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# Thrombotic Microangiopathy Score as a New Predictor of Neurologic Outcomes in Patients after Out-of-Hospital Cardiac Arrest

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**Purpose:** Given the morphological characteristics of schistocytes, thrombotic microangiopathy (TMA) score can be beneficial as it can be automatically and accurately measured. This study aimed to investigate whether serial TMA scores until 48 h post admission are associated with clinical outcomes in patients undergoing targeted temperature management (TTM) after out-of-hospital cardiac arrest (OHCA).

**Materials and Methods:** We retrospectively evaluated a cohort of 185 patients using a prospective registry. We analyzed TMA scores at admission and after 12, 24, and 48 hours. The primary outcome measures were poor neurological outcome at discharge and 30-day mortality.

**Results:** Increased TMA scores at all measured time points were independent predictors of poor neurological outcomes and 30-day mortality, with TMA score at time-12 showing the strongest correlation [odds ratio (OR), 3.008; 95% confidence interval (CI), 1.707–5.300; $p<0.001$ and hazard ratio (HR), 1.517; 95% CI, 1.196–1.925; $p<0.001$]. Specifically, a TMA score ≥2 at time-12 was closely associated with an increased predictability of poor neurological outcomes (OR, 6.302; 95% CI, 2.841–13.976; $p<0.001$) and 30-day mortality (HR, 2.656; 95% CI, 1.675–4.211; $p<0.001$).

**Conclusion:** Increased TMA scores predicted neurological outcomes and 30-day mortality in patients undergoing TTM after OHCA. In addition to the benefit of being serially measured using an automated hematology analyzer, TMA score may be a helpful tool for rapid risk stratification and identification of the need for intensive care in patients with return of spontaneous circulation after OHCA.

**Key Words:** Out-of-hospital cardiac arrest, targeted temperature management, thrombotic microangiopathy, mortality, predictor

## INTRODUCTION

Despite advances in post-resuscitative care, a significant proportion of patients after out-of-hospital cardiac arrest (OHCA) experience poor neurological outcomes and face a high risk of mortality.[1,2] Regardless of causes, cardiac arrest (CA) and resuscitation lead to severe damage in multiple organs because of associated hypoxemia, ischemia, and reperfusion,[3] with the severity thereof varying between patients. Accordingly, effective post–CA care requires identification and mitigation of the precipitating cause of CA and ischemia-reperfusion injury to multiple organ systems.[1] Recent guidelines have recommended targeted temperature management (TTM) for neuroprotective intervention in resuscitation care of CA.[1] In the pathophysiology of multiorgan injury after CA, cardiovascular ischemia/reperfusion injury and cardiovascular toxicity are significantly

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associated with excessive levels of inflammatory cytokine activation and catecholamines, among other contributing factors.[4] Systemic ischemia/reperfusion injury after return of spontaneous circulation (ROSC) leads to the release of inflammatory cytokines and the development of systemic inflammatory response syndrome that mimics sepsis without infection.[4]

The application of new biomarkers that simply and accurately predict the development of poor neurological outcomes and mortality after post-resuscitation may improve the prognosis of patients by enabling innovative monitoring, early aggressive treatment, and therapeutic strategies.[5,6] Thrombotic microangiopathy (TMA) is characterized by three important elements including higher levels of lactate dehydrogenase, thrombocytopenia, and fragmented erythrocytes (schistocytes).[7] Several critical conditions lead to the development of systemic endothelial injury in critically ill patients.[8,9] In endothelial injury, severe hemolysis from mechanical damage in circulation occasionally produces schistocytes in turbulent areas of the microcirculation that are partly occluded by platelet aggregations.[8,10] The occurrence of schistocytes in blood reflects a high risk of thrombocytopenia-associated multiple organ failure (TAMOF).[11] Schistocytes indicate specific characteristics of increased red cell distribution width (RDW), hemoglobin distribution width (HDW), and microcytic hyperchromic red blood cells (RBCs).[9,11] Based on the development of and changes in the morphological characteristics of schistocytes, TMA score was developed as a rapid, simple marker of TAMOF in critically ill patients.[9] An automated complete blood cell analyzer can automatically determine TMA score based on RBC parameters and the volume/hemoglobin concentration (V/HC).[9,11]

We previously found that increased TMA scores significantly predicted short-term mortality in patients with severe sepsis and septic shock.[9,12] To the best of our knowledge, no studies have reported that the new TMA score can predict the clinical outcomes of patients with OHCA. As such, we aimed to investigate whether serial TMA scores over time are significantly associated with neurological outcomes at hospital discharge and 30-day mortality in patients undergoing TTM after OHCA. We hypothesized that the TMA score could be used to predict the severity of organ damage in TTM patients who achieved sustained ROSC after OHCA.

## MATERIALS AND METHODS

### Study design and population

This retrospective, observational cohort study was performed between July 2015 and May 2019 based on a prospective registry of the emergency department (ED) of Yonsei University College of Medicine affiliated with Severance Hospital, which is a tertiary-level referral hospital with a population of average 100000 patients per year. The study was approved by the Institutional Review Board (IRB) of Yonsei University Health System (3-2019-0308). Because of the retrospective nature of the study, the need for informed consent was waived by the IRB of Yonsei University Health System.

We included consecutive patients who were prospectively integrated into the Critical leaders, Optimal care Of Life (COOL) threatening post cardiopulmonary resuscitation (CPR) protocol as a critical pathway (CP) program. However, we retrospectively conducted data analysis based on OHCA records from the prospective registry of the ED COOL CP. Considering the theoretical characteristics of TMA score, we excluded patients who received a transplant or prosthetic valves and those undergoing chemotherapy within 14 days from this study. To validate the usefulness of TMA scores over time, we also excluded patients who were transferred to our ED from another hospital, those who transferred out to another hospital within the first 72 h, and those who died within 24 hours. Fig. 1 summarizes the patient inclusion process.

### COOL protocol

Since September 2011, we have implemented the COOL CP in our institution as part of a quality improvement initiative to provide proper and professional treatment of TTM with bundle management to patients who had achieved sustained ROSC after OHCA. In the ED, emergency physicians screened candidates for the COOL CP program as soon as feasible. According to a predetermined protocol based on the advanced cardiac life support guidelines published by the American Heart Association,[3] a multidisciplinary treatment group involving a cardiologist, intensivist, neurologist, and emergency physicians immediately identifies patient status and simultaneously provides intensive and critical care. We provided post-CA care to

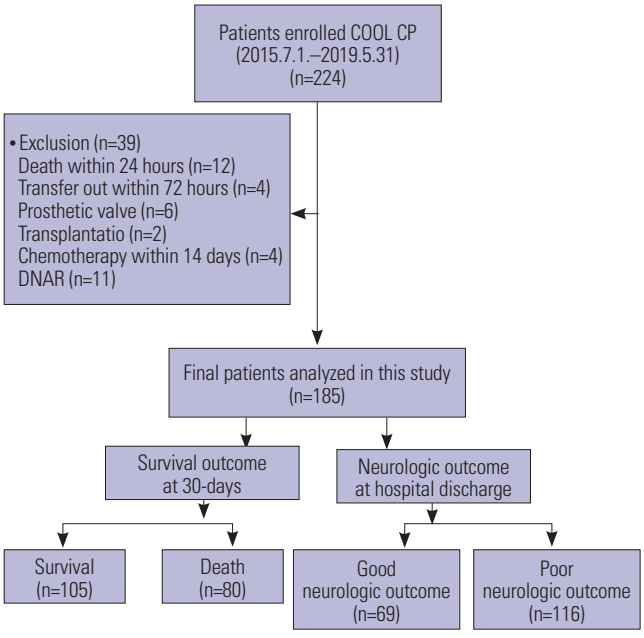


**Fig. 1.** Flow diagram of patient inclusion. DNAR, do-not-attempt-resuscitation; COOL, Critical leaders, Optimal care Of Life; CP, critical pathway.


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patients who achieved sustained ROSC after OHCA following a standardized protocol within at least 72 hours after CP activation. The COOL CP program is available 24 hours a day, 7 days a week. According to this protocol, we actively applied TTM with a target core body temperature of 32°C–36°C for all adult non-traumatic survivors who were unable to obey commands. We strictly controlled blood pressure, glucose, electrolyte, ventilator minute volume, and fluid balance and performed essential emergency procedures. Patients were deemed ineligible for the CP based on the following criteria: age <18 years, pregnancy, trauma, intracranial hemorrhage, active gastrointestinal bleeding, terminal illness, do-not-resuscitate status, and pre-existing coma prior to CA.

### Data collection

Basic characteristics, including age, sex, body mass index, and comorbidities, including hypertension, diabetes mellitus, malignancy, and cerebrovascular, pulmonary, and prior arrhythmia, cardiac disease, such as coronary artery disease, or cardiomyopathy, were investigated. Data on CA characteristics including first monitored rhythm, presence of a witness on collapse, etiology of arrest (cardiac or non-cardiac origin), low-flow time (defined as the time with active CPR by a bystander and/or a medical provider), no-flow time (defined as time between the CA and initiation of CPR), and bystander CPR were also collected. The first available laboratory data for hematologic (white blood cell count) and chemistry (total bilirubin, lactate, total $CO_2$, and glucose) parameters were also collected in patients who achieved sustained ROSC after OHCA.

### Assessment of TMA score

TMA score ranges from 0 to 5 points, with 1 point given for each of the following: 1) RDW >15%, 2) HDW >3.2%, 3) percentage of microcytes ≥0.4% (percentage of microcytes indicates the percentage of RBCs smaller than 60 fL), 4) percentage of hyperchromic red cells ≥1.9% (percentage of hyperchromic red cells indicates the percentage of RBCs with more than 41 g/dL of hemoglobin), and 5) platelet count $<140\times10^9$/L.[9,11] All RBC parameters as well as the TMA score were measured using an automated blood cell analyzer (ADVIA 120; Siemens, Forchheim, Germany) and reported in the electronic health records. The percentages of microcytes and hyperchromic red cells were calculated using the V/HC cytogram.[11] We analyzed the TMA scores from the time of ED admission to 48 hours. Venous blood was collected in ethylenediaminetetraacetic-containing vacutainers on ED admission (time-0) and 12 hours (time-12), 24 hours (time-24), and 48 hours (time-48) after admission.

### Statistical analysis

The primary outcome measure was poor neurological outcome at hospital discharge, which was evaluated according to the cerebral performance category (CPC) scale.[13] The CPC scale score ranges from 1 to 5 points, with 1–2 defined as a good outcome and 3–5 as a poor outcome. The secondary outcome measure was 30-day all-cause mortality. CPC score was determined by an investigator blinded to the study hypothesis through a review of the medical records. Clinicodemographic data are presented as medians and interquartile ranges (IQRs), means and standard deviations, percentages, or frequencies, as appropriate. Continuous variables were compared using the two-sample t-test or Mann-Whitney U-test, and categorical variables were compared using the $\chi^2$ test or Fisher's exact test. To identify the significance of differences between groups over time, we conducted a linear two-factor mixed model using a repeated-measures covariance pattern and unstructured covariance within patients. We identified two fixed effects for this model: a time effect (TMA from time-0 to time-48) and a diagnostic effect for the clinical endpoint (good and poor neurological outcome; survival and non-survival after 30 days). We performed univariable analyses to identify significant associations between the clinicodemographic data and study outcomes. To identify independent predictors of 30-day mortality and neurological outcome during TTM after OHCA, variables with $p<0.05$ in univariable analysis were entered into multivariable logistic regression analysis and multivariable Cox regression analysis, respectively.

The predictive performance of TMA score was evaluated according to receiver-operating characteristic (ROC) curves and area under the curve (AUC). The optimal cutoff of TMA score to discriminate between good and poor neurological outcome was determined used Youden's method. The results are presented as odds ratios (ORs) and 95% confidential intervals (CIs). 30-day survival was plotted using Kaplan-Meier curves and compared using log-rank test. Unlike previous studies that estimated cut-off values based only on events, we estimated these values using the technique devised by Contal and O'Quigley to determine the optimal cut-off values for the dichotomization of the clinical outcome variable for 30-day mortality based on time-to-event data.[13] The optimal cut-off points were selected by maximizing HR. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA) and MedCalc Statistical Software version 16.4.3 (MedCalc Software bvba, Ostend, Belgium). $p<0.05$ was considered significant.

## RESULTS

### Study population, clinical evaluation, and treatment

A total of 224 adult CA patients who achieved ROSC was registered with the COOL CP program during the study period. Of them, 39 patients were excluded, leaving 185 patients in the final analysis (Fig. 1). In total, 69 and 116 patients belonged to good outcome and poor outcome groups, respectively. The incidence of all-cause 30-day mortality was 43.2%, and that of poor outcomes was 62.7%. Table 1 shows the patients' clinical

characteristics stratified by neurological outcomes and mortality. The mean age of the overall population was 60.1±16.4 years, and 131 (70.8%) of them were male. Among the patients who achieved ROSC after OHCA, nonsurvivors were older than survivors. Patients with poor neurological outcomes were also older than those with good outcomes. The incidence of diabetes was higher in patients with poor neurological outcomes and in the non-survivors. They were also more likely to have a non-shockable rhythm, a non-cardiac etiology, a longer no-flow time, and a longer low-flow time. Table 1 also shows the distributions of

**Table 1.** Clinical Characteristics of the Patients Stratified by 30-Day Mortality and Neurological Outcome

| Variables | Total n=185 | 30-day mortality | | | Neurological outcome | | |
|---|---|---|---|---|---|---|---|
| | | Survival n=105 (56.8%) | Death n=80 (43.2%) | *p* value | Good n=69 (37.3%) | Poor n=116 (62.7%) | *p* value |
| Age (yr) | 60.05±16.43 | 56.25±16.50 | 65.05±15.04 | <0.001* | 54.36±15.42 | 63.44±16.14 | <0.001* |
| Male sex | 131 (70.81) | 80 (76.19) | 51 (63.75) | 0.065 | 96 (73.28) | 35 (26.71) | 0.422 |
| BMI (kg/m$^2$) | 22.74±4.00 | 22.37±3.86 | 23.27±4.16 | 0.137 | 22.86±3.77 | 22.67±4.15 | 0.752 |
| Medical history | | | | | | | |
| Hypertension | 72 (38.92) | 38 (36.19) | 34 (42.50) | 0.383 | 21 (30.43) | 51 (43.97) | 0.068 |
| Diabetes mellitus | 47 (25.41) | 19 (18.10) | 28 (35.00) | 0.009* | 9 (13.04) | 38 (32.76) | 0.003* |
| Chronic pulmonary disease | 12 (6.49) | 4 (3.81) | 8 (10.00) | 0.090 | 1 (1.45) | 11 (9.48) | 0.034* |
| Cardiovascular disease | 42 (22.70) | 27 (25.71) | 15 (18.75) | 0.263 | 18 (26.09) | 24 (20.69) | 0.397 |
| Arrhythmia | 13 (7.03) | 8 (7.62) | 5 (6.25) | 0.718 | 5 (7.25) | 8 (6.90) | 0.999 |
| Cerebrovascular disease | 11 (5.95) | 5 (4.76) | 6 (7.50) | 0.535 | 2 (2.90) | 9 (7.76) | 0.215 |
| Malignancy | 16 (8.65) | 9 (8.57) | 7 (8.75) | 0.966 | 6 (8.70) | 10 (8.62) | 0.986 |
| Cardiac arrest characteristics | | | | | | | |
| Witnessed collapse | | | | 0.004* | | | 0.064 |
| No | 75 (40.54) | 33 (31.43) | 42 (52.50) | | 22 (31.88) | 53 (45.69) | |
| Yes | 110 (59.46) | 72 (68.57) | 38 (47.50) | | 47 (68.12) | 63 (54.31) | |
| Bystander CPR | | | | 0.017* | | | 0.103 |
| No | 59 (31.89) | 26 (24.76) | 33 (41.25) | | 17 (24.64) | 42 (36.21) | |
| Yes | 126 (68.11) | 79 (75.24) | 47 (58.75) | | 52 (75.36) | 74 (63.79) | |
| First monitored rhythm | | | | <0.001* | | | <0.001* |
| Non-shockable | 109 (58.92) | 43 (40.95) | 66 (82.50) | | 18 (26.09) | 91 (78.45) | |
| Shockable | 76 (41.08) | 62 (59.05) | 14 (17.50) | | 51 (73.91) | 25 (21.55) | |
| Etiology of arrest | | | | <0.001* | | | <0.001* |
| Non-cardiac | 66 (35.68) | 25 (23.81) | 41 (51.25) | | 7 (10.14) | 59 (50.86) | |
| Cardiac | 119 (64.32) | 80 (76.19) | 39 (48.75) | | 62 (89.86) | 57 (49.14) | |
| No-flow time (min) | 2.10±4.44 | 1.40±3.20 | 3.01±5.56 | 0.022* | 1.22±2.78 | 2.62±5.12 | 0.017* |
| Low-flow time (min) | 24.73±15.73 | 20.09±12.99 | 30.83±16.95 | <0.001* | 16.62±11.49 | 29.55±15.96 | <0.001* |
| Targeted temperature | | | | | | | |
| TTM at 33°C | 85 (45.95) | 28 (26.7) | 57 (71.3) | <0.001* | 9 (13.0) | 76 (65.5) | <0.001* |
| TTM at 36°C | 100 (54.05) | 77 (73.3) | 23 (28.8) | <0.001* | 60 (87.0) | 40 (34.5) | <0.001* |
| Laboratory data after ROSC | | | | | | | |
| White blood cell count (10$^3$ μL) | 12.66±5.79 | 12.71±5.37 | 12.59±6.32 | 0.897 | 13.62±5.48 | 12.09±5.91 | 0.081 |
| Total bilirubin (mg/dL) | 0.59±0.50 | 0.56±0.38 | 0.64±0.63 | 0.316 | 0.55±0.29 | 0.62±0.59 | 0.275 |
| Lactate (mmol/L) | 10.56±4.45 | 9.20±4.33 | 12.39±3.96 | <0.001* | 8.65±4.18 | 11.72±4.22 | <0.001* |
| $tCO_2$ (mmol/L) | 17.48±5.32 | 17.22±4.81 | 17.81±5.95 | 0.469 | 16.28±4.49 | 18.19±5.66 | 0.013* |
| Glucose (mg/dL) | 279.8±120.2 | 259.3±104.3 | 306.7±134.3 | 0.010* | 260.7±99.1 | 291.2±130.2 | 0.075 |
| TMA score time-0 (point) | 0.72±0.89 | 0.55±0.82 | 0.95±0.94 | 0.003* | 0.39±0.62 | 0.92±0.97 | <0.001* |
| TMA score time-12 (point) | 1.13±1.09 | 0.85±0.93 | 1.53±1.17 | <0.001* | 0.64±0.79 | 1.45±1.14 | <0.001* |
| TMA score time-24 (point) | 1.34±1.25 | 1.08±1.17 | 1.78±1.26 | <0.001* | 0.86±0.96 | 1.69±1.32 | <0.001* |
| TMA score time-48 (point) | 1.48±1.23 | 1.17±1.06 | 2.07±1.32 | <0.001* | 0.96±0.96 | 1.90±1.27 | <0.001* |

BMI, body mass index; CPR, cardiopulmonary resuscitation; TTM, targeted temperature management; ROSC, return of spontaneous circulation; $tCO_2$, total carbon dioxide; TMA, thrombotic microangiopathy.
Data are presented as mean±standard deviation or n (%).
*$p$<0.05.


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the first available laboratory results after ROSC. Patients who died within 30 days or those with poor neurological outcomes had significantly higher TMA scores than those who did not. As shown in Fig. 2, there were significant differences between groups in the TMA scores according to the 30-day mortality (group, $p$<0.001; time, $p$<0.001; and group×time, $p$=0.139) and neurological outcome after ED admission (group, $p$<0.001; time, $p$<0.001; and group×time, $p$=0.241) (Fig. 2A and B).

### TMA score as a predictor of poor neurological outcomes for patients undergoing TTM after OHCA

In univariable analysis, TMA scores at several time points revealed significant differences in neurological outcomes of patients undergoing TTM after OHCA (Supplementary Table 1, only online). In further multivariable logistic regression analyses, elevated TMA score was identified as an independent predictor of poor neurological outcomes at time-0 (OR, 2.270; 95% CI, 1.242–4.151; $p$=0.008), time-12 (OR, 3.008; 95% CI, 1.707–5.300; $p$<0.001), and time-24 (OR, 1.797; 95% CI, 1.178–2.740; $p$=0.007) (Table 2). The AUC for TMA score on ED admission for predicting poor neurological outcome was 0.654 ($p$<0.001) (Fig. 2C). ROC curve analysis of the prediction of poor neurological outcomes indicated that the highest AUC for TMA score was 0.704 (95% CI, 0.632–0.777; $p$<0.001) at time-12 (Fig. 2D). Accordingly, the optimal cut-off value of TMA score at time-12 was 2 [sensitivity, 0.486 (95% CI, 0.388–0.585); specificity: 0.870 (95% CI, 0.767–0.939)] (Fig. 2D). A TMA score ≥2 at time-12 was significantly associated with increased predictability of poor neurological outcome (OR, 6.302; 95% CI: 2.841–13.976; $p$<0.001) (Fig. 2D). The sensitivity and specificity of the TMA

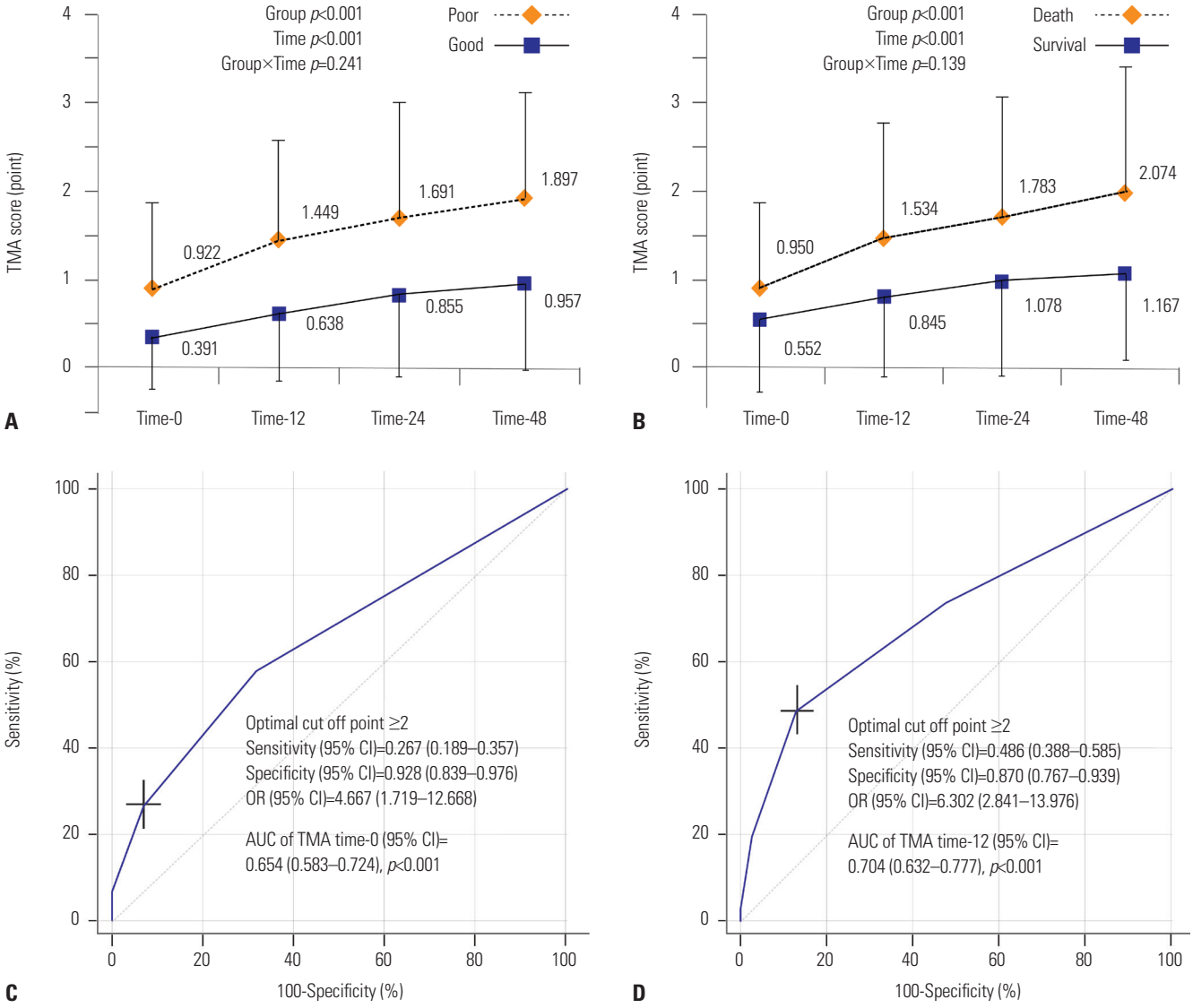


**Fig. 2.** Linear mixed model of TMA score to estimate significant differences between groups over time according to neurologic outcome (A) and 30-day mortality (B). Receiver operating characteristic curves for predictive capability of TMA scores at admission (C) and 12 h after admission (D) according to unfavorable neurologic outcomes. TMA, thrombotic microangiopathy; AUC, area under the curve; OR, odds ratio; CI, confidence interval.

**Table 2.** Multivariable Logistic Regression Analysis for Predictors of Poor Neurological Outcome (A) and Adjusted Association between Poor Neurological Outcome and TMA Score by Time (B)

**(A)**

| Variable | Adjusted OR (95% CI) | *p* value |
|---|---|---|
| Age | 1.025 (0.994–1.057) | 0.111 |
| Witnessed collapse | 0.570 (0.196–1.654) | 0.301 |
| Bystander CPR | 1.048 (0.250–4.397) | 0.949 |
| Initial shockable rhythm | 0.329 (0.124–0.877) | 0.026* |
| No-flow time | 1.026 (0.880–1.197) | 0.742 |
| Low-flow time | 1.074 (1.034–1.115) | <0.001* |
| Etiology of arrest | | |
| Non-cardiac origin | Reference | |
| Cardiac origin | 0.243 (0.074–0.794) | 0.019* |
| History of diabetes | 2.167 (0.678–6.930) | 0.192 |
| Arterial $tCO_2$ | 1.111 (0.997–1.237) | 0.056 |
| Arterial lactate | 1.135 (1.014–1.271) | 0.027* |
| TMA score time-0 | 2.270 (1.242–4.151) | 0.008* |

**(B)**

| Variable | Adjusted† OR (95% CI) | *p* value |
|---|---|---|
| TMA score time-0 | 2.270 (1.242–4.151) | 0.008* |
| TMA score time-12 | 3.008 (1.707–5.300) | <0.001* |
| TMA score time-24 | 1.797 (1.178–2.740) | 0.007* |
| TMA score time-48 | 1.889 (1.213–2.941) | 0.005* |

OR, odds ratio; CI, confidence interval; CPR, cardiopulmonary resuscitation; $tCO_2$, total carbon dioxide; TMA, thrombotic microangiopathy.
*$p$<0.05; †Adjusted for: Age, Witnessed collapse, Bystander CPR, Initial shockable rhythm, No-flow time, Low-flow time, Etiology of arrest, History of diabetes, Arterial $tCO_2$, Arterial lactate.

**Table 3.** Multivariable Cox Proportional Hazard Regression Analysis for Predictors of 30-Day Mortality and Adjusted Association between 30-Day Mortality and TMA Score by Time (B)

**(A)**

| Variable | Adjusted HR (95% CI) | *p* value |
|---|---|---|
| Age | 1.029 (1.011–1.047) | 0.001* |
| Witnessed collapse | 0.575 (0.341–0.971) | 0.038* |
| Bystander CPR | 0.827 (0.391–1.747) | 0.618 |
| Initial shockable rhythm | 0.554 (0.281–1.090) | 0.087 |
| No-flow time | 1.016 (0.946–1.091) | 0.668 |
| Low-flow time | 1.023 (1.008–1.039) | 0.003* |
| Etiology of arrest | | |
| Non-cardiac origin | Reference | |
| Cardiac origin | 0.853 (0.498–1.461) | 0.563 |
| History of diabetes | 1.314 (0.751–2.300) | 0.339 |
| Arterial lactate | 1.128 (1.054–1.208) | <0.001* |
| TMA score time-0 | 1.334 (1.032–1.724) | 0.028 |

**(B)**

| Variable | Adjusted† HR (95% CI) | *p* value |
|---|---|---|
| TMA score time-0 | 1.334 (1.032–1.724) | 0.028* |
| TMA score time-12 | 1.517 (1.196–1.925) | <0.001* |
| TMA score time-24 | 1.251 (1.004–1.565) | 0.048* |
| TMA score time-48 | 1.452 (1.114–1.892) | 0.006* |

HR, hazard ratio; CI, confidence interval; CPR, cardiopulmonary resuscitation; TMA, thrombotic microangiopathy.
*$p$<0.05; †Adjusted for: Age, Witnessed collapse, Bystander CPR, Initial shockable rhythm, No flow time, Low flow time, Etiology of arrest, History of diabetes, Arterial lactate.

score ≥2 for predicting unfavorable neurological outcome were 26.7% and 92.8% at time-0 and 48.6% and 87.0% at time- 24, respectively (Supplementary Table 2, only online).

### TMA score as a predictor of 30-day mortality for patients undergoing TTM after OHCA

Univariable analysis also showed significant differences in TMA scores at different time points between survivors and non-survivors within 30-days (Supplementary Table 3, only online). Further multivariable Cox regression analyses demonstrated that increased TMA score at time-0 [hazard ratio (HR), 1.334; 95% CI, 1.032–1.724; $p$=0.028], time-12 (HR, 1.517; 95% CI, 1.196–1.925; $p$<0.001), and time-24 (HR, 1.251; 95% CI, 1.004–1.565; $p$=0.048) were independent predictors of 30-day mortality (Table 3). The optimal cut-off value of the TMA score at time-12 was 2. Considering time to event, TMA ≥2 at time-12 was significantly associated with increased 30-day mortality (Fig. 3). TMA score ≥2 at time-12 was associated with increased predictability of 30-day mortality in patients undergoing TTM after OHCA (HR, 2.656; 95% CI, 1.675–4.211; $p$<0.001) (Fig. 3).

## DISCUSSION

The current study demonstrated that higher TMA scores are associated with mortality after 30 days and poor neurological outcomes in patients undergoing TTM after OHCA. Increased TMA score was an independent predictor of 30-day mortality and poor neurological outcomes. Multivariate logistic regression analysis revealed that initial shockable rhythm, arrest of cardiac etiology, concentration of lactate, time from start of CPR to ROSC, and TMA score were independently associated with neurological outcomes. In multivariable Cox proportional hazard regression analysis, independent risks for 30-day mortality included older age, non-witnessed collapse, longer duration from start of CPR to ROSC, higher lactate level, and TMA score. TMA scores at all measured time points showed the highest odds ratios for poor neurological outcomes in multivariable analysis. This was consistent with a previous study of severe sepsis and septic shock in which sepsis patients who died 30 days after ED admission had significantly higher TMA scores than those who survived, with increased TMA scores being significant predictors of 30-day mortality.[9]

It is difficult to completely understand the exact pathophysiologic processes underlying the clinical relationship between TMA score and poor outcomes after OHCA. However, several


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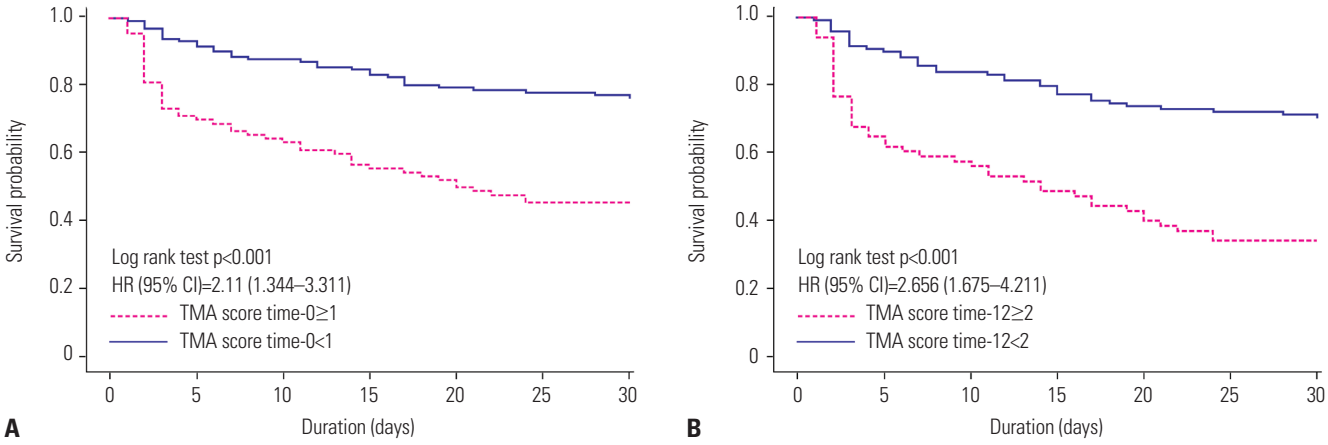


**Fig. 3.** TMA score as a predictor of 30-day mortality. Higher TMA scores at admission (A) and 12 h after admission (B) were significantly associated with an increased risk of 30-day mortality among patients with ROSC undergoing TTM after OHCA. HR, hazard ratio; CI, confidence interval; TMA, thrombotic microangiopathy; ROSC, return of spontaneous circulation; TTM, temperature management, OHCA, out-of-hospital cardiac arrest.

hypotheses could be proposed in this study. First, whole-body ischemia/reperfusion induced by endothelial injury contributes to thrombotic occlusion of the vessels following activation of coagulation and impairment of fibrinolysis.[14,15] With respect to erythrocytes, the hemorheological state after ischemia and reperfusion may negatively impact the deformability and aggregation behavior of RBCs through several complex processes, including acute phase reactions, free radical and inflammatory response, hemodynamic deteriorations, and coagulopathy.[16] Several studies have demonstrated that aggregation, deformability, and the shape of RBC are altered in critical illness and different diseases.[17] Yu, et al.[18] assessed the rheological properties of RBCs after ischemic/reperfusion and reported that stiffer erythrocytes resulting from reduced deformability help increase vascular resistance by limiting movement to small tissue capillaries. This eventually leads to no-reflow phenomenon from cells trapped in capillaries. Poor neurological outcomes can be attributed to cerebral microvascular occlusion that causes the no-reflow phenomenon.[19]

Second, post-CA syndrome (PCAS) can be a contributing factor to the high mortality rate and severe brain damage of patients who achieve ROSC after CA.[3,20] In patients who achieve ROSC after CA, PCAS mimics immunologic and coagulation disorders in severe sepsis.[21] Given that PCAS has similar clinical characteristics to severe sepsis with respect to systemic and sterile inflammation, increases in the number and changes in the characteristics of schistocytes may also be similar to severe sepsis and septic shock.[21,22]

Ko, et al.[9] reported that the optimal cutoff values of TMA scores at time-0 and time-24 were 2 and 3 in patients with sepsis and that TMA scores ≥2 at time-0 and ≥3 at time-24 increased the predictability of 30-day mortality. Similarly, in the present study, a TMA score ≥2 at time-12 was closely associated with the increased predictability of 30-day mortality and a poor neurological outcome in patients undergoing TTM after OHCA. Moreover, results from the linear mixed model indicated a significant difference in increases in TMA values over time between good and poor outcomes.

The International Council for Standardization in Hematology (ICSH) guideline states that presence of >1% schistocytes without other moderate changes in RBCs upon a peripheral blood smear can be considered as a critical criterion for the diagnosis of TMA.[7] During the early stage of TTM after OHCA, TMA score can be valuable because it can indicate changes in the morphological characteristics of schistocytes. rather than the absolute schistocyte counts.[23] Our findings support that TMA score can improve the predictability of prognosis and risk stratification of patients undergoing TTM after OHCA. Importantly, we found that increased TMA score is a reliable predictor of clinical outcomes in patients undergoing TTM after OHCA. Further prospective, multicenter trials are required to validate the prognostic value of cell deformability in RBCs in 12 h and 24 h after admission in patients with PCAS undergoing TTM after OHCA.

The current study has several limitations. First, the possibility of selection bias cannot be eliminated. Although we used a prospective CP with a predetermined standardized protocol, we retrospectively analyzed this using a cohort derived from the CP of a single center. Second, we could not directly compare TMA scores from an automated hematology analyzer and schistocyte counts determined manually through a microscope. As we stated in our previous study, TMA score was created based on significant changes in the morphological characteristics of schistocytes and is determined automatically. Third, in multivariable regression analysis adjusting for covariates, TMA value was significantly associated with the neurological and survival outcomes in OHCA patients, independent of low flow time, which indicates the duration of chest compression. Due to the retrospective nature of this study, the probability that TMA elevation was caused by mechanical trauma due to chest compression could not be excluded. To clarify the usefulness of TMA score in ischemic-reperfusion injury, further study is required

to validate the relationship between the elevation of TMA and chest trauma by compression in patients undergoing TTM after OHCA. Fourth, despite the prospective registry of the CP, we were only able to investigate neurological outcomes at the time of hospital discharge because this CP did not include the exact neurological status of patients after discharge. However, the outcomes reported in our study may represent the natural course of OHCA patients treated with TTM in hospitals because withdrawing life-sustaining therapy based on prognostication was not applied to these patients. Finally, the present study evaluated the usefulness of TMA score for predicting the severity of organ failure in patients undergoing TTM after OHCA. ADAMTS-13 (the thirteenth member of a disintegrin-like and metalloprotease with thrombospondin type 1 motif family) activity, which is known as von Willebrand factor-cleaving protease, is a critical factor in the pathophysiology of the classic form of TMA. Without the cleaving function of ADAMTS-13, unfolded von Willebrand factor monomers can form large multimers that lead to the formation of intravascular microthrombi. ADAMTS-13 has an explicit relationship with the occurrence of platelet aggregation, microthrombi formation in the circulation, endothelial cell injury, and TMA.[24] Despite the importance of ADAMTS-13 in TMA, ADAMTS-13 is a laboratory test with a high cost, and it is difficult to perform routine tests in suspected patients in clinical practice. We could not investigate the association between ADAMTS-13 activity and TMA score. Further prospective multicenter trials are required to validate the explicit relationship and to validate the usefulness of TMA scores as a prognostic factor in patients undergoing TTM after OHCA.

Increased TMA scores predicted neurological outcome and 30-day mortality in patients undergoing TTM after OHCA. In addition to the benefit of being quickly and serially measured using an automated hematology analyzer without additional effort or costs, TMA score may be a helpful tool for rapid risk stratification and identification of the need for intensive care in patients with ROSC after OHCA.

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