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ORIGINAL ARTICLE

SURVIVAL AND NEUROLOGIC RECOVERY AFTER OUT-OF-HOSPITAL CARDIAC ARREST

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ABSTRACT

Introduction/Objective: Survival and neurologic recovery after out-of-hospital cardiac arrest remain poor despite significant advances in the therapeutic approach. The study aimed to evaluate predictors of intrahospital survival and neurologic outcome among patients after out-of-hospital cardiac arrest as well as to evaluate the influence of mild therapeutic hypothermia introduction on intrahospital survival and neurologic outcome among comatose patients after out-of-hospital cardiac arrest.

Methods The research was conducted as a retrospective observational study among patients hospitalized at the Cardiac Intensive Care Unit of the Institute for Cardiovascular Diseases of Vojvodina from January 2007 until November 2019 as a result of an out-of-hospital cardiac arrest.

Results. The research included 506 survivors of OHCA. Multivariate regression analysis showed that initial shockable rhythm, cardiopulmonary resuscitation efforts lasting no longer than 20 minutes and a Glasgow Coma Score above 8 at admission, were predictors of intrahospital survival and good neurological outcome. Introduction of mild therapeutic hypothermia improved intrahospital survival (54.1% vs. 24.4%; $p < 0.0005$) and neurological outcome (42.9% vs. 18.3%; $p < 0.0005$) in comatose patients with initial shockable rhythm.

Conclusion. In our study group of out-of-hospital cardiac arrest patients, initial shockable rhythm, cardiopulmonary resuscitation efforts lasting no longer than 20min and a Glasgow Coma Score above 8 at admission were predictors of intrahospital survival and favourable neurological outcome. The introduction of mild therapeutic hypothermia significantly improved survival and neurological outcomes in comatose patients with initial shockable rhythms.

Keywords: out-of-hospital cardiac arrest; cardiopulmonary resuscitation; mild therapeutic hypothermia; predictors, good neurologic outcome.

Introduction

Survival rate and neurologic outcome in patients after out-of-hospital cardiac arrest (OHCA) have not improved in the past several decades despite the advances in diagnostic and therapeutic algorithms. According to different registries, the in-hospital survival rate after OHCA with both initial shockable and non-shockable rhythms varies from 2.7% to 26.5%, with higher rates reported for patients with initial shockable rhythm (from 26.4% to 44.3%) [1] and very low rates for patients with initial non-shockable rhythm [2].

When it comes to favourable neurologic outcomes after OHCA, nearly 65% of cardiac arrest patients with initial shockable rhythm achieve good neurologic outcomes, in contrast to those with non-shockable rhythm in whom the good neurological outcome is seen in 2-15% of the cases. [3].

Different studies report initial shockable rhythm, resuscitation efforts lasting no longer than 20 min, witnessed cardiac arrest, bystander cardiopulmonary resuscitation (CPR), as well as early coronary angiography and percutaneous coronary intervention (PCI) as independent predictors of in-hospital survival among patients successfully resuscitated after OHCA [4,5].

There have been very few randomized controlled studies in the field of post-resuscitation hypothermia. Current guidelines published by the American Heart Association (AHA), European Resuscitation Council (ERC), and Neurocritical Care Society (NCS) recommend targeted temperature management (TTM) after OHCA as an effort to improve survival and alleviate post-hypoxic brain injury [6-8].

The European Resuscitation Council (ERC) Guidelines for CPR published in 2021 strongly support TTM for patients with OHCA and initial shockable rhythm. On the other hand, recommendations for patients with OHCA and initial non-shockable rhythm are still weak and based upon results of applying TTM among successfully resuscitated patients after OHCA with initial non-shockable rhythm [8].

Objective

The objective of our study is to evaluate predictors of intrahospital survival and neurologic outcome among patients resuscitated after OHCA, as well as to evaluate the influence of targeted temperature management (TTM) on comatose patients successfully resuscitated after OHCA, based on their intrahospital survival and neurologic outcome.

Methods

The research was conducted as a retrospective observational analysis of 506 comatose patients after OHCA, treated at the Cardiac Intensive Care Unit (CICU) of the Institute of Cardiovascular Diseases of Vojvodina from January 2007 to November 2019. Data was collected through the hospital information system.

This study included 506 patients, 322 of which were male, aged 64.08 ± 12.52 years, and 184 female, aged 66.45 ± 14.27 years.

Data relevant to our trial study, acquired through the hospital information system, were as follows: type of cardiac arrest, witnessed/unwitnessed cardiac arrest, duration of resuscitation, defibrillation performed, state of consciousness at hospital admission, electrocardiographic (ECG) signs of ST-segment elevation myocardial infarction (STEMI), early PCI.

The type of cardiac arrest was defined as follows: ventricular fibrillation (VF) and ventricular tachycardia (VT) were defined as shockable rhythms, and asystole and pulseless electrical activity (PEA) as non-shockable rhythms. Duration of cardiopulmonary resuscitation was defined as ≤ 20 minutes and > 20 minutes. The level of consciousness at hospital admission was assessed against the Glasgow Coma Scale (GCS), according to which all patients with values of GCS ≤ 8 were identified as comatose. ECG signs of STEMI included an ST elevation of ≥ 2mm in two or more consecutive leads covering the same myocardial wall. Early PCI was defined as PCI performed within 24 hours of admission.

In our cohort study, we evaluated predictors of intrahospital survival and favourable neurologic outcome. A favourable neurologic outcome was defined by the Cerebral Performance Score (CPC). A score of ≤ 2 was considered to be a favourable neurologic outcome without significant neurological deficits and the ability to independently perform daily activities.

In our trial study, comatose patients at admission (387) were divided into two groups according to their type of OHCA (shockable rhythm or non-shockable rhythm). Each of the two groups was then divided into two subgroups depending on whether the patients had been treated with targeted temperature management (TTM).

In both groups, the decision to introduce TTM was made by the Emergency Department physician at hospital admission. The decision about whether to use an intravascular catheter (ZOLL ICY Intravascular Heat Exchange Catheter Model IC-3893A) connected to an intravascular cooling device (ZOLL Coolgard 3000/Thermogard XP Thermal Regulation System) or to apply the surface cooling method using cold pads (EMCOOLS Flex. Pad) and targeted cooling temperature was at the discretion of the admitting physician at the Cardiac Intensive Care Unit. With all patients, the achieved targeted temperature was maintained for 24 hours, followed by spontaneous or active rewarming.

The study was approved by the Ethical Committee of the Institute for Cardiovascular Diseases of Vojvodina.

The following descriptive statistics measures have been applied: arithmetic mean, standard deviation, median and percentiles, frequencies, and percentages. To compare the median of the two group variables, the independent samples t-test was used. The association between the categorical variables was tested by the contingency table Chi-Square test or by Fisher's exact test. The effects of variables on the treatment outcome were determined using the univariate and multivariate binary logistic analysis. The results are shown in tables and graphs. A statistical test significance value of $p < 0.05$ was applied. Statistical data management was done in SPSS 17.0 software package.

Results

The study included 506 successfully resuscitated comatose patients after OHCA, 322 (63.6%) of which were male. The average age of the study population was 65.7 ± 12.8 years. The average age of the male patients was 64.1 ± 12.5, whereas the average age of the female patients was 66.5 ± 14.3 years, and statistically, there was not a significant difference ($p = 0.090$) in age.

In the patient cohort study, cardiac arrest was witnessed in 412 (81.4%) cases, bystander CPR was initiated in 197 (38.9%) cases, resuscitation lasted less than 20 minutes in 291 (57.5%) cases, and the initial rhythm was shockable in 304 (60.1%) cases. ECG upon admission showed STEMI in 176 (34.8%) cases and early PCI was performed in 145 (28.6%) cases. In-hospital survival accounted for 225 (45.5%) patients and 185 (36.6%) patients had a favourable neurologic outcome.

Multivariant regression analysis showed that predictors of in-hospital survival were: initial shockable rhythm, early PCI, CPR ≤ 20 min and GCS > 8. Results of univariant and multivariant predictors regression analysis of in-hospital survival are shown in **Table 1.** Hosmer Lemeshow test has shown that our model is good ($p = 0.987$).

In our cohort study, the results of multivariant regression analysis showed that predictors of good neurological outcome were: initial shockable rhythm, initial ECG upon admission showing STEMI, duration of CPR ≤ 20 min and GCS > 8. Both univariant and multivariant analyses of predictors of good neurological outcomes are shown in **Table 2.** Hosmer Lemeshow test has shown that our model is good ($p = 0.973$).

Table 1. Predictors of intrahospital survival

Variable	Univariant analysis		Multivariant analysis	
	OR(95%CI)	P value	OR(95%CI)	P value
Initial shockable rhythm	3.391(2.310-4.977)	< 0.0005	2.507(1.598-3.933)	< 0.0005
ECG signs of STEMI	0.346(0.237-0.505)	< 0.0005	/	ns
Early PCI	0.260(0.173-0.392)	< 0.0005	0.368(0.226-0.599)	< 0.0005
Defibrillation	0.423(0.286-0.626)	< 0.0005	/	ns
Witness present	0.436(0.268-0.709)	0.001	/	ns
CPR initiated	0.538(0.374-0.772	0.001	/	ns
CPR ≤ 20 min	5.872(3.926-8.781)	< 0.0005	4.249(2.688-6.718)	< 0.0005
GCS > 8	0.098(0.058-0.165)	< 0.0005	0.194(0.110-0.343)	< 0.0005

Legend: ECG – electrocardiogram; STEMI – ST-segment elevation myocardial infarction; PCI – percutaneous coronary intervention; CPR – cardiopulmonary resuscitation; GCS – Glasgow Coma Scale

Table 2. Predictors of favourable neurologic outcome

Variable	Univariant analysis		Multivariant analysis	
	OR(95%CI)	P value	OR(95%CI)	P value
Initial shockable rhythm	4.041(2.659-6.141)	< 0.0005	3.301(2.002-5.441)	< 0.0005
ECG signs of STEMI	0.401(0.274-0.586)	< 0.0005	0.528(0.326-0.853)	0.009
PCI	0.320(0.215-0.477)	< 0.0005	/	ns
Defibrillation	0.373(0.244-0.570)	< 0.0005	/	ns
Witness present	0.435(0.258-0.735)	0.002	/	ns
CPR initiated	0.411(0.283-0.596)	< 0.0005	/	ns
CPR ≤ 20 min	7.411(4.706-11.671)	< 0.0005	5.144(3.090-8.565)	< 0.0005
GCS > 8	0.087(0.053-0.143)	< 0.0005	0.152(0.088-0.260)	< 0.0005

Legend: ECG – electrocardiogram; STEMI – ST-segment elevation myocardial infarction; PCI – percutaneous coronary intervention; CPR – cardiopulmonary resuscitation; GCS – Glasgow Coma Scale

At admission, 387 (76.5%) patients were comatose (GCS < 8) and TTM was introduced in 177 (45.7%) patients. Among them, 215 (55.6%) patients had an initial shockable rhythm and 172 (44.4%) patients had an initial non-shockable rhythm.

There was a significant difference in intrahospital survival rate between the OHCA patients with an initial shockable rhythm, and those with an initial non-shockable rhythm (42.8% vs. 19.8%, p < 0.0005). Among the OHCA patients with an initial shockable rhythm, TTM considerably increased intrahospital survival (54.1% of patients treated with hypothermia as opposed to 24.4% of patients not treated with hypothermia), which presented a significant difference (p < 0.0005). In OHCA patients with the initial non-shockable rhythm, TTM also increased the intrahospital survival rate (29.5% in patients treated with TTM versus 16.4% in patients not treated with TTM; p < 0.0005). **Figure 1** shows the intrahospital survival rate according to initial rhythm and introduction of hypothermia.

When the effect of TTM on intrahospital neurological outcome was evaluated among cardiac arrest patients with an initial shockable rhythm, mild induced hypothermia significantly influenced a favourable

neurologic outcome (42.9% among patients who received hypothermia versus 18.3% among those who did not receive hypothermia; p < 0.0005), while no statistically significant difference was found among patients with initial non-shockable rhythm (13.6% among patients who received hypothermia versus 10.9% among those who did not receive hypothermia; p = 0.388) (**Figure 2**).

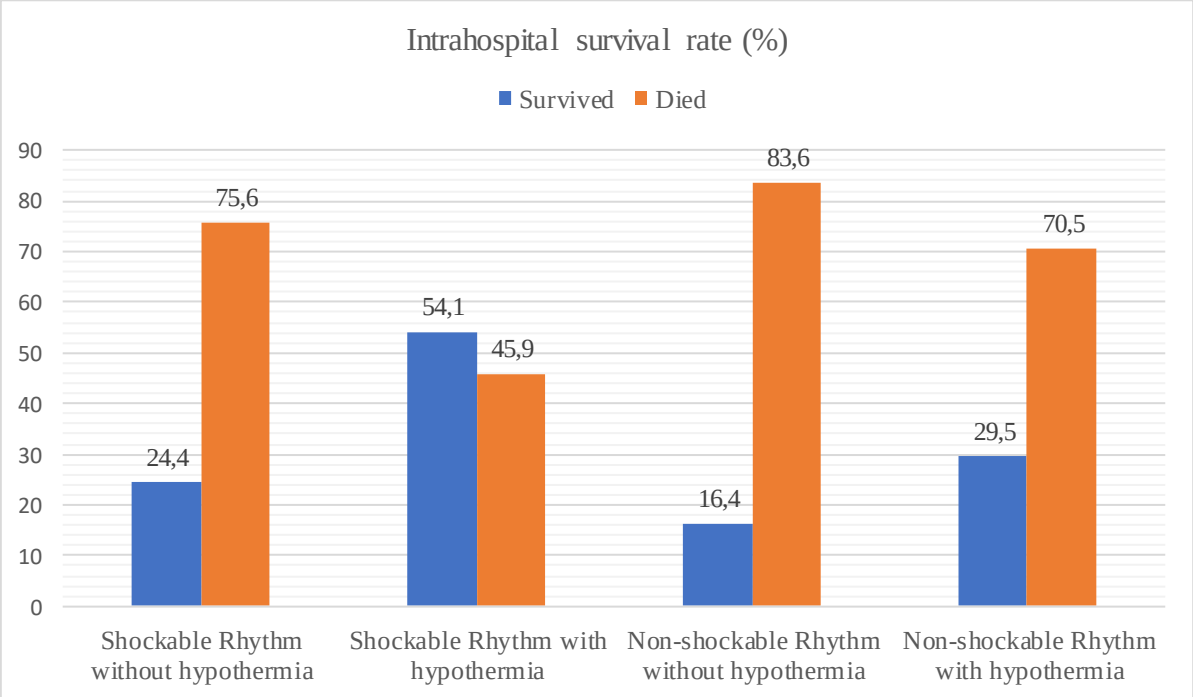

Figure 1. Intrahospital survival rate according to initial rhythm and introduction of hypothermia

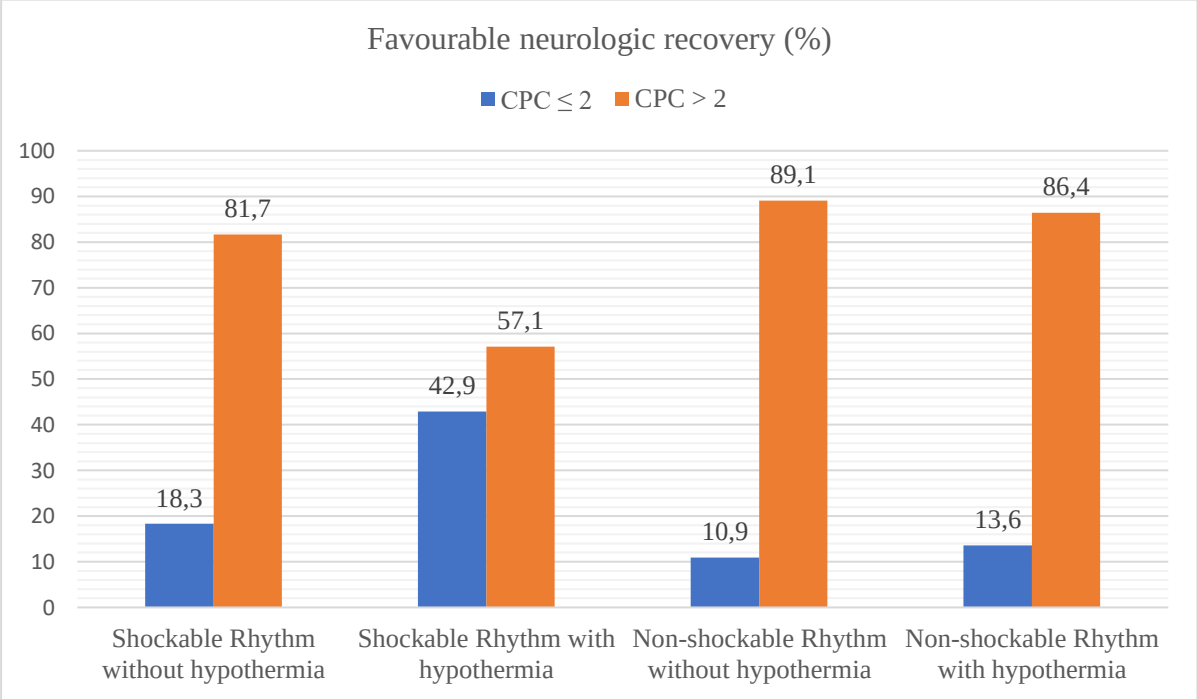

Figure 2. Favourable neurologic recovery at discharge according to initial rhythm and introduction of hypothermia
Legend: CPC – cerebral performance category

Discussion

In our study cohort, we analyzed predictors of in-hospital survival and favourable neurologic outcome among patients after OHCA. We also analyzed the effects of TTM on intrahospital survival and neurologic outcome in comatose patients after OHCA.

Regarding the effects of prehospital factors closely related to resuscitation on intrahospital survival and good neurological outcome, Mathiesen et al., who analyzed 1138 OHCA patients, concluded that bystander CPR and resuscitation duration affect intrahospital survival rate [9].

Navab et al. have published similar results, observed in their study group of 3214 OHCA patients, where initial shockable rhythm and bystander CPR impacted intrahospital survival rate [10].

In their study trial of 11368 OHCA patients, included in the ROC-PRIMED multicenter cluster-randomized clinical trial, Reynolds et al. concluded that patients with an initial shockable rhythm, witnessed cardiac arrest, and shorter resuscitation efforts were more likely to survive with favourable neurologic outcomes [11].

According to our study results, initial shockable rhythm, resuscitation efforts lasting less than 20 minutes and GCS > 8 were predictors of not only intrahospital survival but also of favourable neurological outcomes in patients successfully resuscitated after OHCA.

Despite that, according to our study results, early PCI was an independent predictor of intrahospital survival and ECG showing STEMI upon admission was an independent predictor of good neurological outcome. Similar results were published by Lahmann et al. in their recently published study of 519 patients hospitalized after OHCA, where they found that the 30-day and 1-year survival rates were significantly higher among patients undergoing immediate coronary angiography compared to patients on whom immediate coronary angiography was not performed (221/370 (59.7%) vs. 30/131 (22.9%), p = 0.001) and that in patients on whom immediate coronary angiography was performed, a good neurologic outcome at discharge, defined as CPC 1 or 2, was achieved in 164/299 (54.8%) [12]. This is a very important finding since the benefit of early revascularization has been proven in patients with STEMI, while diagnostic pathways remain unclear in the absence of STEMI.

There have been very few randomized controlled studies in the field of post-resuscitation hypothermia.

Data from a prospective HACORE study, that analyzed the effects of mild induced hypothermia in 233 patients successfully resuscitated after out-of-hospital cardiac arrest, outlined the arguments in favour of targeted temperature management in relation to intrahospital survival, which was reported to be 56% [13].

Our study showed similar results to such an extent that the intrahospital survival rate in patients after cardiac arrest by type of shockable rhythm, who had received induced hypothermia, was 54.1%. Among the patients who had suffered cardiac arrest with non-shockable rhythm in our study group, targeted temperature management increased the likelihood of intrahospital survival to 29.5%.

Until recently, guidelines for unconscious survivors of out-of-hospital cardiac arrest with non-shockable rhythm were deduced from trial studies of patients with shockable rhythm and have led to much debate. In 2019, the HYPOTERION trial showed the potential benefits of 33℃ targeted temperature management on survival and neurological outcomes in patients after non-shockable cardiac arrest, as compared to targeted normothermia (37℃) at 90 days. On day 90, a total of 29 of 284 patients (10.2%) in the hypothermia group were alive with a CPC score of 1 or 2, as compared with 17 of 297 (5.7%) in the normothermia group [3].

Furthermore, Seok Goo Kim et al. analyzed a clinical trial group of 401 resuscitated patients with initial non-shockable rhythm, including 89 (22%) with induced hypothermia, and found that TTM was related to a three-fold increase in neurologically favourable survival at 30 days [14].

According to several clinical trials, a favourable intrahospital neurological outcome has been reported in 26%-39% of the patients after out-of-hospital cardiac arrest, whereas targeted temperature management increased this percentage to 49%-55% [1,15].

Similar results have been found in our trial study. Among the patients with out-of-hospital cardiac arrest and shockable rhythm, 18.3% had favourable neurological outcomes, as compared to a significantly lower percentage of 10.9% in the initial non-shockable rhythm group.

The introduction of TTM in our study group significantly influenced favourable neurologic outcomes to 42.9% among patients with initial shockable rhythms, which is in line with previously cited trials, while it did not influence neurologic outcomes among patients with initial non-shockable rhythms.

Randomized trials analysing the effects of therapeutic hypothermia versus regular care on out-of-hospital cardiac arrest patients usually included fewer than 500 participants, and many of the trials were small and at a high risk of bias [16].

Eagerly awaited results of a large multicenter, randomized TTM2 trial were recently published. This randomized study included 1900 patients after out-of-hospital cardiac arrest in whom TTM was introduced. It compared the effects of a target temperature of 33℃ with a strategy to maintain normothermia (36°C) and early treatment of fever (≥37.8°C), which presents one of the leading concerns within the patient rewarming phase. The results of the study showed that at 6 months follow-up, targeted hypothermia did not lower death incidence nor did it improve neurological outcomes in comparison with targeted normothermia [16].

Conclusion

In our trial, prehospital predictors that increase both intrahospital survival and influence favourable neurologic outcomes were initial shockable rhythm, resuscitation efforts lasting less than 20 minutes and GCS ≥ 8 upon admission. Along with these, early PCI among resuscitated OHCA patients was a predictor of intrahospital survival and ECG showing STEMI upon admission was a predictor of good neurologic outcome.
The introduction of TTM significantly improved both survival and neurologic outcome in comatose patients with initial shockable rhythms. Despite significantly lower intrahospital survival and neurologic outcome levels in patients resuscitated after OHCA with non-shockable rhythm, TTM also improved 95

intrahospital survival, but it did not affect the neurologic outcome.

Conflict of interest: None declared.

ABBREVIATIONS

OHCA – out-of-hospital cardiac arrest; CPR – cardiopulmonary resuscitation; PCI – percutaneous coronary intervention; TTM – targeted temperature management; ECG – electrocardiograph/electrocardiographic; STEMI – ST-segment elevation myocardial infarction; GCS – Glasgow Coma Scale; CPC – Cerebral Performance Score

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ORIGINALNI RAD

PREŽIVLJAVANJE I NEUROLOŠKI OPORAVAK NAKON VANHOSPITALNOG SRČANOG ZASTOJA

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SAŽETAK

Uvod/cilj: Uprkos terapijskom napretku, preživljavanje i neurološki oporavak nakon vanhospitalnog srčanog zastoja su i dalje loši. Cilj istraživanja je bio da se odrede prediktori intrahospitalnog preživljavanja i neurološkog oporavka kod bolesnika nakon vanhospitalnog srčanog zastoja, kao i uticaj uvođenja blage terapijske hipotermije na intrahospitalno preživljavanje i neurološki ishod kod komatoznih bolesnika nakon vanhospitalnog srčanog zastoja.

Metode Istraživanje je osmišljeno kao retrospektivna opservaciona studija na osnovu uzorka bolesnika hospitalno lečenih u Jedinici intenzivne kardiološke nege Instituta za kardiovaskularne bolesti Vojvodine u periodu od januara 2007. do novembra 2019. godine zbog vanhospitalnog srčanog zastoja.

Rezultati Istraživanje je obuhvatilo 506 bolesnika nakon vanhospitalnog srčanog zastoja. Multivarijanta regresiona analiza je pokazala da su: inicijalni šokabilni ritam, trajanje kardiopulmonalne reanimacije ≤ 20 minuta i Glazgov koma skor > 8 na prijemu prediktori intrahospitalnog preživljavanja i dobrog neurološkog oporavka. Inicijacija blage hipotermije je popravila kako intrahospitalno preživljavanje (54,1% nasuprot 24,4%; $p < 0,0005$), tako i neurološki oporavak (42,9% nasuprot 18,3%; $p < 0,0005$) kod komatoznih bolesnika sa inicijalnim šokabilnim ritmom.

Zaključak U našoj grupi bolesnika, nakon vanhospitalnog srčanog zastoja, inicijalni šokabilni ritam, trajanje kardiopulmonalne reanimacije ≤ 20 minuta i Glazgov koma skor > 8 na prijemu su uticali na intrahospitalno preživljavanje i povoljan neurološki oporavak. Primena blage terapijske hipotermije je poboljšala preživljavanje i neurološki oporavak kod komatoznih bolesnika sa inicijalnim šokabilnim ritmom.

Ključne reči: vanhospitalni srčani zastoj; kardiopulmonalna reanimacija; blaga terapijska hipotermija; prediktori; dobar neurološki oporavak