Resuscitation 131 (2018) 108–113

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Clinical paper

Quantitative assessment of pupillary light reflex for early prediction of outcomes after out-of-hospital cardiac arrest: A multicentre prospective observational study☆

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ARTICLE INFO

Keywords:
Out-of-hospital cardiac arrest
Post-cardiac arrest syndrome
Outcome prediction
Pupillary light reflex
Quantitative pupillometry

ABSTRACT

Aim: To clarify whether quantitative assessment of pupillary light reflexes (PLR) can predict the outcome of post-cardiac arrest (CA) patients during the first 72 h after the return of spontaneous circulation (ROSC).
Methods: Fifty adults resuscitated after non-traumatic out-of-hospital CA (OHCA) (mean age 64.1 years old, 36 males) were enrolled in four emergency hospitals. PLR was sequentially measured at 0, 6, 12, 24, 48, and 72 h after ROSC by an automated portable infrared pupillometry. PLR values for each time point were compared between both survivors and non-survivors, and patients with either favourable (Cerebral Performance Category (CPC) 1 or 2) or unfavourable neurological outcomes.
Results: Twenty-three patients survived for 90 days after CA, and 13 patients achieved favourable neurological outcomes. The PLR values of the survivors and patients with favourable neurological outcomes were consistently greater than those of non-survivors ($P < 0.001$) and those with unfavourable neurological outcomes ($P < 0.001$), respectively. The change in PLR over time was not statistically different between the outcome groups. The 0-hour PLR best predicted both 90-day survival (AUC = 0.82, cutoff 3%, sensitivity 0.87, specificity 0.80) and favourable neurological outcomes (AUC = 0.84, cutoff 6%, sensitivity 0.92, specificity 0.74). No patient with a 6-hour PLR less than 3% survived for 90 days after CA.
Conclusions: Quantitatively measured PLR was consistently greater in survivors and patients with favourable neurological outcomes during the 72 h after ROSC. Quantitative assessment of PLR at as early as 0 h has a potential role for prognostication in post-CA patients.

Introduction

The evaluation of pupillary light reflex (PLR) is a fundamental element of neurological examinations. Traditionally, PLR is qualitatively assessed as absent, sluggish, or brisk by an examiner flashing a penlight and is, therefore, known to have poor inter-rater consistency [1–3]. A hand-held portable pupilometer has recently become available and has enabled the quantitative assessment of PLR at the patient's bedside. Both its clinical utility and reliability has been reported in critical care settings [2–5].

Post-cardiac arrest syndrome (PCAS) is a complex pathophysiological condition occurring after the return of spontaneous circulation (ROSC). Hypoxic brain damage is the most critical consequence of this syndrome and remains the main cause of mortality in CA-survivors [6]. Early, accurate prognostication is vital for identifying candidates for favourable neurological recovery and survivors with irreversible brain damage. Several approaches for predicting the outcome after CA have been tested to date, but outcome prediction based on clinical

☆ A Spanish translated version of the abstract of this article appears as Appendix in the final online version at https://doi.org/10.1016/j.resuscitation.2018.06.027.

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https://doi.org/10.1016/j.resuscitation.2018.06.027
Received 30 March 2018; Received in revised form 16 June 2018; Accepted 25 June 2018

examination remains challenging. Some investigations suggested that bilaterally absent PLR at 72 h or more after CA indicated a poor outcome irrespective of hypothermia treatment [7,8]. However, the current recommendations regarding PLR as a predictor of outcome are based on clinical studies that were conducted with traditional qualitative assessment of PLR [9,10]. Since the qualitative assessment of PLR may underestimate the presence of PLR, further studies are needed to investigate the reproducibility of PLR for predicting outcomes in patients with PCAS using quantitative pupillometry [11]. The clinical application of a pupillometer for the early prognostication in comatose post-CA patients has been reported in some preliminary studies [12–15]. However, poorly defined and variable timing of PLR measurements is a critical limitation when exploring its early prognostic performance. Although the concept that PLR could recover over time is well accepted, how PLR changes immediately after ROSC has surprisingly never been studied.

In the present study, we sequentially measured PLR of post-CA patients using a pupillometer to clarify whether quantitative assessment of PLR during the first 72 h after ROSC can predict outcomes in post-CA patients.

Patients and methods

Study design

This study was a multicentre single arm, uncontrolled, prospective, observational study performed between December 2014 and January 2017. This study received approval from the IRB of each participating institution and was registered with the University Hospital Medical Information Network (Clinical trial identifier: UMIN000015658). The study methodology complied with the STARD 2015 guidelines for reporting diagnostic accuracy studies [16].

Patients

Fifty adult OHCA patients (≥ 18 years old) in whom spontaneous circulation returned were prospectively enrolled in 4 university hospitals and emergency medical centres in the Kanto region of Japan (Supplemental Fig. 1). Exclusion criteria were: CA due to obvious trauma, a do-not-attempt-resuscitation order, pregnancy, dependence on others for daily support because of impaired brain function, terminal stage of a known malignancy which makes 3-month survival unlikely, and Extracorporeal Membrane Oxygenation use. Written informed consent was obtained from the family.

Data collection and outcome assessments

Baseline demographic data included age, gender, witness status, presence of bystander cardiopulmonary resuscitation, initial arrest cardiac rhythm, location of CA, aetiology of CA, time from collapse to ROSC, and Glasgow Coma Scale (GCS) after ROSC in the emergency department. Result of qualitative PLR assessments, positive or negative, using a penlight, and information on treatment with sedatives, opioids, catecholamines, and temperature management was also collected.

The outcome variables were 90-day survival and neurological outcome 90 days after CA. The Cerebral Performance Category (CPC) scale was used to categorize neurological outcomes as follows: CPC 1, good performance; CPC 2, moderate disability; CPC 3, severe disability; CPC 4, comatose or persistent vegetative status; and CPC 5, brain death or death. A CPC of 1 and 2 were defined as favourable neurological outcomes, whereas a CPC of 3, 4, or 5 as poor neurological outcomes [17].

General management of post-CA patients

Post-CA care was optimized for each patient according to the standardized institutional treatment protocol that was in accordance with the latest guidelines at the time [10,18,19]. Comatose patients, i.e., GCS ≤ 8 with motor response of ≤5, were intubated and mechanically ventilated. Continuous intravenous infusions of midazolam, propofol, and/or dexmedetomidine were used for sedation, and fentanyl or buprenorphine for analgesia. Neuromuscular blocking agents, rocuronium or vecuronium, was used in adjunct to treat shivering. Norepinephrine, dopamine, and/or dobutamine were given when needed to maintain optimum tissue perfusions at the discretion of treating physicians. Patient temperature was managed at a target temperature management (TTM) of 33–36 °C or with fever control for non-cardiogenic CA, due to subarachnoid haemorrhage or sepsis. Temperature management was not performed for patients presenting a GCS > 8 in the emergency department.

Assessment of pupillary reflex using an automated quantitative pupillometry

Pupillary examinations were performed using an automated quantitative pupillometer (NeurOptics®NPi™-100 pupillometer, Neuroptics Inc., Irvine, CA, USA) [12]. Pupillometers were rented for general clinical purposes, and this study was conducted without financial support nor free provision of a pupilometer from any enterprise. This device is a portable, handheld, infrared, monocular pupillometer, which enables a quantitative measurement of the pupillary response. The amplitude of the PLR is referred to as the percent change between maximum pupil diameter before light stimuli and minimum pupil diameter after light stimuli. Quantitative measurement of PLR was conducted by the research physicians or nurses and was duplicated for each eye at every examination. PLR was measured at 0, 6, 12, 24, 48, and 72 h after ROSC. Time variation from each time point of the PLR measurement was strictly minimized. At each time point, the largest PLR value of both eyes was adopted for the analysis as previously reported [13].

Statistical analyses

Descriptive statistics were reported as a median with interquartile range (IQR) or range for continuous variables, and absolute values with percentages for categorical variables, respectively. The Chi-square test or Fisher's exact test were used for comparisons of binary variables.

A mixed effects model was used to evaluate the differences of repeated measurements of PLR between the outcome groups. Hours (i.e. 0, 6, 12, 24, 48, and 72 h), outcome groups and the interaction between hour and outcome group were included as fixed effects, and a random intercept was included for each subject.

Receiver Operating Characteristics (ROC) curve analysis was performed for the comparison of the area under the curve (AUC) values for each time point of PLR. A multivariate regression model was used to assess the effects of the predictors (PLR value at each time point). The optimal cutoff values of the prognostic value of PLR according to Youden's J statistic with corresponding sensitivities, specificities, negative predictive value (NPV), and its 95% confidence interval (CI) were calculated. Then the highest NPV value for each time point was obtained and the corresponding PLR cutoff value was estimated. The highest NPV value indicates that the smallest proportion of the negative cases (non-survivor or unfavourable neurological outcome) is falsely negative.

To address the impact of TTM on the results, the same mixed effects models and ROC analyses as above were conducted exclusively for patients treated with TTM. P values < 0.05 were considered statistically significant. All analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

Table 1
Mean Patient characteristics.

Age; median y/o (IQR)	63	(53–79)
Male sex; n (%)	36	(72)
Witness status; n (%)	36	(72)
Witnessed	13	(26)
Not witnessed	1	(2)
Data missing		
Bystander CPR; n (%)	24	(48)
Performed	25	(50)
Not performed	1	(2)
Data missing		
Location of CA; n (%)	27	(54)
Public location	22	(44)
Home	1	(2)
Data missing		
Initial rhythm documented by EMS; n (%)	14	(28)
VF/VT	11	(22)
PEA	20	(40)
Asystole	5	(10)
Other		
Etiology of CA	29	(58)
Presumed cardiac cause	20	(40)
Non-cardiac cause	1	(2)
Data missing		
Cardiac arrest time; median min (IQR)	33	(15–50)
Prehospital ROSC; n (%)	19	(38)
GCS after ROSC in ED; median (range)	3	(3–15)
Implementation of TTM 33 to 36 °C; n (%)	34	(68)
90-day survival; n (%)	23	(46)
90-day favorable neurological outcome; n (%)	13	(26)

CA, cardiac arrest; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ED, emergency department; EMS, emergency medical service; GCS, Glasgow Coma Scale; IQR, interquartile range; PEA, pulseless electrical activity; TTM, target temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.

Results

Patient characteristics

Baseline patient characteristics are shown in Table 1. Three post-CA patients were not comatose, GCS > 8 in emergency department, and were included in this study. Twenty-nine patients (58%) had CA presumed to be of cardiac cause. Non-cardiogenic aetiology included 8 (16%) with asphyxia, 3 (6%) with aneurysmal subarachnoid haemorrhage, 2 (4%) with strangulation, and 2 (4%) with pneumonia/sepsis. The 0-hour PLR was actually measured at ~32 (12–61) min after ROSC, because of the requisite time for obtaining informed consent before enrollment. The study resulted in a 90-day survival rate of 46% including 26% of patients with favourable neurological outcomes. Table 2 summarizes the usage of pharmacologic agents. Sedatives were used more frequently for the survivors during 6–48 h compared to the non-survivors, whereas catecholamine was frequently required for the non-survivors at 0 h. The frequency of catecholamine use was not statistically different between both groups after 6 h. More detailed information is provided in Supplemental Table 1.

Quantitatively measured PLR values during the first 72 h after ROSC

PLR value was associated with 90-day survival after accounting for random effects associated with individual subjects ($P < 0.001$). This indicates that PLR values were consistently greater among survivors compared to non-survivors at each time point during the first 72 h. The association between hour and PLR was marginally significant ($P = 0.04$), but the interaction of hour by survival status was not significant ($P = 0.89$), indicating that the change in PLR over time was not significantly different for survivors than non-survivors (Fig. 1A). Likewise, PLR value was associated with 90-day favourable neurological outcome ($P < 0.001$). Neither the association between hour and PLR

Table 2
Usage of pharmacologic agents among 90-day survivor and non-survivor.

Type of pharmacologic agent	Time after ROSC	Survivors	Non-survivors	P value
Sedatives; n (%)	0 h	2 (9)	6 (22)	0.19
	6 h	19 (83)	12 (46)	0.008
	12 h	21 (91)	12 (57)	0.009
	24 h	21 (91)	11 (58)	0.01
	48 h	18 (78)	19 (56)	0.14
	72 h	17 (74)	12 (86)	0.40
Analgesia; n (%)	0 h	1 (4)	3 (11)	0.38
	6 h	14 (61)	9 (35)	0.05
	12 h	14 (61)	10 (48)	0.38
	24 h	13 (57)	8 (42)	0.35
	48 h	13 (57)	8 (50)	0.69
	72 h	11 (48)	6 (43)	0.77
Catecholamine; n (%)	0 h	4 (17)	21 (78)	< 0.001
	6 h	12 (52)	18 (69)	0.22
	12 h	13 (57)	15 (71)	0.30
	24 h	11 (48)	12 (63)	0.32
	48 h	12 (52)	12 (75)	0.15
	72 h	9 (39)	9 (64)	0.14

Percentage of non-survivors is expressed by the proportion of alive patients receiving pharmacologic agent at each time point who were 90-day non-survivors. ROSC, return of spontaneous circulation. $p < 0.05$ is statistically significant.

($P = 0.30$) or the interaction of hour by neurological outcome status ($P = 0.50$) were significant. Thus, patients who achieved a 90-day favourable neurological outcome had consistently greater PLR values compared to patients with unfavourable neurological outcomes, but the change in PLR over time was not significantly different between outcome groups (Fig. 1B).

To address the impact of the TTM on the PLR results, we further conducted the same analyses exclusively for patients for whom TTM was implemented. PLR values were consistently greater for 90-day survivors compared to non-survivors (Fig. 1C) and patients who achieved a 90-day favourable neurological outcome compared to patients with unfavourable neurological outcomes (Fig. 1D), but the change in PLR over time was not significantly different between respective outcome groups.

ROC analysis for prediction of 90-day survival and neurological outcome

The 0-hour PLR value best predicted 90-day survival with an AUC value of 0.82 and a cutoff value of 3% (Fig. 2A, Table 3). The PLR cutoff values with corresponding sensitivities, specificities, NPV and its 95% CIs at each time point are shown in Table 3. The max NPV is 1.0 at 6 h, with a PLR cutoff of 3%, indicating that a PLR value less than 3% at 6 h after ROSC predicts a 100% 90-day mortality with a 0% false negative rate (Table 3) according to our data. As observed in the overall post-CA patients, the 0-h PLR value was the best predictor for 90-day survival in the TTM subgroup with an AUC of 0.81 and a PLR cutoff value of 6% (Fig. 2B, Table 3).

The 0-hour PLR value best predicted not only the survival but also a favourable neurological outcome, with an AUC value of 0.84 and a PLR cutoff value of 6% (Fig. 3A, Table 3). The max NPV reached 1.0 at all time points from 0 through 72 h with the PLR cutoff values ranging from 3% at 0 h to 10% at 72 h irrespective of TTM implementation (Table 3). The 0-hour PLR was the strongest predictor of 90-day favourable neurological outcome when assessed exclusively in the TTM subgroup, with an AUC of 0.80 and a PLR cutoff value of 6% (Fig. 3B, Table 3). Quantitative PLR showed better prognostic accuracy over 72 h than qualitative assessment (Supplemental Table 2 and 3).

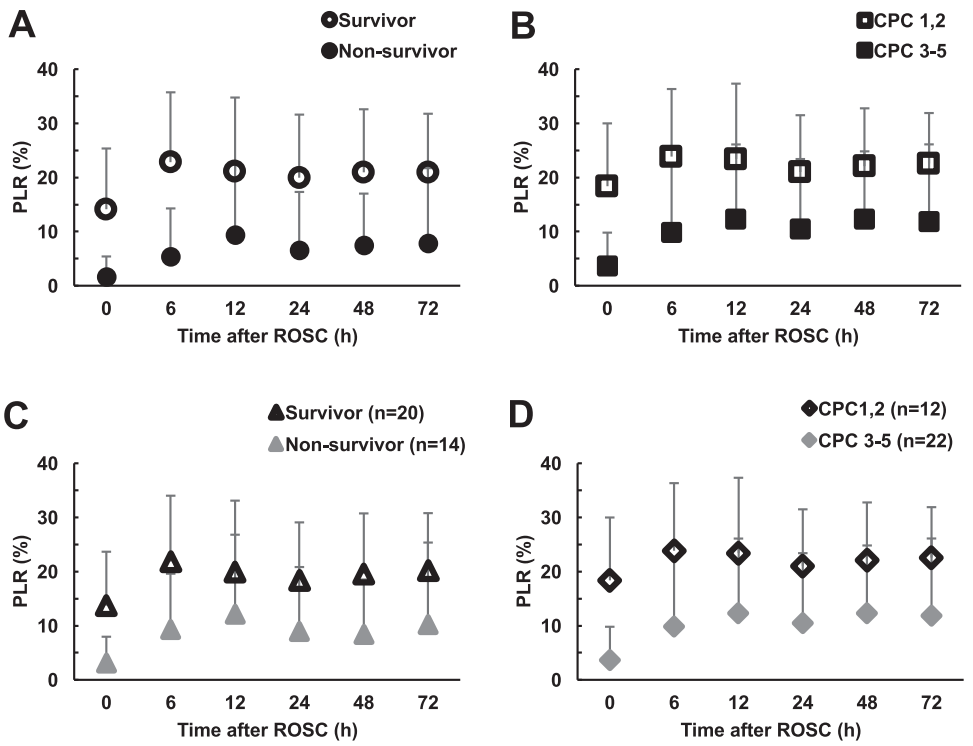

Fig. 1. Serial measurement of PLR after return of spontaneous circulation to 72 h.
(A) PLR of survivors and non-survivors. (B) PLR of favourable and unfavourable neurological outcomes. (C) PLR of survivors and non-survivors treated with TTM. (D) PLR of favourable and unfavourable neurological outcomes treated with TTM. PLR, pupillary light reflex.

Discussion

To the best of our knowledge, this is the first study that has sequentially measured quantitative PLR at 0 through 72 h after ROSC in adult post-CA patients and compared PLR values with outcomes. Surprisingly, the PLR values measured at 0 h were the best predictor for both survival (cutoff PLR value of 3%) and favourable outcome (cutoff PLR value of 6%) in post-CA patients of all measurement time points, irrespective of TTM. Since the clinical research required informed consent prior to enrollment and data acquisition, it took about half an hour to measure PLR in the emergency department after ROSC. However, a 30-min delay in the PLR measurement is reasonable in post-CA care immediately after ROSC.

Prognostication with quantitative measurements of PLR have been previously reported, both during CA [12] and post-CA [13–15]. The PLR cutoff value of 15% for predicting 90-day neurological outcome at 48 h after ROSC in patients who underwent TTM is in line with previous studies [13–15]. PLR was measured on day 1 and day 2 (average of 4 and 24 h, or 16 and 46 h after CA) [13,14], or average of 24 and 48 h after CA [15] in previous studies. In addition to the considerable time variation of the PLR measurements, the prognostic performance of PLR has only previously been evaluated at two time points and the optimal timing for prognostication including immediately after ROSC remains unexplored. Conversely, the current study has shown with a precise timeline of serial PLR measurements, that the PLR was distinctly greater from immediately after ROSC to 72 h for those patients who achieved favourable outcomes, with 0-hour PLR being the best predictor of both 90-day survival and favourable neurological outcomes.

Obtaining information from the brainstem could be important for early prognostication of CA outcome because it reflects the minimum

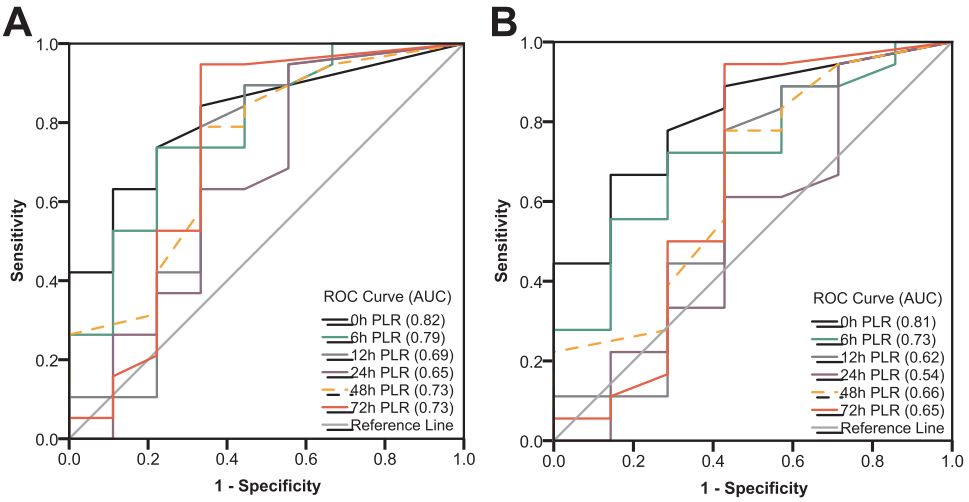

Fig. 2. ROC analysis for the prediction of 90-day survival.
(A) The prediction of 90-day survival with PLR in all patients. (B) The prediction of 90-day survival with PLR only in patients treated with TTM. AUC, area under the curve; ROC, receiver operating characteristic.

Table 3
Prediction of 90-day survival and favorable neurological outcome with ROC analysis.

Time after ROSC (h)	PLR cutoff value (%)	Sensitivity	Specificity	NPV (95% CI)	Max NPV	PLR cutoff value (%) for Max NPV
90-day survival (ALL)						
0	3	0.87	0.80	0.87 (0.66–0.97)	0.87	3
6	12	0.77	0.90	0.78 (0.56–0.93)	1.00	3
12	6	0.91	0.65	0.85 (0.55–0.98)	0.91	4
24	5	0.91	0.65	0.85 (0.55–0.98)	0.91	3
48	12	0.82	0.75	0.69 (0.39–0.91)	0.80	4
72	8	0.90	0.75	0.82 (0.48–0.98)	0.89	5
90-day survival (TTM)						
0	6	0.80	0.77	0.71 (0.42–0.92)	0.80	3
6	12	0.75	0.82	0.64 (0.35–0.87)	1.00	3
12	6	0.90	0.58	0.78 (0.40–0.97)	0.86	4
24	5	0.90	0.50	0.75 (0.35–0.97)	0.83	3
48	12	0.80	0.70	0.64 (0.31–0.89)	0.75	4
72	8	0.90	0.67	0.75 (0.35–0.97)	0.83	5
90-day favorable neurological outcome (ALL)						
0	6	0.92	0.74	0.96 (0.81–1.00)	1.00	3
6	16	0.77	0.76	0.88 (0.69–0.98)	1.00	5
12	4	1.00	0.42	1.00 (0.72–1.00)	1.00	4
24	6	1.00	0.54	1.00 (0.77–1.00)	1.00	6
48	15	0.85	0.62	0.87 (0.60–0.98)	1.00	4
72	10	1.00	0.60	1.00 (0.74–1.00)	1.00	10
90-day favorable neurological outcome (TTM)						
0	11	0.75	0.81	0.85 (0.62–0.97)	1.00	3
6	16	0.75	0.68	0.81 (0.54–0.96)	1.00	5
12	9	0.91	0.45	0.90 (0.56–1.00)	1.00	4
24	6	1.00	0.45	1.00 (0.66–1.00)	1.00	6
48	15	0.83	0.61	0.85 (0.55–0.98)	1.00	4
72	10	1.00	0.56	1.00 (0.66–1.00)	1.00	10

ALL denotes all patients, whereas TTM denotes only patients treated with target temperature management.

perfusion of vital brain tissues. As patients often experience full reversal of loss of cerebral function after general anaesthesia, monitoring cerebral function in post-CA patients may not be useful for early prognostication [12,15,20]. Moreover, during the period of neurological recovery following ROSC in post-CA patients with favourable outcomes, brainstem reflexes return earlier than both cortical function and consciousness [21]. Against the hypothesis that a better PLR restoration is associated with favourable neurological outcomes [15], our results revealed that a change in PLR over time during the first 72 h was not statistically different between the outcome groups. Given the distinctly different PLR values between outcome groups, with its consistency throughout the 72 h, prognostication with quantitative PLR is feasible as early as within an hour after ROSC.

The PLR cutoff value of 3% measured at 0 h after ROSC indicated 100% NPV for favourable neurological outcomes. As neuro-protective therapies for PCAS are time sensitive, prognostication of poor outcomes as early as possible after ROSC is critical in determining the indication of neuro-critical care and enabling the effective allocation of resources to potential candidates with favourable neurological recovery. Furthermore, our results revealed that a PLR of 0%, i.e. bilateral absence of PLR even with quantitative measurements, meant a 100% NPV for predicting favourable outcomes during all time points up to 72 h after ROSC. Since our sample size was small, further research is warranted to better determine probable neurological outcome in post-CA patients and subsequent consideration for the termination of intensive therapies.

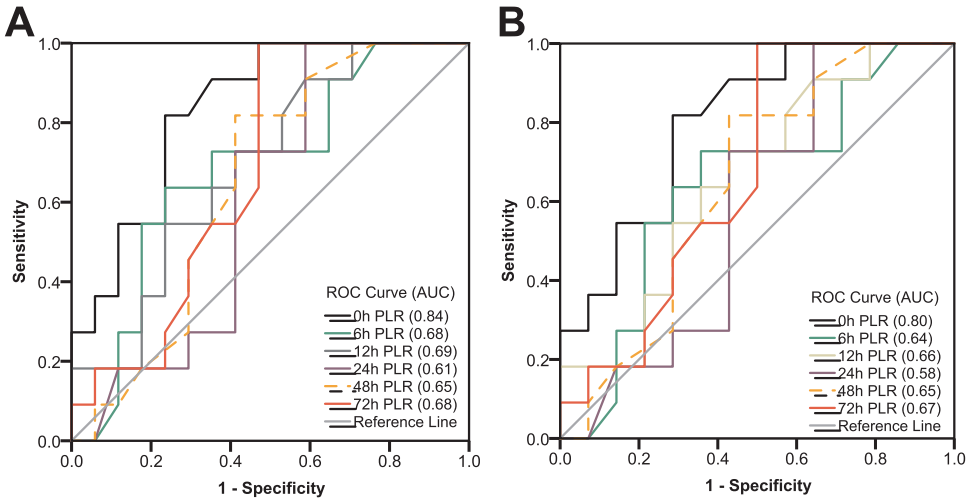

Fig. 3. ROC analysis for the prediction of 90-day favourable neurological outcomes.
The prediction of 90-day favourable neurological outcomes by PLR in all patients.
The prediction of 90-day favourable neurological outcomes by PLR only in patients treated with TTM.

Outcome prediction with qualitative PLR has been strongly recommended to be performed 72 h or more after CA because of its low predictive value immediately after achieving ROSC [10]. Our results showed cutoff PLR values of between 0–10% prior to 72 h post CA, which are hardly detectable with qualitative assessment by an examiner. It has been reported that the presence of PLR is undetectable when the PLR is less than a reduction of 0.3 mm, which is a 10% PLR in a 3.0 mm pupil diameter [22]. Therefore, it is no wonder that quantitative PLR with a pupillometer can predict outcomes in the post-CA care earlier than qualitative assessments.

Mortality after CA is primarily accounted for by the withdrawal of life-sustaining therapy (WLST) [23]. Multi-modal prognostication was performed in line with the guidelines [10,19]. When poor neurological prognosis is perceived, most Japanese physicians withhold aggressive treatments and seldom adopt active WLST. Consequently, mortality did not concentrate within a week after CA and continued to increase over 3 weeks (Supplemental Fig. 2). Moreover, the results of quantitative PLR were obtained exclusively for our observational study and were never used for clinical decision making of WLST. Thus, removing the risk of creating a self-fulfilling prophecy with a lack of blindness to the results of the quantitative PLR measurements and the WLST, in our study.

Our study has several limitations. First, the sample size was relatively small. A substantial number of patients were excluded because informed consent could not be obtained from an accompanied family member / guardian immediately after ROSC. However, our study was a multicentre study, which avoids the bias pertaining to previous single-centre studies. Second, the study does not compare the prognostic accuracy of quantitative PLR measurements with other physiological or biomarker tests, which are currently used for prognostication in post-CA care. This study focused specifically on evaluating the prognostic accuracy of quantitative PLR in the very early phase with repeated assessments. A multimodal prognostication approach is recommended to minimize the rate of false-positive results for predicting poor outcomes [10,19]. Further large multicentre studies are warranted to evaluate the utility of quantitative PLR for early prognostication solely, as well as in a multi-modal prognostic scheme.

Conclusions

Quantitative PLR was consistently greater in 90-day survivors and patients with favourable neurological outcomes during the first 72 h after ROSC. Quantitative PLR as early as 0 h has a potential role in prognostication after OHCA; further larger, multicentre studies are warranted.

Conflict of interest

All authors declare no conflicts of interest.

Acknowledgments

The authors thank Sayuri Suzuki PhD for assistance with data collection. This study was supported by KAKENHI15H05009. The Funder had no role in the study design, data collection, analysis, writing of the manuscript, or the decision to submit the manuscript for publication.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2018.06.027.

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Supplemental materials

Quantitative Assessment of Pupillary Light Reflex for Early Prediction of Outcomes After Out-of-Hospital Cardiac Arrest: A Multicentre Prospective Observational Study

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Supplemental Table 1. Usage of specific pharmacologic agents among 90-day survivors and non-survivors

Pharmacologic agents	Timing	Survivors	Non-survivors	P value
Propofol; n (%)	0 h	2 (9)	6 (22)	0.19
	6 h	18 (78)	11 (42)	**0.002**
	12 h	21 (91)	8 (38)	**<0.001**
	24 h	18 (78)	10 (53)	**0.08**
	48 h	16 (70)	7 (44)	0.11
	72 h	15 (65)	8 (57)	0.34
Midazolam; n (%)	0 h	0	6 (22)	**0.02**
	6 h	3 (13)	1 (4)	0.24
	12 h	5 (22)	1 (5)	0.10
	24 h	3 (13)	0	0.10
	48 h	2 (9)	0	0.23
	72 h	2 (9)	1 (8)	0.87
Dexmedetomidine; n (%)	0 h	0	0	-
	6 h	0	1 (4)	0.34
	12 h	0	1 (5)	0.29
	24 h	1 (4)	0	0.36
	48 h	2 (9)	0	0.23
	72 h	0	0	-
Fentanyl; n (%)	0 h	1 (4)	3 (11)	0.38
	6 h	7 (30)	5 (19)	0.36
	12 h	5 (22)	7 (33)	0.39
	24 h	7 (30)	5 (26)	0.77
	48 h	7 (30)	6 (38)	0.65
	72 h	4 (17)	4 (29)	0.42
Bupurenprphine; n (%)	0 h	0	0	-
	6 h	7 (30)	2 (8)	**0.04**
	12 h	7 (30)	2 (10)	0.09
	24 h	6 (26)	12 (63)	**0.02**
	48 h	6 (26)	2 (13)	0.30
	72 h	7 (30)	2 (14)	0.40
Norepinephrine; n (%)	0 h	1 (4)	9 (33)	**0.01**
	6 h	9 (39)	13 (50)	0.45
	12 h	9 (39)	8 (38)	0.94
	24 h	9 (39)	11 (58)	0.23
	48 h	10 (43)	10 (63)	0.24
	72 h	7 (30)	11 (79)	**0.005**
Dopamine; n (%)	0 h	3 (13)	6 (22)	0.40
	6 h	5 (22)	9 (35)	0.32
	12 h	5 (22)	5 (24)	0.87
	24 h	2 (9)	3 (16)	0.48
	48 h	1 (4)	4 (25)	0.17
	72 h	3 (13)	4 (27)	0.24
Dobutamine; n (%)	0 h	1 (4)	2 (7)	0.65
	6 h	9 (39)	3 (12)	**0.03**
	12 h	10 (43)	7 (30)	0.49
	24 h	10 (43)	7 (37)	0.66
	48 h	10 (43)	4 (25)	0.24
	72 h	10 (43)	7 (36)	0.64

Percentage of the 90-day non-survivors was expressed as the number of patients who were 90-day non-survivors and were receiving pharmacologic agents at each time point.

Supplemental table 2. Prediction of 90-day survival with qualitative PLR assessment

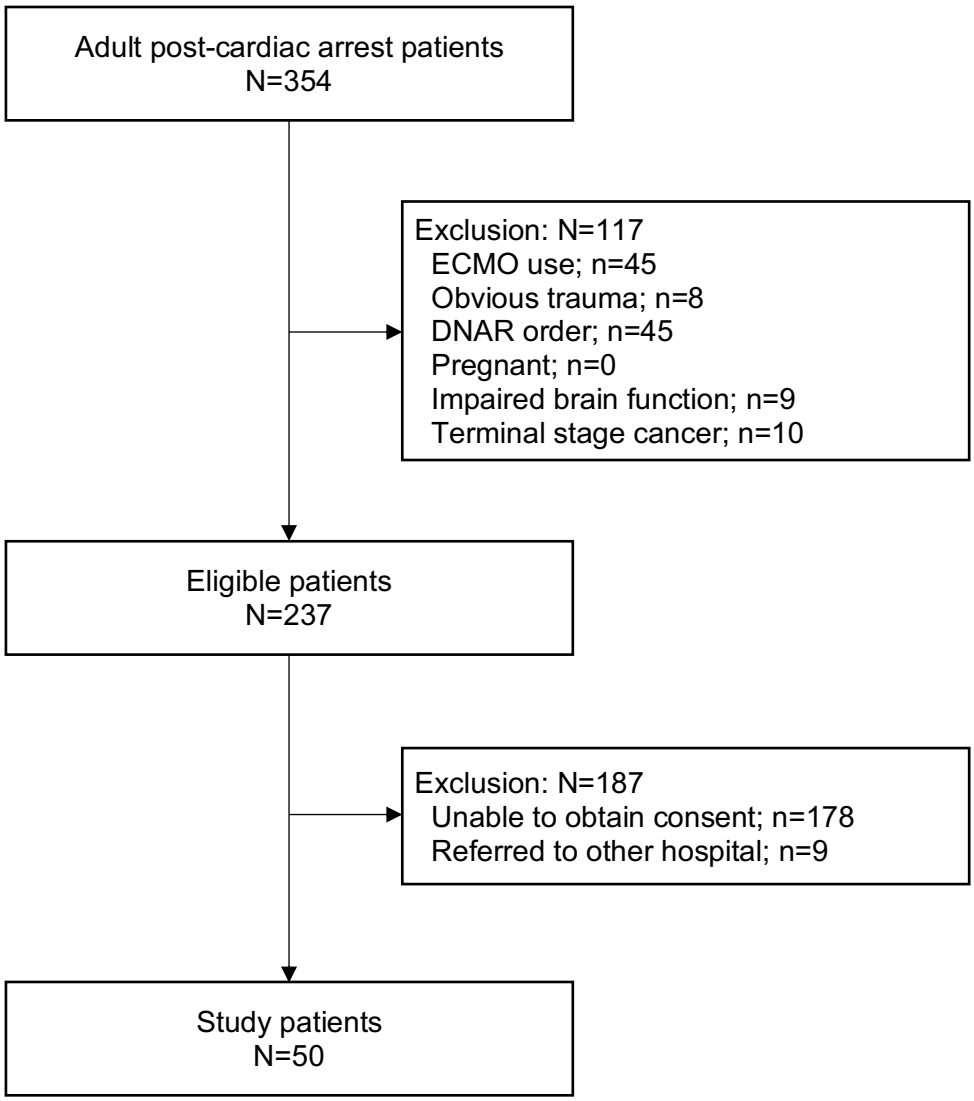
Time after ROSC (h)	Positive PLR in survivors (n)	Negative PLR in non-survivors (n)	Sensitivity	Specificity	NPV (95% CI)
All patients					
0	12 / 23	23 / 27	0.52	0.85	0.68 (0.49 – 0.83)
6	13 / 20	19 / 25	0.65	0.76	0.73 (0.52 – 0.88)
12	13 / 20	14 / 19	0.65	0.74	0.67 (0.43 – 0.85)
24	13 / 21	11 / 16	0.62	0.69	0.58 (0.33 – 0.80)
48	15 / 21	10 / 14	0.71	0.71	0.63 (0.35 – 0.85)
72	17 / 19	12 / 14	0.89	0.86	0.86 (0.57 – 0.98)
TTM subgroup					
0	11 / 20	12 / 14	0.55	0.86	0.57 (0.34 – 0.78)
6	12 / 18	9 / 14	0.67	0.64	0.60 (0.32 – 0.84)
12	12 / 18	9 / 14	0.67	0.64	0.60 (0.32 – 0.84)
24	11 / 19	8 / 13	0.58	0.62	0.50 (0.25 – 0.75)
48	13 / 19	8 / 12	0.68	0.67	0.57 (0.29 – 0.82)
72	16 / 18	9 / 11	0.89	0.82	0.82 (0.48 – 0.98)

CI, confidence interval; PLR, pupillary light reflex; ROSC, return of spontaneous circulation; TTM, target temperature management

Supplemental table 3. Prediction of 90-day favourable neurological outcome with qualitative PLR assessment

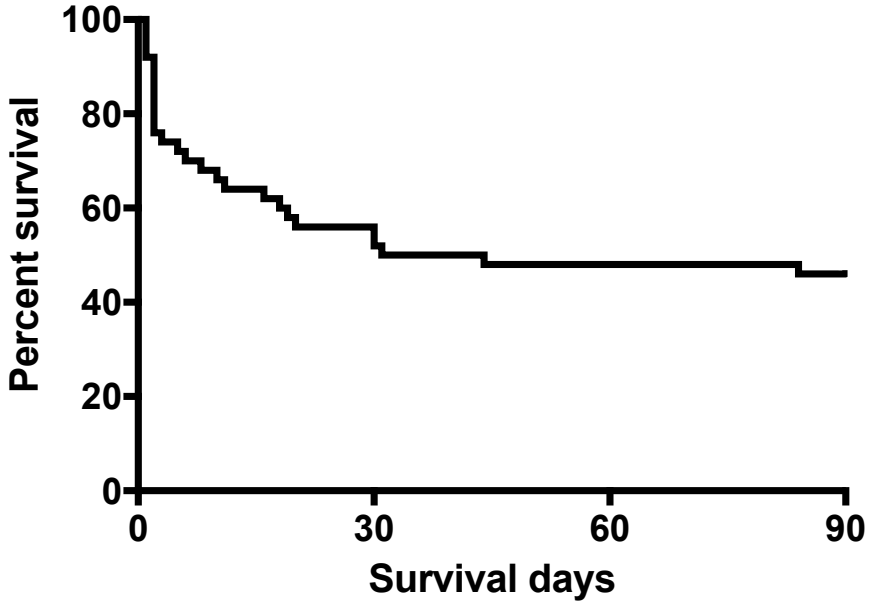
Time after ROSC (h)	Positive PLR in patients who achieved CPC1,2 (n)	Negative PLR in patients who achieved CPC3-5 (n)	Sensitivity	Specificity	NPV (95% CI)
All patients					
0	10 / 13	31 / 37	0.77	0.84	0.91 (0.76 – 0.98)
6	10 / 13	23 / 32	0.77	0.72	0.88 (0.70 – 0.98)
12	9 / 12	18 / 27	0.75	0.67	0.86 (0.64 – 0.97)
24	8 / 13	14 / 24	0.62	0.58	0.74 (0.49 – 0.91)
48	10 / 13	13 / 22	0.77	0.59	0.81 (0.54 – 0.96)
72	10 / 11	13 / 22	0.91	0.59	0.93 (0.66 – 1.00)
TTM subgroup					
0	9 / 12	18 / 22	0.75	0.82	0.86 (0.64 – 0.97)
6	9 / 12	12 / 20	0.75	0.60	0.80 (0.52 – 0.96)
12	8 / 11	12 / 21	0.73	0.57	0.80 (0.52 – 0.96)
24	7 / 12	11 / 20	0.58	0.55	0.69 (0.41 – 0.89)
48	9 / 12	11 / 19	0.75	0.58	0.79 (0.49 – 0.95)
72	10 / 11	10 / 18	0.91	0.56	0.91 (0.59 – 1.00)

CI, confidence interval; CPC, Cerebral Performance Category; NPV, negative predictive value; PLR, pupillary light reflex; ROSC, return of spontaneous circulation; TTM, target temperature management



Supplemental figure 1. Patient selection

DNAR, do-not-attempt-resuscitation; ECMO, extracorporeal membrane oxygenation.



	0h	6h	12h	24h	48h	72h	30d	90d
Number of survivors at risk	50	49	44	42	39	37	26	23

Supplemental Figure 2. Kaplan-Meier survival curve