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Clinical paper

Long-term survival in out-of-hospital cardiac arrest patients treated with targeted temperature control at 33 °C or 36 °C: A national registry study

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Abstract

Aim: There are limited data on long-term outcome in out-of-hospital cardiac arrest patients following the treatment shift of target temperature management (TTM) from 33 °C to 36 °C outside the controlled settings of randomised trials. The aim of this study was to evaluate the adherence to TTM guidelines after the publication of the TTM trial and if the change in temperature level influence six-month survival.

Methods: OHCA patients admitted to intensive care units (ICU) and recorded in the Swedish Intensive Care Registry (January 2010–March 2016) were included. Each ICU in Sweden provided information on their TTM target (i.e. 33 °C [TTM33] or 36 °C [TTM36]) used and the date of shift to 36 °C. The primary outcome was six-months survival. Multivariate logistic regression and propensity score match was used to adjust for confounders.

Results: In total, 2899 OHCA patients from 69 ICUs were assessed; of those, 1038 patients were treated with TTM (TTM33, n = 755 and TTM36, n = 283). Patients receiving any TTM decreased during the study period from 70.5% to 54.5% (p for trend <0.001). There was no significant difference in six-month survival between the TTM33 (47.2%) and the TTM36 (47.3%) groups (adjusted OR 1.12 [0.80–1.56]. In the propensity score matched analysis the six-months survival was 52.7 vs 47.3 %, OR 1.29 [0.90–1.85]).

Conclusions: The proportion of patients receiving therapeutic hypothermia in Sweden has decreased significantly since the publication of the TTM-trial indicating lower adherence to guidelines. This was not associated with any significant difference in long term outcome.

Keywords: Out-of-hospital cardiac arrest, Therapeutic hypothermia, Targeted temperature management

Introduction

Experimental data indicate that mild hypothermia is neuroprotective after a period of global cerebral hypoxia-ischemia.[1,2] Targeted temperature management (TTM) at 33 °C for 12–24 h has been routinely used in patients resuscitated from out-of-hospital cardiac arrest (OHCA) since the publication of two randomised controlled trials in 2002.[3,4] These trials demonstrated an increased probability of good neurologic outcome in a selected population of OHCA patients with an initial shockable rhythm when compared to standard of care. In 2013, Nielsen et al. compared standard target temperature management (TTM) at 33 °C with a higher TTM target at 36 °C. This study showed similar survival rates and neurologic outcome at six months[5] for the two strategies. After the publication of this trial, international guidelines were altered to recommended TTM between 32 °C and

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36 °C in cardiac arrest survivors.[6,7] However, this change has raised clinical concerns that a shift to TTM at 36 °C could reduce the number of patients treated with therapeutic hypothermia.[8]

As such, the aim of this study was to describe changes over time in the use of therapeutic hypothermia in OHCA patients admitted to Swedish ICUs and to compare six-month survival between patients treated with TTM at 33 °C (TTM33) or 36 °C (TTM36).

Materials and methods

Study design

This was an observational retrospective study using prospectively collected data from four Swedish National Health registries. The study was performed in Sweden from the 1st of January 2010 to the 29th of March 2016. Sweden's population was 9,851,017 inhabitants as of the 31st of December 2015. The study was approved by the Regional Ethics Committee (2016/172-31).

Patients

All OHCA patients admitted to an ICU with the primary diagnosis of cardiac arrest who were subsequently reported to the Swedish Intensive Care Registry (SIR) during the study period were included. Exclusion criteria were: (a) patients under the age of 18; (b) in-hospital cardiac arrests; (c) patients with a Glasgow Coma Scale (GCS) score more than 8 who did not receive invasive mechanical ventilation; (d) inclusion in the TTM-trial[5] during the study period. A total number of 69 hospitals (85.6 % of all OHCA patients registered) in the Swedish Intensive Care Registry participated in the study. All the non-participating hospitals are small with only a few cases of OHCA patients per year.

Data collection

Data from four registries (the Swedish Intensive Care Registry, the Swedish Register for Cardiopulmonary Resuscitation, the National Patient Register and the Cause of Death Register) were merged and information regarding previous comorbidities, causes of death, emergency medical services (EMS) treatment for cardiac arrest and intensive care treatment following OHCA patients was collected.

Swedish Intensive Care Registry (SIR)

The Swedish Intensive Care Registry is a non-commercial national health registry with high coverage and includes the majority of the Swedish intensive care units. It was founded in 2001 and has been described previously.[9]

Swedish Register for Cardiopulmonary Resuscitation (SRCR)

SRCR includes all EMS organizations in Sweden and reports OHCA cases in whom cardiopulmonary resuscitation (CPR) was attempted by EMS in accordance with the Utstein guidelines.[10] It is one of many national quality registries of the Swedish National Board of Health and Welfare and is funded by the Swedish Association of Local Authorities and Regions. The registry predominantly contains pre-hospital variables. It has previously been described in detail.[11]

The National Patient Register (NPR) and the Cause of Death Register (CDR)

The NPR and the CDR are registries of the Swedish National Board of Health and Welfare and contain individual patient data of co-morbidities and primary cause of admission from hospital admissions in Sweden from 1987 to date. Reporting is mandatory by Swedish law and done by physicians. Mortality at thirty days and six months were obtained from CDR data based on social security numbers assigned to all Swedish citizens which minimizes the risk of lost to follow up. The completeness of data for mortality during the study period was 100% and the national completeness for comorbidities and primary diagnosis for hospital admission in the NPR is almost 100%.[12,13]

TTM targets and definitions

Information regarding the TTM targets with therapeutic hypothermia is registered in the SIR as "active hypothermia". As the registry does not discriminate between TTM33 and TTM36, a survey was conducted among all participating ICUs in Sweden (n = 69). The survey was answered by one physician (in general the Head of the ICU or the physician in charge of the local guidelines for cardiac arrest management) and contained two questions: (1) Have you changed from TTM33 to TTM36 for OHCA patients? (2) If so, at what date was the change to TTM36 treatment strategy implemented? According to these two questions and the data of ICU admission for OHCA, patients were separated into a TTM33 and a TTM 36 group. Patients admitted within one month after the date of TTM shift were excluded (i.e. "wash-out" period). We had no means of controlling if the ICU in real life had changed the target temperature treatment strategy at the date given and the actual temperature used at an individual patient level.

Statistical analysis

Categorical variables are presented as counts and proportions and continuous variables as medians and quartiles. To test baseline differences, chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables were used. To test if there have been any changes in probability of survival after the transition to TTM36, a binary logistic regression analysis was performed as well as a propensity score match. The logistic regression analysis was adjusted for bystander cardiopulmonary resuscitation, gender, age, witnessed status, location, Charlson comorbidity index (CCI) and SAPS-3 score. The logistic regression analysis was then performed on the following subgroups; OHCA with asystole/PEA as primary rhythm, OHCA with ventricular fibrillation or ventricular tachycardia (VF/VT) as primary rhythm and patients fulfilling the criteria of the initial randomised trials (i.e. witnessed cases with VF/VT as first rhythm, age 18–75 years, presumed cardiac cause, EMS response times $<$15 min — the "HACA" criteria).[4] A p value $<$ 0.05 was considered significant.

In addition to the multivariate logistic regression we performed a propensity score matching. We used 1:1 nearest neighbour matching with a caliper width of 0.2 to match cases of TTM33 and TTM36. To optimize balance between the groups we remade the matching procedure until all standardized mean difference was below 0.1. We included the same variables in the propensity score calculation as in

the multivariate logistic regression and used conditional logistic regression to test differences in survival. All statistical analysis was performed using R software version 3.5.1.

Results

A total of 4092 patients were found in SIR. Of these a total of 2899 OHCA patients were included in the study for comparison for primary outcome. Of those, 1402 OHCA patients (48%) received treatment with therapeutic hypothermia and after excluding for missing variables there were finally 1038 patients for analysis, 755 in the TTM33 and 283 in the TTM36 group (Fig. 1).

Baseline characteristics

Baseline characteristics for both groups are reported in Table 1. We found significant differences in the EMS response time (4 vs. 5 min, $p < 0.001$), SAPS-3 score (72.7 vs. 69.9, $p < 0.001$) and the use of EEG monitoring (10% vs. 22%, $p < 0.001$) between the TTM33 and the TTM36 group, respectively.

Change of treatment protocol and adherence to treatment

After the TTM trial, the proportions of ICUs adopting TTM36 increased rapidly (Supplementary Fig. S1). By the end of the study period only one of 69 ICUs reporting to SIR still used TTM33 after OHCA. During

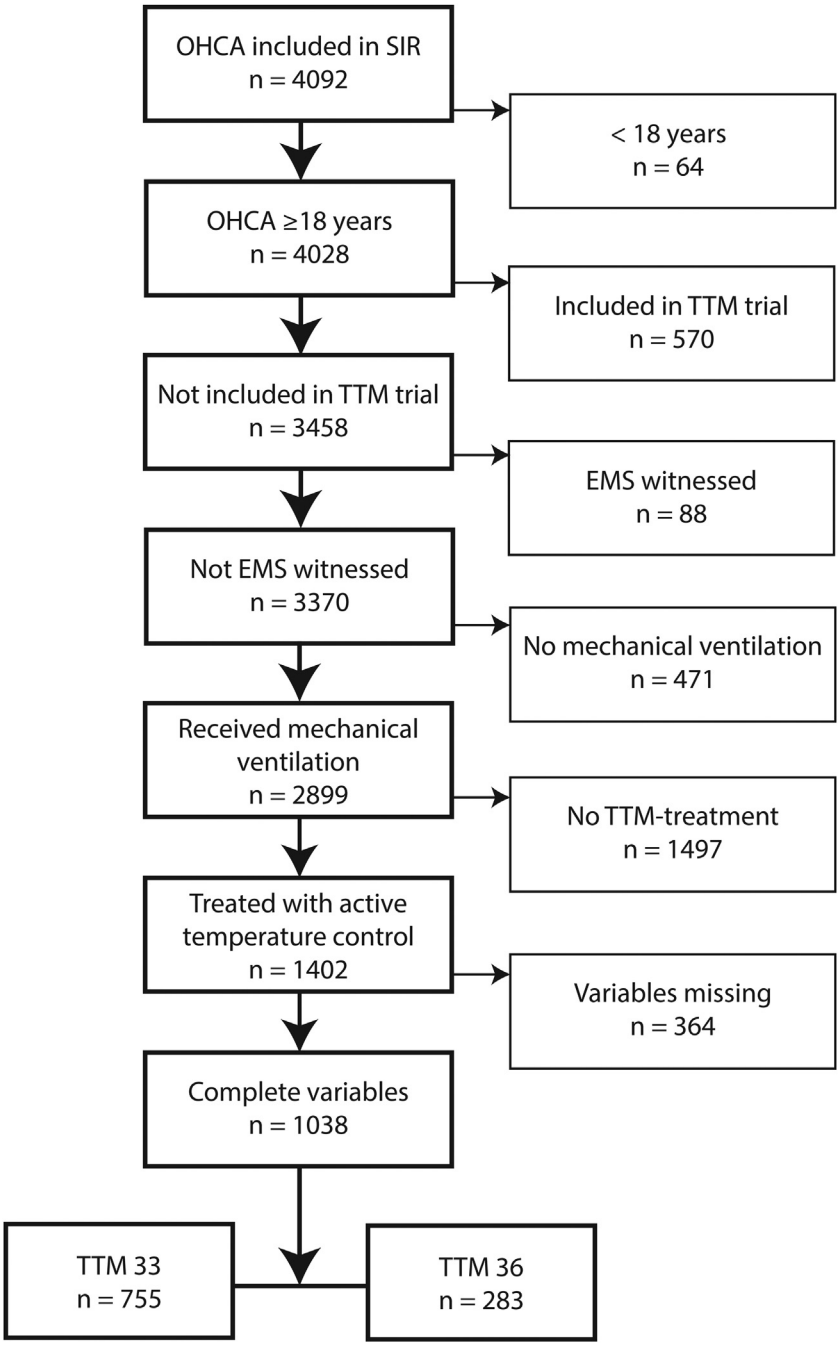

Fig. 1 – Inclusion and exclusion of patients.

Table 1 – Comparison of arrest and patient characteristics for OHCA patients admitted to ICU and registered in SIR and treated with TTM 33 and TTM 36.

Patient characteristics	TTM33	TTM36	p
Total number	755	283	
Gender female (%)	178 (23.6)	77 (27.2)	0.259
Witnessed (%)	611 (80.9)	227 (80.2)	0.864
Bystander CPR (%)	529 (70.1)	212 (74.9)	0.144
VF/VT (%)	492 (65.2)	181 (64.0)	0.772
Age (median [IQR])	66.00 [56.00, 74.00]	66.00 [57.00, 73.00]	0.577
Cardiac cause (%)	535 (75.5)	207 (74.5)	0.807
Location at home (%)	423 (56.0)	169 (59.7)	0.318
EMS response time (median [IQR])	4.00 [1.00, 6.00]	5.00 [1.00, 7.00]	<0.001
Survival 30 days (%)	356 (47.2)	135 (47.7)	0.929
Survival 6 months (%)	356 (47.2)	134 (47.3)	1.000
SAPS3 score (mean (sd))	72.68 (11.51)	69.99 (12.21)	<0.001
pH minimal (mean (sd))	7.21 (0.16)	7.22 (0.16)	0.458
PaO_2 (mean (sd))	20.03 (28.16)	21.66 (39.65)	0.469
Temperature maximum (mean (sd))	35.27 (1.36)	35.48 (1.16)	0.025
FiO_2 (mean (sd))	59.93 (22.37)	61.63 (21.32)	0.302
CPR at ICU (%)	12 (1.6)	4 (1.4)	1.000
Dialysis (%)	13 (1.7)	8 (2.8)	0.380
EEG (%)	73 (9.7)	59 (20.8)	<0.001
ECMO (%)	0 (0.0)	0 (0.0)	NA
Charlson comorbidity index cathegory (%)			0.182
0	511 (67.7)	204 (72.1)	
1–3	212 (28.1)	64 (22.6)	
4	32 (4.2)	15 (5.3)	

this period, the proportion of OHCA patients with initial rhythm VT/VF receiving TTM after hospital admission decreased from 70.5% in 2013 to 54.5% in 2015 (p for trend <0.001) (Fig. 2). For OHCA patients with initial rhythm Asystole/PEA the decrease was from 41,3% in 2013 to 26,7% in 2015 (p for trend <0.001) Supplementary Fig. S2).

Outcomes

Crude outcome data is shown in Table 1 and outcome data from the multivariate logistic regression and after propensity score matching are shown in Fig. 3 (details of propensity score matching are found in

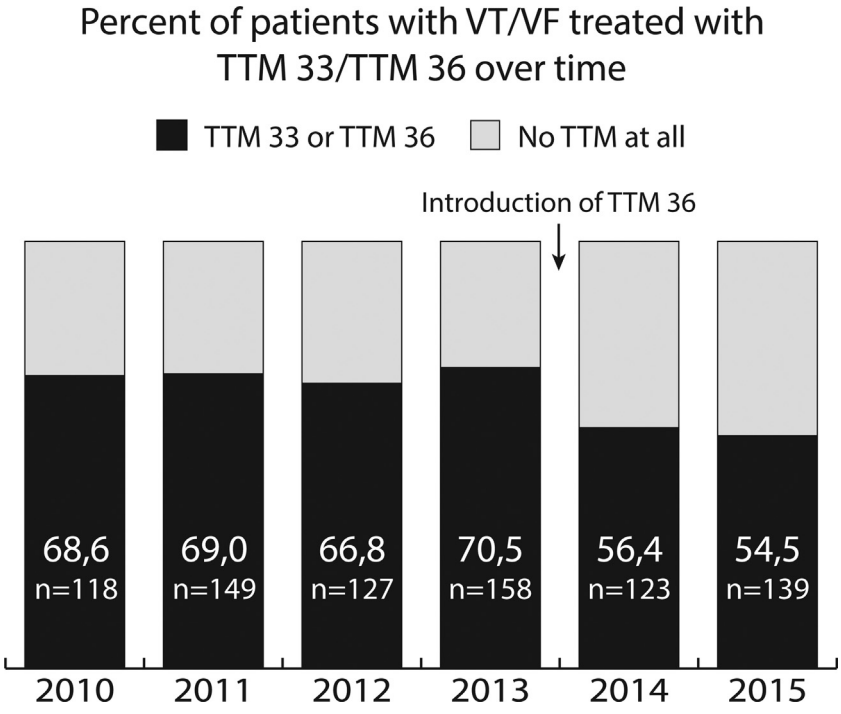

Fig. 2 – Percentage of out-of-hospital cardiac arrests patients with initial rhythm VT/VF treated with therapeutic hypothermia (TTM 33 and TTM 36) in Sweden between 2010-2015. P for trend <0.001.

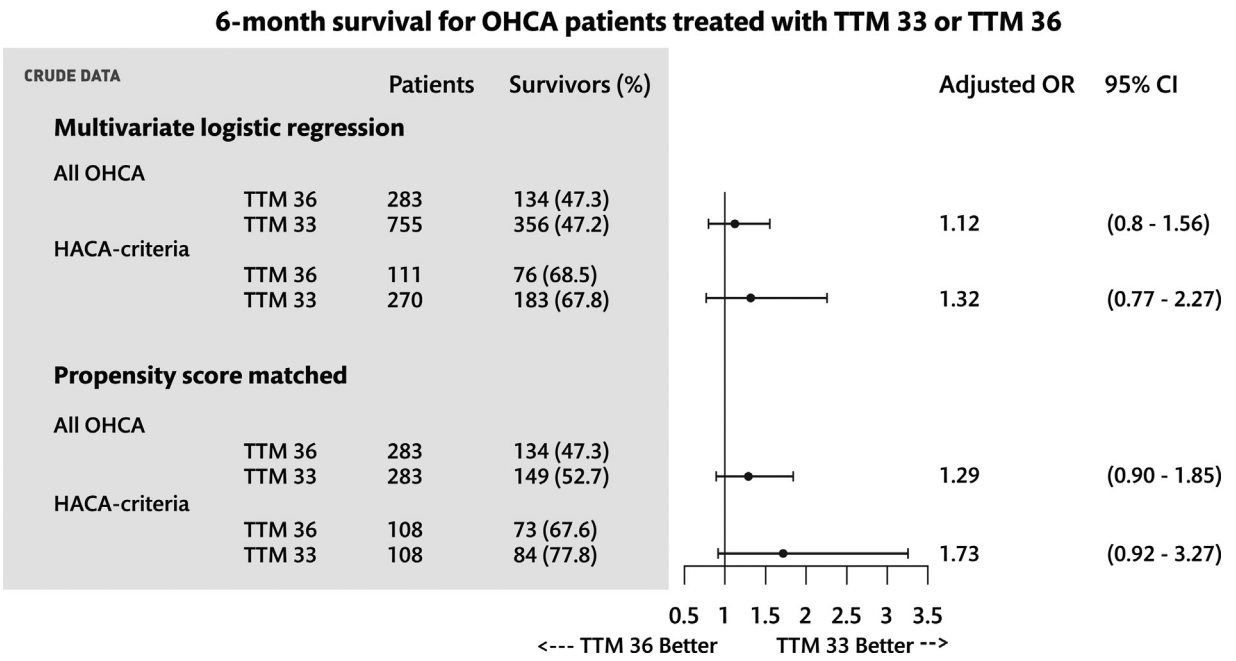

Fig. 3 – Forest plot for six-month survival for out-of-hospital cardiac arrests patients treated with therapeutic hypothermia (TTM 33 or TTM 36), both multivariate logistic regression and propensity score matched.

Supplementary Tables S1 and S2). There was no difference in six-month survival between TTM33 (356/755, 47.2 %) and TTM36 (134/283, 47.3%) groups (unadjusted OR 0.99 [0.75–1.30]). Similar results were found after adjustment for confounders (adjusted OR 1.12 [0.80–1.56]). In the propensity score matched analysis the six-months survival was 52.7 vs 47.3 %, OR 1.29 [0.90–1.85]). Analysis was also performed on the predefined subgroup of patients fulfilling the HACA criteria with no significant difference in six-month survival (Supplementary text).

In total 1497 patients received mechanical ventilation but no TTM, 1072 patients before the introduction of TTM36 and 425 patients after. Data on this patient population can be found in Supplementary Table S3.

Discussion

In this nationwide study we analysed the use of TTM and its potential effects on patients' outcome after the treatment shift from TTM33 to TTM36. The main findings of this study were that the proportion of patients receiving therapeutic hypothermia decreased by 28% after 2013 and that six-months survival was similar between the two TTM strategies.

In Sweden, a significant reduction was observed, from 70.5% to 54.5%, in the number of OHCA patients with initial rhythm VT/VF treated with therapeutic hypothermia since the shift of treatment protocols from TTM33 to TTM36. Current guidelines recommend treatment with therapeutic hypothermia between 32 °C and 36 °C in particular for OHCA with shockable rhythm and a decrease in treatment with therapeutic hypothermia indicates a lower adherence to these guidelines.[6,7] This is consistent with recent findings from USA databases.[14] It has been suggested that a TTM target of 36 °C could be perceived as "normothermia" or as a strategy aimed at avoiding fever and thereby leads to fewer active measures being taken to control temperature in this setting.[8] In addition, some clinicians may have misinterpreted the results from the TTM-trial as an indication of abandoning temperature management after cardiac arrest altogether. Nevertheless, as also stated by the authors of the TTM-trial,[15] this study did not show a benefit of avoiding fever, as a "no-intervention" group was not included, and temperature management should remain the cornerstone of clinical management of OHCA patients.

This study could not show any significant difference in survival but one may argue that the study was underpowered to detect any clinically relevant and several studies point in a similar direction. A recent study involving 45 935 patients in the US showed a decline in the use of therapeutic hypothermia and a significant trend of decreased overall risk-adjusted patient survival from 36.9% in 2013, 37.5% in 2014, 34.8% in 2015, to 34.3% in 2016 ($p < 0.001$ for trend).[14] However, a mediation analysis showed that the decline in use of therapeutic hypothermia was not associated with declined patient survival. In a small retrospective study which include consecutive OHCA patients with an initial shockable rhythm, the shift from TTM33 to TTM36 was associated with less patients receiving therapeutic hypothermia and less time spent at target temperature; these changes were associated with a reduction of survival from 71% to 58%.[8] In a before-after study, TTM36 was associated with less shivering and post-TTM fever than TTM33, with a hospital survival of 58% for TTM33 vs. 52% for TTM36, $p = 0.49$.[16] In a recent study evaluating a large database (n = 6254), an increase in mean body temperature over 33.80 ± 1.71 °C to 34.70 ± 1.39 °C was observed after the publication of the TTM-trial, with also a 0.6% increase in hospital mortality rate per year.[17]

None of the above-mentioned studies evaluated neurological recovery among survivors and unfortunately none of the registries we used have valuable information in regard to neurological recovery among survivors due to a lot of missing data. Neurological function

assessment can therefore not be reported within this study and as a proxy to neurological outcome we therefore chose 6-month survival. There is a correlation between good neurologic function and long term survival[18] but in the initial studies on therapeutic hypothermia[3,4] the difference in neurologic function was bigger between the groups as compared to that of survival. It could be speculated that if neurologic function had been included a more significant difference between groups may have been observed.

Several limitations of this study must be considered. A retrospective observational design was used and therefore specific causes for the changes observed cannot be given. Due to the retrospective design, there are variables in the intensive care treatment which were not measured but which could have an impact on the reported outcomes. We did for example not have data on the percentage of patients receiving coronary angiography. We also identified treatment with therapeutic hypothermia as reported by the clinicians in the registry and the differences observed could therefore be a result of differences in registry coding. As we did not have any way of controlling the actual temperature received by the patients this study focus is on a hospital level and not on a patient level. Furthermore, despite the information from the ICUs provided a specific date for change in practise there was no way to ensure what temperature level that was actually used. Because patients included in the TTM-trial[5] could treatment with both 33 °C and 36 °C at the same hospital during the same time, these patients had to be excluded. As patients in randomised trials tend to be healthier this could have biased our results.

Conclusions

In this nationwide study on OHCA, the proportion of patients receiving therapeutic hypothermia significantly decreased following the shift from TTM33 to TTM36. Although this study could not demonstrate any significant difference in overall six-month survival following this change, the decline conflicts with current guidelines and warrants further follow up studies.

Sources of funding

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Conflicts of interest

We declare no conflicts of interest in regard of finance or other conflicting circumstances.

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All persons who have made substantial contributions are mentioned in the list of authors.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.08.029.

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