMC Nursing*, *19*(1), 21. https://doi.org/10.1186/s12912-020-00415-z

Devlin, J. W., Skrobik, Y., Gélinas, C., Needham, D. M., Slooter, A. J. C., Pandharipande, P. P., Watson, P. L., Weinhouse, G. L., Nunnally, M. E., Rochwerg, B., Balas, M. C., van den Boogaard, M., Bosma, K. J., Brummel, N. E., Chanques, G., Denehy, L., Drouot, X., Fraser, G. L., & Harris, J. E., … W. Alhazzani (2018). Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Critical Care Medicine*, *46*(9), e825–e873. https://doi.org/10.1097/CCM.0000000000003299

Ely, E. W., Margolin, R., Francis, J., May, L., Truman, B., Dittus, R., Speroff, T., Gautam, S., Bernard, G. R., & Inouye, S. K. (2001). Evaluation of delirium in critically ill patients: Validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Critical Care Medicine*, *29*(7), 1370–1379. https://doi.org/10.1097/00003246-200107000-00012

Favre, E., Bernini, A., Morelli, P., Pasquier, J., Miroz, J.-P., Abed-Maillard, S., Ben-Hamouda, N., & Oddo, M. (2020). Neuromonitoring of delirium with quantitative pupillometry in sedated mechanically ventilated critically ill patients. *Critical Care*, *24*(1), 66. https://doi.org/10.1186/s13054-020-2796-8

Goldberg, T. E., Chen, C., Wang, Y., Jung, E., Swanson, A., Ing, C., Garcia, P. S., Whittington, R. A., & Moitra, V. (2020). Association of delirium with long-term cognitive decline a meta-analysis supplemental content. *JAMA Neurology*, *77*(11), 1373–1381. https://doi.org/10.1001/jamaneurol.2020.2273

Ho, M. H., Chen, K. H., Montayre, J., Liu, M. F., Chang, C. C., Traynor, V., Shen Hsiao, S. T., Chang, H. R., & Chiu, H. Y. (2020). Diagnostic test accuracy meta-analysis of PRE-DELIRIC (PREdiction of DELIRium in ICu patients): A delirium prediction model in intensive care practice. *Intensive and Critical Care Nursing*, *57*, 102784. https://doi.org/10.1016/j.iccn.2019.102784

Krewulak, K. D., Stelfox, H. T., Leigh, J. P., Ely, E.W, & Fiest, K. M. (2018). Incidence and prevalence of delirium subtypes in an adult ICU: A systematic review and meta-analysis. *Critical Care Medicine*, *46*(12), 2029–2035. https://doi.org/10.1097/CCM.0000000000003402

Maldonado, J. R. (2018). Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *International Journal of Geriatric Psychiatry*, *33*(11), 1428–1457. https://doi.org/10.1002/gps.4823

Natzeder, S., Mack, D. J., Maissen, G., Strässle, C., Keller, E., & Muroi, C. (2019). Portable infrared pupillometer in patients with subarachnoid hemorrhage: Prognostic value and circadian rhythm of the neurological pupil index (NPi). *Journal of Neurosurgical Anesthesiology*, *31*(4), 428–433. https://doi.org/10.1097/ANA.0000000000000553

Olson, D. M., Stutzman, S., Saju, C., Wilson, M., Zhao, W., & Aiyagari, V. (2016). Interrater reliability of pupillary assessments. *Neurocritical Care*, *24*(2), 251–257. https://doi.org/10.1007/s12028-015-0182-1

Ong, C., Hutch, M., & Smirnakis, S. (2019). The effect of ambient light conditions on quantitative pupillometry. *Neurocritical Care*, *30*(2), 316–321. https://doi.org/10.1007/s12028-018-0607-8

Riker, R. R., Sawyer, M. E., Fischman, V. G., May, T., Lord, C., Eldridge, A., & Seder, D. B. (2020). Neurological pupil index and pupillary light reflex by pupillometry predict outcome early after cardiac arrest. *Neurocritical Care*, *32*(1), 152–161. https://doi.org/10.1007/s12028-019-00717-4

Sakuramoto, H., Subrina, J., Unoki, T., Mizutani, T., & Komatsu, H. (2015). Severity of delirium in the ICU is associated with short term cognitive impairment. A prospective cohort study. *Intensive and Critical Care Nursing*, *31*(4), 250–257. https://doi.org/10.1016/j.iccn.2015.01.001

Shirozu, K., Setoguchi, H., Tokuda, K., Karashima, Y., Ikeda, M., Kubo, M., Nakamura, K., & Hoka, S. (2017). The effects of anesthetic agents on pupillary function during general anesthesia using the automated infrared quantitative pupillometer. *Journal of Clinical Monitoring and Computing*, *31*(2), 291–296. https://doi.org/10.1007/s10877-016-9839-3

Stollings, J. L., Kotfis, K., Chanques, G., Pun, B. T., Pandharipande, P. P., & Ely, E. W. (2021). Delirium in critical illness: Clinical manifestations, outcomes, and management. *Intensive Care Medicine*, *47*(10), 1089–1103. https://doi.org/10.1007/s00134-021-06503-1

Tamura, T., Namiki, J., Sugawara, Y., Sekine, K., Yo, K., Kanaya, T., Yokobori, S., Abe, T., Yokota, H., & Sasaki, J. (2020). Early outcome prediction with quantitative pupillary response

parameters after out-of-hospital cardiac arrest: A multicenter prospective observational study. *PLoS One*, *15*(3), e0228224. https://doi.org/10.1371/journal.pone.0228224

Yang, E., Kreuzer, M., Hesse, S., Davari, P., Lee, S. C., & García, P. S. (2018). Infrared pupillometry helps to detect and predict delirium in the post-anesthesia care unit. *Journal of Clinical Monitoring and Computing*, *32*(2), 359–368. https://doi.org/10.1007/s10877-017-0009-z

Zaal, I. J., & Slooter, A. J. C. (2012). Delirium in critically ill patients epidemiology, pathophysiology, diagnosis and management. *Drugs*., *72*(11), 1457–1471. https://doi.org/10.2165/11635520-000000000-00000

Zhao, W., Stutzman, S., DaiWai, O., Saju, C., Wilson, M., & Aiyagari, V. (2016). Inter-device reliability of the NPi-100 pupillometer. *Journal of Clinical Neuroscience*, *33*, 79–82. https://doi.org/10.1016/j.jocn.2016.01.039