European Review for Medical and Pharmacological Sciences 2024; 28: 3430-3438

Evaluation of the factors affecting mortality after cardiac arrest – do lactate and procalcitonin concentrations have any implications?

M. KANDILCIK[1], M. ARSLAN[2], H. ÖKSÜZ[2], G. GIŞI[2], C. YAVUZ[2], G. ÖKSÜZ[2], A. DOĞANER[3]

[1]Department of Anesthesiology and Reanimation, Pazarcık State Hospital, Kahramanmaraş, Türkiye
[2]Department of Anesthesiology and Reanimation, Faculty of Medicine, Kahramanmaraş Sütçü Imam University, Kahramanmaraş, Türkiye
[3]Department of Biostatistics and Medical Informatics, Faculty of Medicine, Kahramanmaraş Sütçü Imam University, Kahramanmaraş, Türkiye

Abstract. – OBJECTIVE: Mortality and morbidity rates are very high in patients admitted to the Intensive Care Unit (ICU) after cardiac arrest. In this study, we aimed to determine the mortality rates, risk factors, and predictive factors for mortality in post-cardiac arrest patients admitted to the ICU.

PATIENTS AND METHODS: Following approval from the Ethics Committee, we conducted a retrospective review of patient files for individuals over the age of 18 who received treatment for cardiac arrest in the ICU from January 2017 to June 2020. Demographic data of the patients, comorbidities, arrest location, etiology of arrest, duration of hospitalization, CPR duration, APACHE 2 scores, pH and HCO_3 measurements in initial blood gases, lactate levels (1st, 6th, 12th, 24th hour), change in lactate levels (24-1), rate of lactate change, procalcitonin (PRC) levels (1st and 24th hour), change in PRC levels (24-1), rate of PRC change, and blood glucose levels were recorded. The patients were divided into two groups (survivors and non-survivors groups).

RESULTS: 151 patients were included in the study. pH and HCO_3 levels were lower in the non-survivors group than in the survivors group. Initial PRC levels were similar in both groups, but the 24th-hour PRC levels were higher, and the changes in PRC levels in the first 24 hours were greater in the non-survivors group. The lactate changes in the first 24 hours were higher in the non-survivors group. The receiver operating characteristic (ROC) curve showed that the HCO_3 levels, 1st-, 6th-, 12th-, and 24th-hour lactate levels, and changes in lactate levels had predictability for mortality. In logistic regression analysis, we found that high 24th-hour lactate levels and changes in lactate levels were independent risk factors for mortality.

CONCLUSIONS: Considering PRC and lactate levels, along with clinical examination and laboratory findings, may improve the accuracy of determining the prognosis of patients experiencing cardiac arrest.

Key Words:
Cardiac arrest, Procalcitonin, Lactate, Prognosis.

Introduction

Cardiac arrest (CA) is a condition in which a person's circulation stops for any reason. The triad of symptoms in a CA patient includes unconsciousness, absence of breathing, and lack of a pulse[1,2]. ICPR should be performed as soon as possible to prevent death. Immediate cardiopulmonary resuscitation (CPR) is necessary to restore the patient's circulation and oxygenation. The most common causes of CA are cardiac diseases[3].

After successful CPR, patients are followed up in the intensive care unit with the diagnosis of post-cardiac arrest syndrome[4]. Oxygenation, ventilation, and target temperature management are important in post-cardiac arrest care. Titration of oxygen levels (PaO_2=69-195 mmHg) should be used cautiously, as hypoxemia and hyperoxemia are known to be associated with high mortality in these patients[5]. Implementation of protective mechanical ventilation strategies and regulation of ventilator settings, especially drive pressure and respiratory rate, are associated with improved patient outcomes[6]. Because moderate or deep hypothermia in targeted temperature management has been found to increase the risk of arrhythmias in patients and may be more harmful than normo-

Corresponding Author: Mehmet Kandilcik, MD; e-mail: dr.mehmetkandilcik@gmail.com; mehmet.kandilcik@saglik.gov.tr

thermia, caution should be exercised in its routine use[7,8].

Technological and scientific developments play an important role in improving the success of CPR. Guidelines for CPR, including information on resuscitation, are updated at different intervals by the European Resuscitation Council[9] (ERC) and the American Heart Association[10] (AHA).

Cardiac arrest is a condition with high mortality. Efforts are being made worldwide to reduce mortality and morbidity through studies, training, and guidelines on post-cardiac arrest care. Despite all these efforts, even in developed Western countries, survival is 10% in out-of-hospital cardiac arrest, and it is around 15-20% in in-hospital cardiac arrests[11]. While there are studies in the literature that reveal prognostic factors for the outcome of these patients, both the mortality rate and the prognostic factors may differ because each center has different treatment facilities and approaches.

The objective of this study is to analyze the mortality rates and risk factors for mortality, as well as examine prognostic factors of patients who received treatment after experiencing cardiac arrest at a tertiary intensive care unit between January 2017 and June 2020.

Patients and Methods

The Ethics Committee of Kahramanmaraş Sütcü Imam University Health Practice and Research Hospital approved the study on July 22, 2020, with the decision numbered 2020/14 session and board decision numbered 08. The data of patients admitted to Kahramanmaraş Sütçü İmam University Health Practice and Research Hospital Intensive Care Unit with a diagnosis of cardiac arrest between 01.01.2017 and 01.06.2020 were examined retrospectively after receiving ethics committee approval. Patients were divided into two groups: survivors and non-survivors.

The study examined the patients' age, gender, duration of hospitalization, duration of cardiopulmonary resuscitation, location of cardiac arrest, causes of cardiac arrest, comorbidities, APACHE 2 score, and laboratory parameters. The laboratory parameters recorded in the initial blood gas analysis included pH, HCO_3, and lactate levels. Additionally, lactate levels were recorded at the 6th hour, 12th hour, and 24th hour, along with the first and 24th-hour procalcitonin (PRC) levels.

As this was a retrospective study, laboratory parameters were evaluated based on measurements taken within ±1 hour of the specified time periods. In addition to laboratory parameters, we calculated changes in lactate and PRC within the first 24 hours and their ratios. Lactate change was determined by subtracting the initial lactate level from the 24th-hour lactate level. The rate of lactate change was calculated by dividing the 24-hour lactate change level by the initial lactate level. PRC change was determined by subtracting the initial procalcitonin level from the 24th-hour procalcitonin level. The rate of procalcitonin change was calculated by dividing the 24-hour procalcitonin change by the initial procalcitonin level. The most common comorbidities of the patients were recorded: chronic obstructive pulmonary disease, heart disease, diabetes mellitus, chronic renal failure, and cancer.

Inclusion Criteria

- Patients admitted to the intensive care unit after cardiac arrest;
- Patients over 18 years of age;
- Patients who survived more than 24 hours after CA.

Exclusion Criteria

- Patients under 18 years of age;
- Those who died within the first 24 hours of admission to the intensive care unit.

Statistical Analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 21.0 (IBM Corp., Armonk, NY, USA). The suitability of the data for normal distribution was evaluated with the Shapiro-Wilk normality test. Descriptive statistics of continuous variables are mean±standard deviation for those with normal distribution and median (minimum-maximum) in those who do not comply. In categorical variables, they were expressed as numbers and percentages. In pairwise group comparisons of continuous variables, the independent samples *t*-test was used for data that complied with normal distribution (APACHE 2, pH, and HCO_3). For data that did not comply with a normal distribution, the Mann-Whitney U test was used. The Chi-square test was used to compare groups in categorical variables. The significance limit for all statistics was chosen as $p<0.05$.

Multivariable logistic regression analysis was performed to identify independent risk factors for

mortality. ROC analyses were performed to determine the predictive levels of independent variables for mortality.

Results

Between January 2020 and June 2021, a total of 3,450 patients admitted to intensive care were examined based on their admission diagnoses. It was determined that 260 patients were admitted to intensive care due to cardiac arrest. The study excluded 22 patients under the age of 18 and 87 patients who died within the first 24 hours. The study analyzed 151 patients, with 36 in the survivors group and 115 in the non-survivors group.

The median age of all patients included in the study was 69 years. There was no significant difference in age between the survivors and non-survivors groups. There were 80 male patients and 71 female patients. The mortality rate was 80.3% for females and 72.5% for males. No significant difference was observed between the groups in terms of gender. When analyzing the patients in terms of CPR duration, it was found that the median duration of CPR was 10 minutes for the non-survivor group and 6 minutes for the survivor group. There was no difference in CPR duration between the two groups (Table I).

We examined the presence of comorbidities such as chronic obstructive pulmonary disease (COPD), heart disease, diabetes mellitus (DM), chronic renal failure (CRF), and cancer. We found that 87 patients had heart disease, 26 patients had COPD, 44 patients had DM, 11 patients had CRF, and 8 patients had cancer. There was no difference between the groups in terms of the presence of comorbid diseases. The most common etiologies of cardiac arrest (69 patients) were cardiac diseases, and no difference was observed between the groups for cardiac arrest etiology (Table I).

Survivors had higher initial pH and HCO_3 levels compared to non-survivors. Glucose levels were similar in the two groups (Table II).

There were no significant differences in initial PRC levels between the groups. In the non-survivors group, the 24th-hour PRC level and the PRC increase in the first 24 hours were higher. The median 1st-, 6th-, 12th-, and 24th-hour lactate levels were higher in the non-survivors group than in the survivors group. There was no significant difference in the lactate change rate between the groups (Table III). Of the 151 patients in our study, 105 were out-of-hospital cardiac arrest cases, and 46 were in-hospital cardiac arrest cases. 78.1% of out-of-hospital cardiac arrest cases resulted in non-survivors, and 71.7% of in-hospital cardiac arrest cases resulted in non-survivors. There was no significant difference in mortality rates between in-hospital and out-of-hospital cardiac arrest patients.

In the logistic regression analysis, it was determined that high 24th-hour lactate levels and low lactate change rate were independent risk factors for mortality (Table IV).

ROC analysis revealed that PRC change, HCO_3, 6th-hour lactate, 24th-hour lactate, 24th-hour PRC, and lactate change rate had a weak predictive value; initial lactate level and 12th-hour lactate level had medium predictive value (AUC: 0.719 and AUC: 0.704, respectively; Figures 1 and 2).

Discussion

Cardiac arrest is a condition with high mortality. Early return of spontaneous circulation and recovery without sequelae are aimed with cardiopulmonary resuscitation. In recent years, studies, training, and guidelines on post-cardiac arrest care have been implemented to reduce mortality and morbidity.

With the introduction of chest compression in 1960, CPR became the standard practice in cases of cardiac arrest. The appropriateness of re-

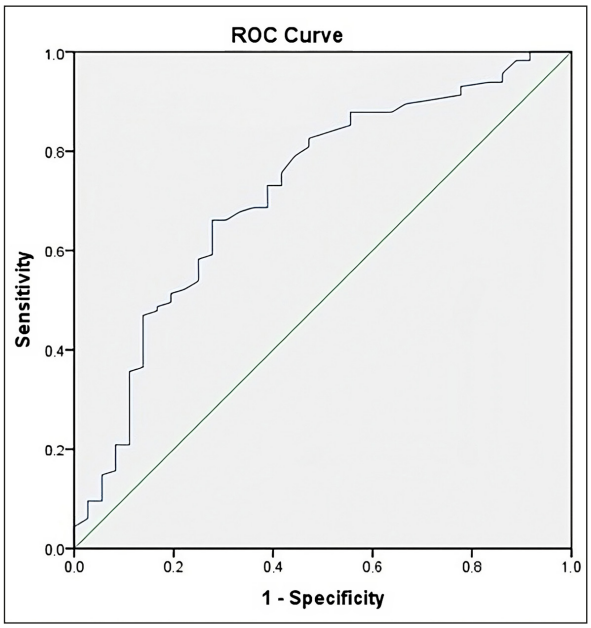

Figure 1. ROC curve of initial lactate level for predicting mortality.

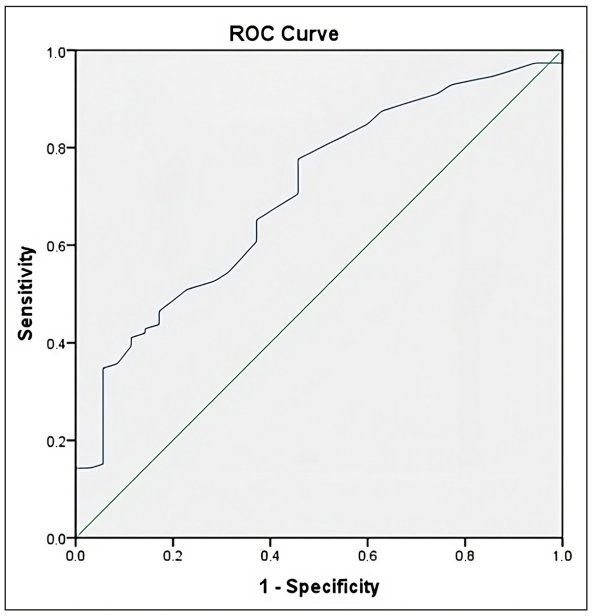

Figure 2. ROC curve of 12th-hour lactate level for predicting mortality.

suscitation as a medical treatment for the aging population has become a matter of ethical debate. Post-arrest mortality is high, and neurological sequelae are more common for elderly cases[12]. In a meta-analysis conducted by Van Gijn et al[13], it was shown that the average age of cardiac arrest patients was between 60 and 75 years. In our study, the average age of all patients was found to be similar to studies on this subject, and no significant difference in age was observed between the groups (p=0.459).

In their study of 4,789 patients who underwent CPR, Wallace et al[14] found that 54.50% of the patients were male. Our findings are consistent with the literature, showing higher rates of cardiac arrest in men. There was no significant difference in gender between the non-survivors and survivors groups (p=0.23).

The time until CPR begins after arrest and the duration of resuscitation itself are important for prognosis[15]. In a study conducted by Van Walraven et al[16], it was shown that long resuscitation time was associated with increased mortality in patients undergoing CPR. In our study, no significant difference was observed between the two groups in CPR duration (p=0.086).

We also investigated the causes of cardiac arrest in patients in our study. In a review by Nolan[17], it was determined that approximately 65% of the causes of CA were of cardiac origin. In our study, we found that the cause of cardiac arrest was cardiac in 69 (46%) patients.

In the 2021 ERC guidelines[18], mortality rates for out-of-hospital cardiac arrest cases were reported to be very high. However, a study[19] conducted on post-cardiac arrest patients examined the mortality rates between in-hospital and out-of-hospital cardiac arrest groups but found no significant difference. In our study, no differences in mortality were found between patients with in-hospital and out-of-hospital cardiac arrest.

Table I. Comparison of groups in terms of demographic characteristics and comorbidities.

	All patients N=151	Non-survivors N=115	Survivors N=36	p-value
Age	69 (20-94)	69 (20-94)	69.5 (22-94)	0.459
Male	80 (53)	58 (72.5)	22 (27.5)	
CPR duration	10 (2-60)	10 (2-60)	6 (2-60)	0.086
Hospitalization duration	8 (2-105)	8 (2-105)	11 (2-80)	0.191
COPD	26 (17.2)	21 (80.8)	5 (19.2)	0.544
Heart disease	87 (57.6)	65 (74.7)	22 (25.3)	0.627
DM	44 (29.1)	35 (79.5)	9 (20.5)	0.531
CRF	11 (7.3)	10 (90.9)	1 (9.1)	0.233
Cancer	8 (5.3)	7 (87.5)	1 (12.5)	0.439
APACHE 2	27.1±8.5	27.8±8.4	23.8±8.2	0.140

CPR: Cardiopulmonary Resuscitation, COPD: Chronic Obstructive Pulmonary Disease, DM: Diabetes Mellitus, CRF: Chronic Renal Failure, APACHE: Acute Physiology and Chronic Health Evaluation.

3433

Table II. Comparison of groups in terms of pH, HCO_3 and glucose.

	All patients N=151	Non-survivors N=115	Survivors N=36	*p*-value
pH	7.27±0.15	7.26±0.15	7.32±0.11	0.028
HCO_3	18.02±5.48	17.4±5.43	19.9±5.28	0.016
Glucose	198 (18-824)	211 (18-814)	175 (78-415)	0.116

Data are expressed as mean ± standard deviation or median (minimum-maximum) levels. pH: Power of Hydrogen.

Following cardiac arrest, lactate is produced, and acidosis ensues due to anaerobic respiration, which results in decreased perfusion and ventilation. As a result, blood gas parameters play a crucial role in determining the prognosis of patients with cardiac arrest.

In a study conducted by Dell'Anna et al[19], 236 patients with cardiac arrest were divided into two groups: in-hospital cardiac arrest (99 patients) and out-of-hospital cardiac arrest (137 patients). The study examined the initial pH levels after the cardiac arrest. Out-of-hospital cardiac arrest patients had lower pH than in-hospital cardiac arrest patients [7.25 (7.16-7.34) *vs.* 7.27 (7.19-7.40), p=0.038]. Similarly, the pH was lower in the non-survivors group in our study (7.26±0.15 *vs.* 7.32±0.11, p=0.028).

Although PRC is primarily a marker for bacterial infection, elevated PRC levels are also commonly associated with shock[20-22]. Following cardiac arrest, inflammatory pathways are activated, leading to an increase in PRC levels[23,24]. In a prospective study conducted by Isenschmid et al[25] with 321 cardiac arrest patients, routine laboratory tests, including PRC and lactate, were investigated. The study found that the initial lactate and procalcitonin levels were significantly higher in the non-survivors group. In the ROC analysis, PRC and lactate were found to have high prognostic potential (AUC: 0.730; AUC: 0.700, respectively).

In a prospective study on PRC, Annborn et al. 22 grouped 84 cardiac arrest patients according to their cerebral performance score (CPS) (Group 1: CPS 1-2, Group 2: CPS 3-5). The 12th-, 24th-, and 48th-hour PRC levels were significantly higher in group 2 patients. They found the mean level of 24th-hour PRC (group 1: 0.2 *vs.* group 2: 1.9) as a predictive factor for poor neurological outcome (AUC: 0.860).

In another study by Hayashida et al[26], which compared the predictability of neurological outcome with serum procalcitonin and glial fibrillary acidic protein in patients after cardiac arrest, 12th-

Table III. Comparison of groups in terms of procalcitonin, lactate, and changes in these parameters.

	All patients N=151	Non-survivors N=115	Survivors N=36	*p*-value
PRC 1	0.33 (0.01-106.1)	0.37 (0.01-106.1)	0.18 (0.01-7.2)	0.074
PRC 24	5.02 (0.06-260.24)	7.51 (0.06-260.24)	2.09 (0.07-42.3)	0.004
PRC change	2.88 (-15.12-260.21)	3.9 (-15.12-260.21)	1.45 (-1.94-41.65)	0.027
PRC change rate	13.02 (-0.79-8673.67)	14.32 (-0.64-8673)	12.31 (-0.79-1209)	0.585
Lactate 1	4.50 (0.6-20)	5.1 (0.7-20)	1.9 (0.6-16)	<0.001
Lactate 6	2.80 (0.6-28)	3.35 (0.6-28)	2.2 (0.6-10.3)	0.001
Lactate 12	2.20 (0.4-21)	2.6 (0.4-21)	1.6 (0.8-7.6)	<0.001
Lactate 24	2.20 (0.6-19)	2.4 (0.7-19)	1.7 (0.6-4.5)	0.003
Lactate change	-1.75 (-13.6-9.30)	-2.4 (-13.6-9.3)	-0.6 (-13.4-3.9)	0.015
Lactate change rate	-0.41 (-0.90-6.50)	-0.42 (-0.9-2.79)	-0.41 (-0.89-6.50)	0.235

Data are expressed as median (minimum-maximum) levels. PRC: Procalcitonin.

Table IV. Logistic regression.

			95% Confidence Interval	
	p	Odds ratio	Lower	Upper
Lactate 24	0.012	1.861	1.145	3.023
PRC 24	0.158	1.177	0.939	1.477
Lactate change rate	0.031	0.501	0.267	0.939
PRC change	0.186	1.169	0.928	1.472

PRC: Procalcitonin.

and 24th-PRC levels were found to have high predictive values (AUC: 0.911; AUC: 0.939, respectively) for the poor neurological outcome.

Krzych et al[27] conducted a study on cardiac arrest patients, dividing them into two groups based on their Glasgow Outcome Score (GOS): Group 1 (GOS 1-3) and Group 2 (GOS 4-5). The median PRC level was 2.43 in Group 1 and 1.5 in Group 2. The ROC analysis indicated that procalcitonin has a prognostic value with an AUC of 0.650 (p=0.02).

In our study, we examined the patients' initial and 24th-hour procalcitonin levels. While initial PRC levels were similar between the two groups, 24th-hour PRC levels were significantly higher in the non-survivors group. ROC analysis showed that 24th-hour PRC had a predictive value (AUC: 0.665).

In contrast to the aforementioned studies, we analyzed the change and rate of change between the 24th-hour and initial procalcitonin levels. The non-survivor group exhibited a higher PRC change, while no significant difference was observed in the rate of PRC change (p=0.585). As a result, considering that the PRC levels are related to the duration of ischemic damage and the magnitude of the subsequent reperfusion injury, it can be postulated that the increase in PRC after cardiac arrest occurs due to inflammation.

Blood lactate concentrations are a sign of post-arrest cellular hypoxia. Patients with high blood lactate levels after CA have a high mortality rate[19,28]. In this clinical situation, lactate concentrations can be considered an indicator of prolonged hypoperfusion and inadequate resuscitation. Higher survival rates are associated with a rapid decrease in lactate concentrations after resuscitation[29,30].

In a retrospective study by Dell'Anna et al[19], the prognostic effects of blood lactate concentrations after cardiac arrest were investigated. The study examined the blood lactate levels (0, 6th, 12th, 24th, 48th hours), lactate change (24-1), and lactate change percentages of 236 patients. Based on their neurological results after three months, the patients were divided into two groups: Group 1 (CPS 1-2) and Group 2 (CPS 3-5), according to their cerebral performance score. The median initial lactate level was 4.3 in all patients, with a significant difference found between group 1 (2.5) and group 2 (5.3) (p<0.001, AUC: 0.689). In our study, we found no significant difference between groups in terms of initial lactate levels (p<0.001, AUC: 0.719). 24th-hour lactate median level was higher in group 2. Similarly, in the current study, 24th-hour lactate levels were higher in the non-survivors group. A significant difference was found for lactate change (24-1), which is consistent with our study (p=0.008). They did not find a significant difference in the percentage of lactate change in terms of prognosis. In their study, a relationship was found between initial lactate and poor prognosis in the multivariate logistic regression analysis (p<0.001; odds ratio: 1.18). In our study, we found that high 24th-hour lactate levels were an independent risk factor for mortality (p=0.012; odds ratio: 1.861).

The study conducted by Kliegel et al[31] with 394 patients who suffered cardiac arrest found a significant relationship between lactate levels (0, 24th, 48th hours) and neurological outcome.

In a study conducted by Karagiannis et al[32] on patients who experienced in-hospital cardiac arrest, the initial lactate levels were found to be significantly higher in the non-survivors group, and the percentages of lactate decrease were found to be lower in the non-survivors group.

In a prospective multicenter study by Donnino et al[33] examining lactate levels and lactate changes after cardiac arrest, the initial lactate

level (AUC: 0.670), 12th-hour lactate level (AUC: 0.760), and 24th-hour lactate level (AUC: 0.780) were found to have predictive value for mortality. There was a significant difference in the 24th-hour lactate change percentage between the non-survivors group (62%) and the survivors group (36%) (p=0.03). In logistic regression analysis, a low percentage of 12th-hour lactate decrease was found to be an independent risk factor for mortality.

In our study, there was a significant difference in lactate change between the groups (p=0.015, AUC: 0.636), but the rate of lactate change in the first 24 hours was similar (p=0.765). In the logistic regression analysis, a low rate of lactate change was identified as an independent risk factor for mortality (p=0.031, odds ratio: 0.501).

Limitations

Our study's limitations include its single-center nature, low sample size, and retrospective design. Additionally, some data could not be accessed from patient files, resulting in a smaller sample size for certain evaluations.

Conclusions

In the non-survivors, pH and HCO_3 levels were lower, while lactate levels at all time points and 24th-hour PRC levels were higher. High 24th-hour lactate levels and a low lactate change rate were identified as independent risk factors for mortality. Lactate, HCO_3, and PRC were found to be important factors in predicting mortality in post-cardiac arrest patients. Considering PRC and lactate levels may improve the prognostication of post-cardiac arrest patients.

Conflict of Interest

The authors declare no conflict of interest.

Informed Consent

Not applicable due to the retrospective nature of the study.

Ethics Approval

The study was conducted following the Declaration of Helsinki and its later amendments and approved by the Clinical Studies Ethics Committee of the Faculty of Medicine at Kahramanmaraş Sütçü İmam University (date: 22.07.2020, approval number: 2020/14-08).

ORCID ID

Mehmet Kandilcik: 0000-0002-8916-5156
Mahmut Arslan: 0000-0002-2820-1547
Hafize Öksüz: 0000-0001-5963-6861
Gökçe Gişi: 0000-0003-1863-6878
Cengizhan Yavuz: 0000-0003-4627-7403
Gözen Öksüz: 0000-0001-5197-8031
Adem Doğaner: 0000-0002-0270-9350

Authors' Contributions

Idea/concept: M.K., M.A., H.Ö.; writing the article, references, materials: M.K., M.A.; design, control, supervision: M.K., M.A., H.Ö; data collection and/or processing, analysis and/or interpretation, literature review: M.K., M.A., A.D.; critical review: G.G., G.Ö., C.Y., H.Ö.; other: M.K., M.A.

Acknowledgments

We would like to express our sincere gratitude to all parties who participated in this study.

Funding

This research received no external funding.

Data Availability

Data to support the findings of this study are available upon reasonable request.

References

1) Winship C, Williams B, Boyle MJ. Cardiopulmonary resuscitation before defibrillation in the out-of-hospital setting: a literature review. Emerg Med J 2012; 29: 826-829.
2) Tintinalli J, Stapczynski J, Ma OJ, Cline D, Cydulka R, Meckler G. Tintinalli's Emergency Medicine: A Comprehensive Study Guide. McGraw-Hill Education 2010; 63-73.
3) Monsieurs KG, Nolan JP, Bossaert LL, Greif R, Maconochie IK, Nikolaou NI, Perkins GD, Soar J, Truhlář A, Wyllie J, Zideman DA. European Resuscitation Council Guidelines for Resuscitation 2015: Section 1. Executive summary. Resuscitation 2015; 95: 1-80.
4) Nolan JP, Sandroni C, Böttiger BW, Cariou A, Cronberg T, Friberg H, Genbrugge C, Haywood K, Lilja G, Moulaert VRM, Nikolaou N, Olasveengen TM, Skrifvars MB, Taccone F, Soar J. European Resuscitation Council and European Society of Intensive Care Medicine guidelines 2021: post-resuscitation care. Intensive Care Med 2021; 47: 369-421.
5) Robba C, Badenes R, Battaglini D, Ball L, Sanfilippo F, Brunetti I, Jakobsen JC, Lilja G, Friberg

3436

H, Wendel-Garcia PD, Young PJ, Eastwood G, Chew MS, Unden J, Thomas M, Joannidis M, Nichol A, Lundin A, Hollenberg J, Hammond N, Saxena M, Martin A, Solar M, Taccone FS, Dankiewicz J, Nielsen N, Grejs AM, Ebner F, Pelosi P; TTM2 Trial collaborators. Oxygen targets and 6-month outcome after out-of-hospital cardiac arrest: a pre-planned sub-analysis of the targeted hypothermia versus targeted normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial. Crit Care 2022; 26: 323.

6) Robba C, Badenes R, Battaglini D, Ball L, Brunetti I, Jakobsen JC, Lilja G, Friberg H, Wendel-Garcia PD, Young PJ, Eastwood G, Chew MS, Unden J, Thomas M, Joannidis M, Nichol A, Lundin A, Hollenberg J, Hammond N, Saxena M, Annborn M, Solar M, Taccone FS, Dankiewicz J, Nielsen N, Pelosi P; TTM2 Trial Collaborators. Ventilatory settings in the initial 72h and their association with outcome in out-of-hospital cardiac arrest patients: a preplanned secondary analysis of the targeted hypothermia versus targeted normothermia after out-of-hospital cardiac arrest (TTM2) trial. Intensive Care Med 2022; 48: 1024-1038.

7) Fernando SM, Di Santo P, Sadeghirad B, Lascarrou JB, Rochwerg B, Mathew R, Sekhon MS, Munshi L, Fan E, Brodie D, Rowan KM, Hough CL, McLeod SL, Vaillancourt C, Cheskes S, Ferguson ND, Scales DC, Sandroni C, Nolan JP, Hibbert B. Targeted temperature management following out-of-hospital cardiac arrest: a systematic review and network meta-analysis of temperature targets. Intensive Care Med 2021; 47: 1078-1088.

8) Sanfilippo F, La Via L, Lanzafame B, Dezio V, Busalacchi D, Messina A, Ristagno G, Pelosi P, Astuto M. Targeted Temperature Management after Cardiac Arrest: A Systematic Review and Meta-Analysis with Trial Sequential Analysis. J Clin Med 2021; 10: 3943.

9) Soar J, Böttiger BW, Carli P, Couper K, Deakin CD, Djärv T, Lott C, Olasveengen T, Paal P, Pellis T, Perkins GD, Sandroni C, Nolan JP. European Resuscitation Council Guidelines 2021: Adult advanced life support. Resuscitation 2021; 161: 115-151.

10) Merchant RM, Topjian AA, Panchal AR, Cheng A, Aziz K, Berg KM, Lavonas EJ, Magid DJ; Adult Basic and Advanced Life Support, Pediatric Basic and Advanced Life Support, Neonatal Life Support, Resuscitation Education Science, and Systems of Care Writing Groups. Part 1: Executive Summary: 2020 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2020; 142: S337-S357.

11) Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, de Ferranti SD, Floyd J, Fornage M, Gillespie C, Isasi CR, Jiménez MC, Jordan LC, Judd SE, Lackland D, Lichtman JH, Lisabeth L, Liu S, Longenecker CT, Mackey RH, Matsushita K, Mozaffarian D, Mussolino ME, Nasir K, Neumar RW, Palaniappan L, Pandey DK, Thiagarajan RR, Reeves MJ, Ritchey M, Rodriguez CJ, Roth GA, Rosamond WD, Sasson C, Towfighi A, Tsao CW, Turner MB, Virani SS, Voeks JH, Willey JZ, Wilkins JT, Wu JH, Alger HM, Wong SS, Muntner P; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation 2017; 135: 146-603.

12) Kim C, Becker L, Eisenberg MS. Out-of-hospital cardiac arrest in octogenarians and nonagenarians. Arch Intern Med 2000; 160: 3439

13) Van Gijn MS, Frijns D, Van de Glind EM, C van Munster B, Hamaker ME. The chance of survival and the functional outcome after in-hospital cardiopulmonary resuscitation in older people: a systematic review. Age Ageing 2014; 43: 456-463.

14) Wallace SK, Abella BS, Shofer FS, Leary M, Agarwal AK, Mechem CC, Gaieski DF, Becker LB, Neumar RW, Band RA. Effect of time of day on prehospital care and outcomes after out-of-hospital cardiac arrest. Circulation 2013; 127: 1591-1596.

15) Martinez JP. Prognosis in cardia carrest. Emerg Med Clin North Am 2012; 30: 91-103.

16) Van Walraven C, Forster AJ, Parish DC, Dane FC, Chandra KM, Durham MD, Whaley C, Stiell I. Validation of a clinical decision aid to discontinue in-hospital cardiac arrest resuscitations. JAMA 2001; 285: 1602-1606.

17) Nolan JP. Cardiac Arrest and Cardiopulmonary Resuscitation. Semin Neurol 2017; 37: 5-12.

18) Michels G, Pöss J, Thiele H. ERC guidelines 2021 on cardiopulmonary resuscitation. Herz 2022; 47: 4-11.

19) Dell'Anna AM, Sandroni C, Lamanna I, Belloni I, Donadello K, Creteur J, Vincent JL, Taccone FS. Prognostic implications of blood lactate concentrations after cardiac arrest: a retrospective study. Ann Intensive Care 2017; 7: 101.

20) Schuetz P, Aujesky D, Muller C, Muller B. Biomarker-guided personalised emergency medicine for all – hope for another hype? Swiss Med Wkly 2015; 145: w14079.

21) Schuetz P, Christ-Crain M, Müller B. Procalcitonin and other biomarkers to improve assessment and antibiotic stewardship in infections-hope for hype? Swiss Med Wkly 2009; 139: 318-326.

22) Annborn M, Dankiewicz J, Erlinge D, Hertel S, Rundgren M, Smith JG, Struck J, Friberg H. Procalcitonin after cardiac arrest-an indicator of severity of illness, ischemia-reperfusion injury and outcome. Resuscitation 2013; 84: 782-787.

23) Bro-Jeppesen J, Kjaergaard J, Wanscher M, Nielsen N, Friberg H, Bjerre M, Hassager C. Systemic Inflammatory Response and Potential Prognostic Implications After Out-of-Hospital Cardiac Arrest: A Substudy of the Target Temperature Management Trial. Crit Care Med 2015; 43: 1223-1232.

24) Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, Kern KB, Laurent I, Longstreth WT, Merchant RM, Morley P, Morrison LJ, Na-

dkarni V, Peberdy MA, Rivers EP, Rodriguez-Nunez A, Sellke FW, Spaulding C, Sunde K, Hoek TV. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008; 79: 350-379.

25) Isenschmid C, Kalt J, Gamp M, Tondorf T, Becker C, Tisljar K, Locher S, Schuetz P, Marsch S, Hunziker S. Routine blood markers from different biological pathways improve early risk stratification in cardiac arrest patients: Results from the prospective, observational communıcate study. Resuscitation 2018; 130: 138-145.

26) Hayashida H, Kaneko T, Kasaoka S, Oshima C, Miyauchi T, Fujita M, Oda Y, Tsuruta R, Maekawa T. Comparison of the predictability of neurological outcome by serum procalcitonin and glial fibrillary acidic protein in postcardiac-arrest patients. Neurocrit Care 2010; 12: 252-257.

27) Krzych LJ, Gołąb K, Pstras J, Knapik P. Predicting outcome after cardiac arrest with serum S-100B protein and procalcitonin: A prospective observational study. Eur J Anaesthesiol 2017; 34: 846-848.

28) Mullner M, Sterz F, Domanovits H, Behringer W, Binder M, Laggner AN. The association between blood lactate concentration on admission, duration of cardiac arrest, and functional neurological recovery in patients resuscitated from ventricular fibrillation. Intensive Care Med 1997; 23: 1138-1143.

29) Lee TR, Kang MJ, Cha WC, Shin TG, Sim MS, Jo IJ, Song KJ, Jeong YK, Cho JH. Better lactate clearance associated with good neurologic outcome in survivors who treated with therapeutic hypothermia after out-of-hospital cardiac arrest. Crit Care 2013; 17: R260.

30) Hayashida K, Suzuki M, Yonemoto N, Hori S, Tamura T, Sakurai A, Tahara Y, Nagao K, Yaguchi A, Morimura N; SOS-KANTO 2012 Study Group. Early Lactate Clearance Is Associated With Improved Outcomes in Patients With Postcardiac Arrest Syndrome: A Prospective, Multicenter Observational Study (SOS-KANTO 2012 Study). Crit Care Med 2017; 45: e559-e566.

31) Kliegel A, Losert H, Sterz F, Holzer M, Zeiner A, Havel C, Laggner AN. Serial lactate determinations for prediction of outcome after cardiac arrest. Medicine (Baltimore) 2004; 83: 274-279.

32) Karagiannis C, Georgiou M, Kouskouni E, Iacovidou N, Xanthos T. Association of lactate levels with outcome after in-hospital cardiac arrest. Resuscitation 2012; 83: 175-176.

33) Donnino MW, Andersen LW, Giberson T, Gaieski DF, Abella BS, Peberdy MA, Rittenberger JC, Callaway CW, Ornato J, Clore J, Grossestreuer A, Salciccioli J, Cocchi MN; National Post-Arrest Research Consortium. Initial lactate and lactate change in post-cardiac arrest: a multi-center validation study. Crit Care Med 2014; 42: 1804-1811.