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Clinical paper

Time course of platelet counts in relation to the neurologic outcome in patients undergoing targeted temperature management after cardiac arrest☆

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Abstract

Background: Thrombocytopenia is common and associated with mortality in critically ill patients. However, the time course of platelet counts and its association with the neurologic outcome after out-of-hospital cardiac arrest (OHCA) are not well known. The purpose of this study is to describe the time course of platelet counts in relation to the neurologic outcome in patients undergoing targeted temperature management (TTM) after CA.

Methods: Review of consecutive patients receiving TTM after out-of-hospital CA between 2009 and 2016. The blood sample was collected daily until 7 days. The primary outcome was poor neurologic outcome at 6 months after CA defined as Cerebral Performance Category of 3–5 and secondary outcome was mortality at 6 months.

Results: A total of 261 consecutive patients treated with TTM after OHCA between 2009 and 2016. One hundred seventy-five patients (67.0%) had poor neurologic outcomes 6 months after CA. The changes in the platelet counts over time between the good and poor outcome groups were statistically significant ($p < 0.001$). The platelet counts declined during TTM in both groups. The platelet counts recovered to the normal range at the end of the first week in the good neurologic outcome group. However, the platelet counts remained low in the poor outcome group. Low platelet counts on the 7th day were associated with poor neurologic outcomes (aOR 0.975, 95% CI, 0.961–0.989) and mortality at 6 months (aOR 0.986, 95% CI, 0.975–0.997) after adjusting for covariates.

Conclusion: The changes in platelet counts in OHCA patients have a biphasic pattern that is significantly different in patients with good neurologic outcomes and those with poor neurologic outcomes at 6 months. A low platelet count 7 days after CA was associated with a poor neurologic outcome and mortality at 6 months.

Keywords: Cardiac arrest, Platelets, Thrombocytopenia, Outcome, Hypothermia, Induced

Introduction

Despite recent advancements in critical care, out-of-hospital cardiac arrest (OHCA) still has high mortality and morbidity rates.[1] Systemic inflammation, which occurs during the reperfusion period after the return of spontaneous circulation (ROSC), plays an important role in the development of hypoxic ischemic brain injury and multiple organ failure.[2,3] Targeted temperature management (TTM), which has been shown to improve outcomes after OHCA, is now considered standard

☆ This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital; waiver of consent was allowed because of the retrospective nature of the study.

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care for post-cardiac arrest syndrome (PCAS) patients.[3–6] Although significant bleeding has been reported to be uncommon in clinical studies regarding OHCA patients treated with TTM, unintentional hypothermia can increase the risk of bleeding in trauma patients.[7–9] Platelets play an important role in hemostasis and thrombus formation.

Thrombocytopenia is a frequently observed laboratory abnormality in critically ill patients and is associated with mortality.[10–16] In a study from 40 intensive care units (ICUs), patients' platelet counts decreased during their first 4 days after admission, and changes in platelet counts over time were associated with patient outcomes.[10] Moreover, endothelial dysfunction in patients with sepsis causes inflammation and thrombosis, platelets form the cornerstone of this process, and thrombocytopenia may be a prognostic marker for septic shock.[17] In a single-center predefined substudy of the TTM trial, platelet counts were lower in the TTM33-group than in the TTM36-group.[18] However, the associations between platelet counts and patient outcomes are still not known. Moreover, few studies have evaluated the time course of changes in platelet counts and the association of that time course with the neurologic outcomes of PCAS patients treated with TTM.

The aim of this study was to describe the relationship between the time course of platelet counts and neurologic outcomes in patients undergoing TTM after CA.

Methods

Patients and setting

This retrospective observational study based on a prospectively designed registry of OHCA patients was conducted in a single tertiary educational hospital in Seoul, Korea between January 2009 and December 2016. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital and the need to obtain informed consent was waived because of the retrospective nature of the study.

Post-cardiac arrest care

All patients who were comatose after surviving OHCA were considered for treatment with TTM according to a previous post-CA protocol published by our hospital.[19] A target temperature of 33 °C was induced using an endovascular cooling device (Thermoguard, ZOLL Medical Corporation, Chelmsford, MA, USA) or ArticSun (Bard Medical, Louisville, CO, USA) and maintained for at least 24 h. After the maintenance phase, rewarming to 37 °C was performed at a rate of 0.25 °C/h. All patients received sedative and neuromuscular blocking agents prior to induction to control shivering, and these agents were administered continuously throughout the entire TTM phase. In our hospital, we had no policy governing the withdrawal of life-sustaining therapy (WLST) due to legal difficulties.

Measurement

Patient data were collected according to the Utstein Style Criteria for reporting OHCA as follows[20]: age, sex, history of hypertension (HTN), presence of diabetes mellitus (DM), presence of coronary artery disease, witnessed CA, application of CPR by a bystander, first monitored rhythm, cause of arrest, time from collapse to the ROSC, coronary angiography, and percutaneous coronary intervention. Data on the drugs administered during hospitalization, such as heparin and anti-platelet agents, were also collected. White blood cell (WBC) counts, hemoglobin levels, prothrombin time, activated partial thromboplastin time, fibrinogen levels, antithrombin III levels and D-dimer levels were also recorded. Vasopressor requirement was reported by the cumulative vasopressor index (CVI). The CVI is previously developed scale for standardization of equivalent doses of commonly used vasopressors and describing the overall degree of vasopressor support.[21]

The inclusion criteria were patients older than 18 years of age who experienced OHCA and were treated with TTM. Trauma-related etiologies of CA and hemorrhage, such as intracranial bleeding and gastrointestinal bleeding were excluded from this study because they are contraindication of TTM in our hospital. The study outcome was a poor neurologic outcome 6 months after CA, defined as a Cerebral Performance Category (CPC) between 3 and 5. The CPC scale range from 1 to 5, 1 represent good cerebral performance or slightly cerebral disability, 2 moderate disability or independent activities of daily life, 3 severe disability or dependent on others for daily support, 4 coma or vegetative state, 5 death or brain death. Follow-up were performed either face to face or telephone to make this assessment. Blood samples from an arterial line or a central venous catheter were routinely collected at the time of admission to the emergency department; 24 h, 48 h, and 72 h after ROSC; and then daily until the 7th day. Platelet counts were determined using an automated blood cell counter (Sysmex XE-2100, Sysmex Corp., Kobe, Japan).

Statistical analysis

Continuous data are presented as the mean ± standard deviation (SD), and categorical variables are presented as counts and percentages. To compare differences in patient characteristics and outcomes, chi-square tests or Fisher's exact tests were performed for categorical variables, and t tests were performed for continuous variables. A linear mixed model analysis was conducted to assess changes in the platelet counts over time. Post-hoc analyes of platelet counts between neurologic outcome groups at each time points were performed independent samples t-test with Bonferroni correction for multiple comparisons.

To assess the association between platelet counts and poor neurological outcomes and mortality at 6 months after CA, logistic regression analyses were performed. Multivariate logistic regression analysis was performed to select covariates. Variables with p values < 0.2 in the univariate analysis were entered into the multivariate logistic regression model. The variables with p values < 0.05 in the multivariate logistic model were finally selected as covariates.

To evaluate the associations between platelet counts and patient outcomes, thrombocytopenia was defined as a platelet count $< 150 \times 10^9$/L. Platelet counts were also examined as a continuous variable. We estimated receiver operating characteristic (ROC) curves and compared the areas under the ROC curves (AUCs) (C-statistic with 95% CI) in the corresponding logistical models. We also compared the AUCs using the Delong test to assess their equality.[22] Statistical analyses were performed with SPSS version 24.0 (SPSS, Chicago, IL, USA) and MedCalc version 15.2.2 (MedCalc Software, Mariakerke, Belgium), and p values ≤ 0.05 were considered statistically significant.

Results

During the study period, 261 OHCA patients treated with TTM met the inclusion criteria. The mean age of the patients was 54.6 ± 16.5 years, and the majority were male (70.4%). Ninety-nine (37.9%) subjects had an initial shockable rhythm, and 86 (33%) had good neurologic outcomes (CPC 1 or 2) 6 months after CA. Table 1 shows the demographic characteristics of the patients according to their neurological outcome 6 months after CA. Compared with patients with poor neurologic outcomes, patients with good neurologic outcomes were younger; had greater frequencies of witnessed arrests, an initial shockable rhythm, and a cardiac cause of arrest; and had a shorter time from collapse to ROSC. Coronary angiography and percutaneous coronary interventions were more frequently performed in the good outcome group than in the poor outcome group. Table 2 shows the laboratory findings stratified by the patients' neurologic outcomes 6 months after CA. The hemoglobin level, prothrombin time, activated partial thrombin time, antithrombin III level and D-dimer level were significantly different between the groups. The CVI score was significantly higher in the thrombocytopenia group until 6th day after CA (Table 3).

Table 2 – Laboratory findings according to neurologic outcome at 6 months after cardiac arrest.

Characteristic	Good outcome N = 86	Poor outcome N = 175	p
WBC, G/l	14,839 ± 5662	14,175 ± 5852	0.385
Hemoglobin, g/dL	14.60 ± 1.86	12.81 ± 2.53	<0.001
Prothrombin time (s)	12.87 ± 3.76	15.98 ± 5.73	<0.001
aPTT (s)	28.64 ± 12.99	40.52 ± 18.64	<0.001
Fibrinogen, mg/dL	221.17 ± 72.29	238.01 ± 93.96	0.139
Antithrombin III, %	80.16 ± 14.59	68.73 ± 16.26	<0.001
D-dimer, quan, mg/L	8.83 ± 8.20	16.52 ± 11.53	<0.001
Platelet Counts, G/L			
Platelet, admission	230.31 ± 65.21	197.30 ± 71.19	<0.001
Platelet, 24 h after ROSC	187.88 ± 63.48	161.80 ± 65.39	<0.001
Platelet, 48 h after ROSC	169.80 ± 65.39	140.25 ± 55.97	0.003
Platelet, 72 h after ROSC	152.89 ± 44.80	128.31 ± 55.98	0.001
Platelet, 4th day	152.47 ± 49.71	111.33 ± 52.47	<0.001
Platelet, 5th day	163.21 ± 52.01	111.35 ± 52.30	<0.001
Platelet, 6th day	172.42 ± 53.26	119.22 ± 56.94	<0.001
Platelet, 7th day	190.90 ± 59.77	119.97 ± 45.42	<0.001

Abbreviations: WBC = white blood cell; aPTT = activated partial thromboplatin time.

Platelet counts over time

The changes in the platelet counts over time between the good and poor outcome groups were statistically significant (Fig. 1; $p < 0.001$). The platelet counts steadily decreased in both groups until 3–4 days after CA. The platelet counts decreased in a majority of the patients (194/212 patients, 91.5%) in both good (80/84, 95.2%) and poor outcome groups (114/128, 89.1%) at 3 days after CA. The platelet counts began to increase at 5 day after CA in good neurologic outcome and reached normal range at 7 days after CA. However, the platelet counts remained low in the poor outcome group.

Logistic regression analysis

A history of hypertension, a non-shockable rhythm, time from collapse to ROSC, prothrombin time and D-dimer level were finally selected as covariates. When the platelet counts were examined as a continuous

Table 1 – Demographic and clinical findings according to neurologic outcome at 6 months after cardiac arrest.

Characteristics	Good outcome N = 86	Poor outcome N = 175	p
Mean age	48.3 ± 15.1	57.7 ± 16.4	<0.001
Male, N (%)	66 (76.7)	118 (67.4)	0.121
Past history			
HTN, No. (%)	17 (19.8)	61 (34.9)	0.012
DM, No. (%)	5 (5.8)	52 (29.7)	<0.001
Liver cirrhosis	0 (0)	2 (1.1)	0.320
Witnessed arrest, No. (%)	74 (86.0)	110 (63.2)	<0.001
Bystander CPR, No. (%)	53 (61.6)	91 (52.3)	0.155
Shockable rhythm, No. (%)	70 (81.4)	29 (16.6)	<0.001
Cardiac cause of arrest, No. (%)	81 (94.2)	98 (56.0)	<0.001
Time from collapse to ROSC, median (IQR), min	24.1 ± 15.3	38.2 ± 20.2	<0.001
Coronary angiography (CAG), No. (%)	76 (88.4)	33 (18.9)	<0.001
Percutaneous coronary intervention (PCI), No. (%)	27 (31.4)	16 (9.1)	<0.001
TTM method			0.043
Intravascular cooling, No. (%)	75 (87.2)	134 (76.6)	
Surface cooling, No. (%)	11 (12.8)	41 (23.4)	
Medication			
Aspirin	49 (57.0)	24 (13.7)	<0.001
Clopidogrel	32 (37.2)	11 (6.3)	<0.001
Prasugrel	3 (3.5)	0 (0)	0.013
Ticagrelor	12 (14.0)	13 (7.4)	0.092
Heparin	33 (38.4)	37 (21.1)	0.003

Abbreviations: HTN = hypertension, DM = diabetes, CPR = cardiopulmonary resuscitation, ROSC = return of spontaneous circulation, IQR = interquartile range, TTM = targeted temperature management.

Table 3 – Cumulative vasopressor index score according to platelet counts.

	Cumulative vasopressor index		p
	Platelet ≤ 150,000	Platelet > 150,000	
CVI, admission	1.900 ± 1.389	1.339 ± 1.352	0.016
CVI, 24 h after ROSC	1.822 ± 1.452	1.226 ± 1.264	0.002
CVI, 48 h after ROSC	1.870 ± 1.351	1.012 ± 1.232	<0.001
CVI,72 h after ROSC	1.687 ± 1.230	0.895 ± 1.200	<0.001
CVI, 4th day	1.643 ± 1.281	0.642 ± 1.023	<0.001
CVI, 5th day	1.689 ± 1.300	0.657 ± 1.015	<0.001
CVI, 6th day	1.572 ± 1.253	0.882 ± 1.162	0.001
CVI, 7th day	1.512 ± 1.244	1.081 ± 1.270	0.063

Abbreviation: CVI = cumulative vasopressor index.

variable, the platelet counts at the time of admission through the 4th day were not associated with a poor neurologic outcome 6 months after CA. However, low platelet counts on the 5th day after admission were associated with poor neurologic outcomes at 6 months after CA (aOR = 0.988, 95% CI, 0.978–0.998). This association was maintained until day 7. Low platelet counts on the 7th day of admission were associated with mortality 6 months after CA (aOR = 0.986, 95% CI, 0.975–0.997) (Table 4).

Thrombocytopenia (a platelet count $<150 \times 10^9$/L) on the 7th day after admission was associated with a poor neurologic outcome 6 months after CA after adjusting for the same covariates as above (aOR = 4.817, 95% CI = 1.455–15.951) (Table 5).

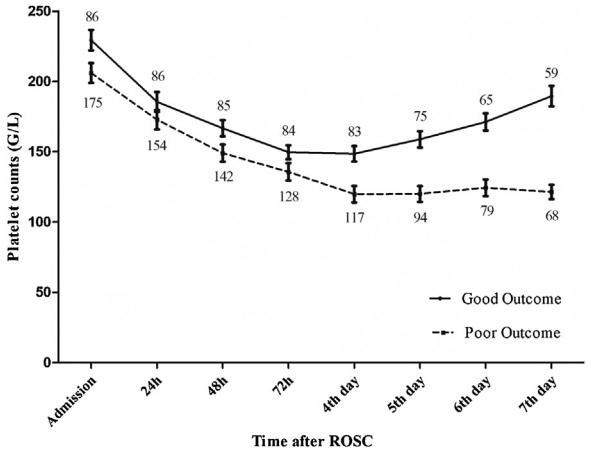

Fig. 1 – Daily platelet counts in the good and poor neurologic outcome groups.
Platelet counts significantly changed over time ($p < 0.001$). Changes in platelet counts overtime between neurologic outcome groups were significantly different ($p < 0.001$). The platelet counts steadily decreased in both groups until 3-4 days after CA. However, the platelet counts began to recover at 5 days after cardiac arrest and reached normal range at 7 days after cardiac arrest in good neurologic outcome group, while the thorombocytopenia sustained in poor neurologic outcome group. Numbers are included number of patients for analyses.

Table 4 – Adjusted OR for poor neurologic outcome and mortality at 6 months.

	OR	95% CI
For poor neurologic outcome at 6 months		
Platelet, admission (n = 261)	0.994	0.987–1.001
Platelet, 24 h after ROSC (n = 240)	0.998	0.991–1.005
Platelet, 48 h after ROSC (n = 227)	0.995	0.986–1.004
Platelet, 72 h after ROSC (n = 212)	0.994	0.986–1.003
Platelet, 4th day (n = 200)	0.991	0.982–1.000
Platelet, 5th day (n = 169)	0.988	0.978–0.998
Platelet, 6th day (n = 144)	0.985	0.974–0.995
Platelet, 7th day (n = 127)	0.975	0.961–0.989
For mortality at 6 months		
Platelet, admission (n = 261)	0.999	0.994–1.004
Platelet, 24 h after ROSC (n = 240)	1.000	0.994–1.006
Platelet, 48 h after ROSC (n = 227)	0.998	0.991–1.006
Platelet, 72 h after ROSC (n = 212)	0.999	0.991–1.006
Platelet, 4th day (n = 200)	0.996	0.988–1.004
Platelet, 5th day (n = 169)	0.995	0.986–1.004
Platelet, 6th day (n = 144)	0.994	0.985–1.003
Platelet, 7th day (n = 127)	0.986	0.975–0.997

Adjusted for HTN, not shockable rhythm, time from collapse to ROSC, Prothrombin time (s) and D-dimer level.

Prognostic value of platelet counts

Fig. 2 shows the AUCs of the platelet counts at different time points for predicting poor neurologic outcome at 6 months after CA. The AUC is highest at the 7th day after admission (AUC = 0.822, 95% CI = 0.739–0.877). And the AUC at the 7th day after admission was significantly higher than the AUC at the 4th day after admission (AUC = 0.661, 95% CI = 0.567–0.747, $p < 0.001$).

Discussion

The main finding of this study is that the changes in the platelet count in OHCA patients treated with TTM have a biphasic pattern that is significantly different between patients with good and poor neurologic outcomes at 6 months. During the TTM period, platelet counts decreased in the majority of patients (83.5%). Platelet counts recovered to the normal range in the good neurologic outcome group but not in the poor neurologic outcome group. Low platelet counts between the 4th and 7th days after CA were associated with poor neurologic outcomes at 6 months. However, prolonged low platelet counts and the lack of an increase in platelet counts were associated with a greater risk of a poor neurologic outcome 6 months after CA, and this association persisted after adjusting for covariates at the patient level.

Thrombocytopenia is a frequently observed laboratory abnormality in critically ill patients.[10–15] One systematic review reported that thrombocytopenia at the time of ICU admission occurred in 8.3%–67.6% of patients and that incident thrombocytopenia during the entire ICU stay occurred in 13.0%–44.1% of patients.[23] Moreover, thrombocytopenia is known to be associated with mortality in critically ill patients. Martin et al. found that thrombocytopenia at the time of ICU admission was associated with mortality after adjusting for covariates.[12] Vandijck et al. found that low platelet counts during the ICU stay were associated with mortality in critically ill patients with blood stream infections.[13] Therefore, a low platelet count may be a

Table 5 – Adjusted OR for poor neurologic outcome at 6 months. (Platelet < 150,000).

For poor neurologic outcome

	OR	95% CI
Platelet < 150,000, at admission	1.670	0.417–6.697
Platelet < 150,000, 24 h after ROSC	1.638	0.615–4.359
Platelet < 150,000, 48 h after ROSC	1.488	0.586–3.782
Platelet <150,000, 72 h after ROSC	1.454	0.587–3.602
Platelet < 150,000, 4th days	1.805	0.695–4.691
Platelet < 150,000, 5th days	2.067	0.764–5.588
Platelet < 150,000, 6th days	2.184	0.780–6.121
Platelet < 150,000, 7th days	4.817	1.455–15.951

Adjusted for HTN, not shockable rhythm, time from collapse to ROSC, Prothrombin time (s) and D-dimer level.

surrogate marker for disease severity and not an epiphenomenon.[24] However, there have been few studies on platelet counts and their associations with outcomes after CA.

The causes of thrombocytopenia in critically ill patients are multifactorial. Endothelial damage due to systemic inflammatory response syndrome, thrombotic microangiopathy and drug-induced thrombocytopenia, such as that caused by heparin and quinine, have been suggested as possible mechanisms.[24] In cases of systemic inflammatory syndrome such as sepsis, endothelial damage with or without disseminated intravascular coagulation (DIC) is considered a major feature of the pathology leading to platelet activation.[24,25] The disruption of endothelial integrity promotes platelet adhesion and aggregation, resulting in platelet reduction.[24] Whole-body ischemic-reperfusion injury after CA leads to a systemic inflammatory response that is similar to the response during sepsis.[1] Bro-Jeppensen et al. reported that endothelial injury and activation were found in the first 72 h after arrest and that endothelial damage was associated with high baseline levels of systemic inflammation.[26] Furthermore, endothelial damage was associated with the severity of post-cardiac arrest syndrome (PCAS), cardiovascular dysfunction and vasopressor requirements.[26,27] Thus, endothelial damage can be considered a major cause of platelet reduction in PCAS patients. The vasopressor requirement was higher in patients with thrombocytopenia in our study.

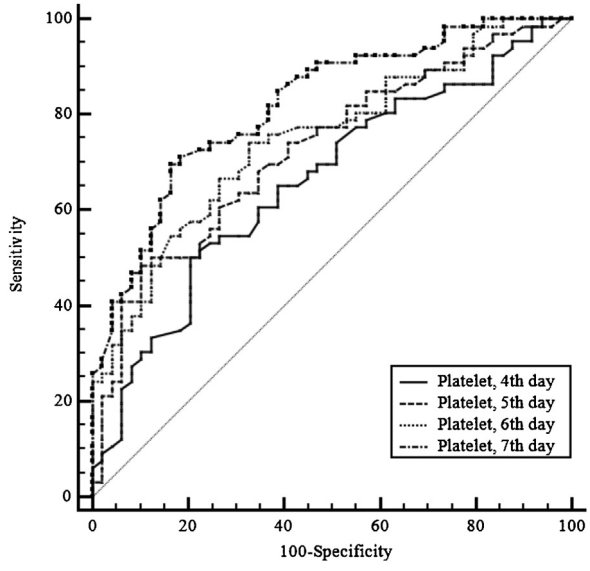

Fig. 2 – Prognostic value of platelet counts for the prediction of a poor neurologic outcome at 6 months after cardiac arrest.
(1) Platelet counts at 4 days after admission (AUC 0.661, 95% CI: 0.567–0.747), (2) platelet counts at 5 days after admission (AUC 0.727, 95% CI: 0.636–0.806), (3) platelet counts at 6 days after admission (AUC 0.749, 95% CI: 0.659–0.825), (4) platelet counts at 7 days after admission (0.822, 95% CI: 0.739–0.887).

Platelet counts can also be affected by several drugs. Heparin is the most common cause of drug-induced thrombocytopenia. Heparin-induced antibodies bind to the heparin-platelet factor IV complex, resulting in massive platelet activation.[28] In our study, heparin was more frequently administered in patients with good outcomes than in those with poor outcomes. Moreover, more patients who used heparin for a long time were in the good outcome group than in the poor outcome group. Therefore, heparin-induced thrombocytopenia is unlikely to account for the biphasic pattern of platelet count changes in OHCA patients treated with TTM.

After the induction of the target temperature, platelet counts decreased in a majority of the patients in both the good and poor outcome groups. Mild hypothermia can induce mild coagulopathy, including platelet dysfunction and a decrease in the platelet count.[29] In fact, platelet counts were lower in the TTM33-group than in the TTM36-group in a single-center predefined substudy of the TTM trial.[18] Therefore, the initial thrombocytopenia in both the good and poor outcome groups can be considered the result of low body temperature in addition to endothelial damage due to systemic inflammation. Most patients in our hospital were cooled to 33 °C for a period of 24 h. However, major bleeding complications were not observed in our cohort.

A similar biphasic pattern that depended on the outcome was reported previously in several studies. Moreau et al. showed that a 30% decline in platelet count was associated with mortality in patients with normal platelet counts at the time of admission to the ICU.[11] Akca et al. found that platelet count changes in the critically ill had a biphasic pattern that was different in survivors and nonsurvivors, and sustained thrombocytopenia was associated with the mortality.[10] Decreased platelet counts in the early phase of disease have also been reported in neonatal hypoxic ischemic encephalopathy and PCAS patients. Shah et al. showed that platelet counts in patients with neonatal hypoxic ischemic encephalopathy in whom TTM was not used tended to decrease after birth, reaching the nadir on days 2 to 3.[30] Jeppssen et al. found that platelet counts decreased from the time of admission to 70 h after TTM treatment in OHCA patients and that the level of platelet aggregation was below the normal range.[31] In our study, platelet counts decreased during the TTM period in both groups, and the relative absence of the recovery of the platelet counts was associated with not only mortality at 6 months but also poor neurologic outcomes at 6 months after CA. A possible explanation for this result is that systemic inflammation during the ischemic-reperfusion period promotes platelet adhesion and consumption, resulting in decreasing platelet counts in first 72 h of PCAS and seem to recover as the cardiac arrest-associated systemic inflammatory response subsides after 4 days of ROSC.

This study has several limitations. First, this was a single-center study, which limits the generalizability of the findings to other hospitals. Second, most patients were managed with a target temperature of 33 °C for 24 h regardless of their initial rhythm, and

the findings may be different when other management strategies are employed. Third, our findings should be confirmed by a larger prospective multicenter study because this was a retrospective study. Forth, neurologic outcome was evaluated by face to face or telephone assessment depending on the patient's availability to the hospital. Evaluating by telephone may be inaccurate and this could be an assessment bias. Fifth, this study is an exploratory study to see the change of platelet counts according to the neurological outcome rather than predicting neurologic outcome of cardiac arrest patients. We caution against using these findings to determine prognostication after CA. Finally, we could not rule out the influence of other parameters that may affect platelet counts such as infection. We adjusted for multiple confounders, but there may still be residual confounding factors that were missed.

In conclusion, changes in platelet counts have a biphasic pattern that is significantly different between OHCA patients treated with TTM with good and poor outcomes. Low platelet counts 7 days after CA were associated with poor neurologic outcomes and mortality at 6 months.

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None.

Conflict of interest

None of the authors has declared a conflict of interest.

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