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Hypothermic to ischaemic ratio and mortality in post cardiac arrest patients

Short title: Hypothermic to ischaemic ratio after cardiac arrest

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Conflicts of interest:

Markus Skrifvars reports having received a research grant from GE Healthcare, travel reimbursements and lecture fees from BARD Medical. CS reports having received travel reimbursements and speaker fees from BD BARD and Zoll GmbH, as well as honorarium for consultancy from BD BARD, Benechill and Sedana Medical. Anders Grejs and Anni Jeppesen reports having received lecture fees from Novartis. All other authors report that they have no conflicts of interest.

Abstract

Background:

We studied associations between ischemia and hypothermia duration i.e. the hypothermic to ischaemic ratio (H/I ratio), with mortality in patients included in a trial on two durations of targeted temperature management (TTM) at 33°C.

Methods:

The TTH48 (NCT01689077) trial compared 24 and 48 hours of TTM in patients after cardiac arrest. We calculated the hypothermia time from return of spontaneous circulation (ROSC) until the patient reached 37°C after TTM and the ischemic time from CA to ROSC. We compared continuous variables with the Mann-Whitney U test. Using COX regression we studied the independent association of the logarithmically transformed H/I ratio and time to death as well as

interaction between time to ROSC, hypothermia duration and intervention group. We visualized variables predictive ability with receiver operating characteristic curve analysis.

Results:

Of 338 patients, 237 (70%) survived six months. The H/I ratio was 155 (IQR 111-238) in survivors and 114 (IQR 80-169) in non-survivors (p<0.001). In a Cox regression model including factors associated with outcome in univariate analysis, the logarithmically transformed H/I ratio was a significant predictor of outcome (hazard ratio 0.52 (0.37-0.72, p=0.001). After removing an outlier we found no interaction between time to ROSC and intervention group (p=0.55) or hypothermia duration in quartiles (p=0.07) with mortality. There was no significant difference in the area under the curve (AUC) between time to ROSC and H/I ratio (ΔAUC 0.03 95% CI -0.006-0.07, p= 0.10).

Conclusions:

We did not find any consistent evidence of a modification of the effect of TTM based on ischemia duration.

Editorial Comment:

In this sub-study of the TTH48 trial, a trial which compared 24 to 48 hours of target temperature management (TTM) at 33˚C in unconscious patients following out-of-hospital cardiac arrest, the authors investigated the interactions between duration of target temperature management and the duration of the hypoxic-ischaemic insult (hypothermia to ischaemia duration ratio, H/I). While the H/I was independently associated with neurological outcome and survival at six months following the cardiac arrest, no modifying effects of TTM or duration were found. The time to return of spontaneous circulation remains of paramount importance for the outcome following cardiac arrest.

Introduction

The long-term prognosis of unconscious out-of-hospital cardiac arrest (OHCA) patients have improved significantly in many parts of the world over the last decades[1]. Although general progress in prehospital care with shorter response times and better bystander cardiopulmonary

resuscitation (CPR) have played crucial roles, active intensive care unit (ICU) treatment with targeted temperature management (TTM) and delayed limitation of life-sustaining therapies based on multimodal prognostication algorithms have also been important contributors to the noted improvement[1]. Many aspects concerning TTM implementation remain, however, under debate. While aiming for a target temperature of 36°C for 24h appeared to produce similar benefits as 33°C[2], the effects of different lengths of cooling on patients' outcome after OHCA are unknown. However in the TTH48 trial[3], a multicenter randomized study, outcomes were similar in the prolonged (48h) and standard (24h) TTM treatment.

TTM of different depth and length may work differently in various subgroups of patients with anoxic brain injury after OHCA[4]. Several observational studies have indicated an interaction between the severity of anoxic injury and the effect of TTM [5,6], but there are also data suggesting the opposite[7]. Kjaergaard et al. found that time to return of spontaneous circulation (ROSC) remained a significant predictor of mortality, but that depth of cooling did not seem to influence this relationship[8]. Interactions between anoxic injury and TTM duration has not been studied in the same detail. Sawyer et al. have proposed a new and more specific way of testing such interactions by calculating the hypothermic to ischemic ratio (H/I) ratio; in one retrospective study, this ratio was a good predictor of survival to hospital discharge[9]. This concept, however, needs further validation in independent samples, especially among patients treated with a larger variation in TTM duration. Therefore we aimed to assess the H/I ratio in the TTH48 cohort. We hypothesized that the H/I ratio would be associated with mortality as well as neurological outcome at six months.

METHODS

Study population and setting

This is a post-hoc analysis of the TTH48 trial (NCT01689077) comparing 48 and 24 hours of TTM at 33°C in patients treated in the ICU following cardiac arrest. The study protocol and the statistical analysis plans have been published previously[10,11]. The study plan received ethical approval at all sites, and the study was conducted in accordance with the Declaration of Helsinki[3].

In the study, we randomized 352 unconscious OHCA patients to treatment with either 48 or 24 hours of TTM at 33°C in 10 European ICUs. The inclusion criteria were age between 18 and 80

years, sustained ROSC for more than 20 minutes (prior to randomization) and a Glasgow Coma Scale score of less than 8. The exclusion criteria included time to ROSC longer than 60 minutes, cardiac arrest due to a non-cardiac cause, in-hospital cardiac arrest, terminal disease or a do-not-resuscitate order, severe coagulopathy, unwitnessed OHCA with asystole as the initial rhythm, time from cardiac arrest to initiation of cooling > 240 minutes, neurological disease with cognitive impairment, persistent cardiogenic shock, systolic blood pressure less than 80 mmHg, acute stroke or intracerebral bleeding and acute coronary bypass surgery. Patients were screened during the first day in the ICU and could be included until 23 hours from reaching target temperature.

Induction of hypothermia, in some patients, included cold fluids administered either in the pre-hospital setting or outside the hospital. Core temperature was measured in the bladder, rectum, oesophagus or with intravascular probes. Hypothermia was maintained with invasive or surface cooling devices. The protocol mandated rewarming with a rate of 0.5°C until a temperature of 37 degrees had been reached. In case of severe adverse events, such as a recurring cardiac arrest, patients could be rewarmed early to 36°C as per the treating clinician.

Data collection and calculation of ischaemia and hypothermia time

The ischemia time was calculated from the start of the arrest to ROSC (min). In the case of an unwitnessed arrest the time of ischemia was calculated from the call to the dispatch center. The collection of temperatures from patients varied between centers during the ICU stay. We identified the exact time when the patient reached 37°C after rewarming. Thus, we did not use a standard time based on treatment group and suggested rewarming rate. As in the primary study on the H/I ratio we defined the total hypothermia time as the time from ROSC to target temperature, total time at target temperature and the time from end of the hypothermia treatment until rewarming when the patient reached 37°C (min)[9]. The H/I ratio was calculated as the ratio of the hypothermia time divided by the ischemia time. We a priori decided to examine and visualize the association between the H/I ratio and outcome by dividing H/I into four groups; less than 50, 50-100, 100-200 and higher than 200. We also conducted additional analysis using intervention group (48 or 24 hours) as a measure of hypothermia duration.

Severity of illness measures

We calculated the OHCA score as a measure of the severity of the cardiac arrest and resuscitation. The OHCA score includes patient age, initial rhythm, the no-flow and low-flow intervals as well as admission lactate and creatinine. The OHCA score has been found to be a fairly accurate predictor of good neurological outcome at hospital discharge in cardiac arrest patients[12].

Outcomes

The primary outcome was time to death until 180 days. Secondary outcomes were survival status at 180 days as well as good neurological outcome determined by blinded assessors at six months from the arrest. Good neurological outcome was defined as cerebral performance category (CPC) of 1 or 2 and a poor outcome as a CPC of 3 to 5[13].

Statistical analysis

The statistical analysis plan was planned a priori but changed with additional analysis undertaken during the editorial review process. Categorical data are presented as counts and percentages and compared using a chi-square test. Continuous data are presented with medians including interquartile ranges in parentheses and compared using the Mann-Whitney U test. We explored the linearity of the continuous variables time to ROSC and hypothermia duration with fit plots and divided both variables into quartiles. We used COX regression and report results as hazard ratios (HR) with corresponding 95% confidence intervals (95% CI). In a primary analysis we entered into the COX regression model covariates from the univariate analysis and the H/I ratio. As the time to ROSC is the denominator in the H/I ratio, to avoid collinearity issues, these variables could not be simultaneously included in the same model. We investigated the relationship between survival and the H/I ratio, in four COX regression models with different a priori defined variable selection:

1. The primary model included all patient-specific and event-specific variables that had a p-value less than 0.1 in the univariate analysis.
2. The second model included our pre-defined model used in the original TTH48 study including trial site, age, gender, shockable or non-shockable rhythm, bystander-initiated life support, treatment group and the logarithmic conversion of the H/I ratio.

3. The third model included predictors used in modeling in the original pilot study on the H/I ratio[9] e.g. patient gender and age, whether the arrest was witnessed or not, whether the patient received bystander-initiated life support, time to reaching target temperature, admission temperature and the logarithmic conversion of the H/I ratio[9].
4. The fourth model included the OHCA score and the logarithmic conversion of the H/I ratio.

The hypothermia/ischemia ratio was logarithmically transformed for the multivariate analysis[9]. To further explore the relationship between time to ROSC and hypothermia time (in quartiles) we tested interactions between these with time to death and the likelihood of good neurological outcome at six months, as well as treatment group (24 or 48 hour TTM). These analysis were repeated excluding significant outliers (Time to ROSC exceeding 120 minutes). For the multivariate model we also checked the collinearity of all variables included in the models by calculating the variance inflation factor (VIF) and determining variable tolerance. We also visualized the diagnostic accuracy of time to ROSC, hypothermia time and the H/I ratio with receiver operating characteristic curves (ROC) and compared the area under the curve (AUC) assuming equivalence as suggested by Delong et al.[14] A p-value of less than 0.05 was considered significant in the main analysis. As this was mainly an exploratory study we did not adjust the p-values for multiple comparisons. The analyses were conducted using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp.), ANALYZE-IT (Analyse-it Software, Leeds, United Kingdom) and GraphPad Prism 7 (GraphPad Software, San Diego, USA).

RESULTS

Included patients

The study included 352 patients in whom data on long-term neurological outcome was available in 351 patients. In three patients, the time to ROSC was missing and in 10 patients the exact time when the patient reached 37°C was unavailable. Thus, 338 patients were included in the overall analysis and due to missing covariates 331 in the multivariable analysis (Figure 1). In addition a per protocol analysis were conducted in 319 patients and interaction analysis in 330 patients (excluding a patient with a long time to ROSC) (Figure 1). Of the 338 patients 101 (30%) had died before six months. Of those who died, 51 (50%) died while in the ICU, 26 (26%) elsewhere in the hospital after ICU discharge and 24 after hospital discharge (25%). A total of 226 (67%) patients were alive with good neurological outcome at six months (one patient was lost to follow-up but was known to be alive). The main differences between the survivors and non-survivors are shown in Table 1.

Time to ROSC and hypothermia time and outcome

Time to ROSC was available in 349 patients. The mean time to ROSC was significantly lower in survivors (median 19, IQR 15-25) than non-survivors (median 26, IQR 20-36) ($p<0.001$) (Figure 2A). A similar difference was observed in patients with good neurological outcome (median 19, IQR 15-25) when compared to those with a poor outcome (median 27, IQR 20-37) ($p<0.001$) (Figure 2A). We identified a linear relationship between time to ROSC and outcome as visualized with a fit plot (Supplementary Figure 1A).

The total hypothermia time was available in 338 patients. There was no difference in the total hypothermia time between survivors (median 3420 min IQR 2328-3786) and non-survivors (median 2615 min IQR 2310-3786) ($p=0.39$) (Figure 2B). Similarly, there was no difference in total hypothermia time between those with a good neurological outcome (median 3420 min, IQR 2338-3786) compared to those with a poor outcome (median 2638 min, IQR 2314-3803) ($p=0.42$) (Figure 2B). Visualized with a fit plot we did not find any linear relationship between hypothermia

time and outcome as visualized with a fit plot (Supplementary Figure 1B). Therefore, we used hypothermia time divided into quartiles in the multivariable analysis interaction analysis.

Hypothermic to ischaemic ratio

In all 338 patients, there was enough data enabling the calculation of the H/I ratio. The H/I ratio was greater in survivors (median 155 IQR 111-238) than non-survivors (median 114 IQR 80-169) (p<0.001) (Figure 2C). Similar findings were observed in patients with a good neurological outcome (median 158 IQR 116-243) when compared to those with a poor outcome (median 112 IQR 84-162) (p<0.001) (Figure 2C). A scatterplot showing time to ROSC and total hypothermia dose indexed by survival is shown in Figure 3.

Multivariate model of time to death and neurological outcome.

Using COX regression analysis, several factors were associated with time to death in the first multivariate model (Table 2). The adjusted HR for the logarithmic transformation of the H/I was 0.52 (95% CI 0.37-0.72) (p<0.001). In an analysis including only the per protocol treated patients and excluding a significant outlier (n=318), the corresponding HR was 0.56 (95% CI 0.38-0.83, p=0.004).

The additional models including analyses of only per protocol treated patients yielded comparable results (Supplementary Table 1 and 2). In a model adjusting for the OHCA-score the HR for time to death was 0.6 (95% CI 0.4-0.9, p=0.01). The logarithmic transformation of the H/I ratio was associated with neurological outcome at six months in model 1 (OR 2.5 95% CI 1.5-4.2, p<0.001). The other conducted multivariable models resulted in similar results (data not shown).

Interaction tests between time to ROSC, duration of hypothermia and treatment group

We did not find any significant interaction with time to ROSC and hypothermia duration as quartiles and time to mortality using a COX model excluding a clear outlier (Time to ROSC>120 minutes) (0.07). Further on we did not any evidence of interaction in a similar model with time to ROSC and intervention group (p=0.55). We also conducted the same analysis in the per protocol treated patients and found no significant interaction (p=0.12 and 0.63). We also repeated the

analyses with logarithmic conversion of both variables as well as variable sizes of ranked groups of hypothermia duration and found similar results. Finally, we found that with a model for predicting good outcome at six months including time to ROSC and hypothermia duration in quartiles and treatment group, showed no significant interaction (p=0.591 and p=0.89 respectively).

The ROC curves of time to ROSC, hypothermia duration and the logarithmic conversion of the H/I ratio are depicted in Figure 4. There was no significant difference in the AUC between time ROSC and H/I ratio (ΔAUC 0.03 95% CI -0.006-0.07, p= 0.10).

Discussion

Main findings

In this secondary analysis of the TTH48 cohort [3], H/I ratio defined as the relationship between hypothermia duration relative to ischemia duration was associated with time to mortality and neurological outcome at six months. However, we did not observe any statistically significant interaction between time to ROSC and hypothermia duration or any improvement of outcome prediction accuracy with the H/I ratio compared to time to ROSC. Taken together these findings suggest that the association between the H/I ratio and outcome, is mostly the result of the strong association between time to ROSC and outcome. Whilst the limited sample size of this

study needs to be acknowledged, it remains unclear whether the effect of TTM on outcome may be optimized by titrating TTM duration based on ischemia duration remains unclear.

The use of TTM is recommended as standard practice in OHCA patients. The recommended target is 32-36°C and the duration should be at least 24 hours[15]. The TTH48 study was the first study that evaluated the feasibility, safety and effects on outcome of prolonged TTM (48 hour) in adults[3]. The study found that whilst TTM for 48 hours was safe, this did not result in significantly improved neurological outcome at six months. Survival and neurological outcome were numerically slightly higher in the 48 hour group, and while but not statistically significant, provide an impetus for further research on this topic[16]. One way forward would be to identify those patients who might benefit from prolonged TTM and focus future trials on such patients. The duration of the cardiac arrest is an important marker of outcome but this study suggests that it may not be an ideal variable in isolation for deciding on duration of TTM. Other factors such as quality of CPR may influence severity of the ischemic insult but thus far few studies have assessed whether the quality of CPR influences the severity of brain injury in the ICU[17]. Another option would be to use some admission marker of the severity of the ischaemic insult, such as the OHCA score[12].

As in many studies, we observed that patients who survived OHCA were more likely to be younger, have witnessed arrests, present with an initial shockable arrest rhythm and shorter time to ROSC. Importantly, there were no significant differences in initial temperature, time to target temperature, or total hypothermia duration among survivors and non-survivors in this cohort. A possible important modifiable factor regarding hypothermia time would be how rapid cooling initiation is initiated. Of note, the time from the arrest to target temperature was shorter in the TTH48 trial than in some other conducted TTM trials[2,18]. This has been tested using infusion of cold fluid boluses without improved outcome[19]. The use of cold fluids may not be optimal, since fairly large volumes may be required. This can potentially cause pulmonary oedema or even worsening circulatory shock in case of right heart failure, which is common after cardiac arrest[20]. Trans-nasal cooling has recently been shown to be feasible and safe in the pre-hospital setting and leads to rapid cooling[21]. Although the study did not result in a statistically significant difference in outcome in patients with a good neurologicalal outcome defined as a

CPC of 1 or 2, the proportion of patients with a CPC of 1 was higher in the group receiving intra-arrest cooling[22].

In this study, we calculated the length of hypothermia as the actual time until the patient achieved 37°C. Even though the protocol stipulated rewarming to 37°C, not all patients actually achieved the targeted rewarming temperature as stipulated by the protocol. It may be that patients with a more severe neurologicalal injury and with a concomitant infection rewarmed earlier due to a fever response[23]. Indeed there is very limited data on temperature management in TTM patients beyond 72 hours. One challenge regarding the hypothermia/ischemia ratio is the fact that it is a ratio, whereby either the numerator or denominator may carry the weight of its influence. There has been the reservation that the association between H/I ratio and outcome may largely be driven by the relationship of time to ROSC with outcome. Our results support this conclusion. It is likely that more refined means of identifying the patient with a high risk of brain injury and those without such risks are needed for optimization of TTM.

Strengths and limitations

This study has several strengths. This is the first time the H/I ratio is being tested in a patient sample randomized to different durations of cooling and with prospective data collection including granular details of patient-level TTM variables and variation in hypothermia duration. In addition the multicenter design increase the generalizability of our findings. In addition, we employed several statistical models that provided comparable results. Nonetheless some limitations need to be mentioned. Inherent to studies of cardiac arrest resuscitation that evaluate in-hospital treatments, our study is subject to inclusion and survivor bias. To be included in the parent trial and multivariable analyses, patients needed to survive long enough to have TTM initiated and survive long enough to receive ICU care, which may partly explain the high survival rates. There were few patients ultimately included in the trial with missing data or who were rewarmed early, and these patients were included in per protocol analysis. In addition as the H/I ratio is defined as the time from ROSC to the patient has reached 37°C after being rewarmed, a delay in initiating TTM would in fact increase the total hypothermia time. Nonetheless, it appears well founded not to delay the initiation of TTM in OHCA patients. We

tested for interactions between ischaemia and hypothermia duration and found no statistically significant interactions. It remains possible that this finding reflects insufficient study power[24].

Additionally, unmeasured confounders, such as smoking history, other in-patient treatments, or other reasons for death or neurological impairment before 6 months, may also have a large influence on our primary and secondary outcome. Larger prospective clinical trials on variable hypothermia duration based on ischemia intervals complemented with other measures of illness severity are needed to further investigate the possibility of more individualized TTM within post resuscitation care. Finally, the quality of the evidence supporting the use of TTM in cardiac arrest patients is thus far based on low level of evidence and further large scale studies are needed[25].

Conclusions

The H/I ratio was independently associated with time to death and neurological outcome in TTM treated OHCA patients, but this appeared mainly to be the result of the strong association between time to ROSC and outcome. We did not find any consistent evidence of a modification of the effect of TTM by intervention group or the actual hypothermia duration.

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Figure legends

FIGURE 1 Flow chart of the included patients in the main and sensitivity analysis.

FIGURE 2A Time to return of spontaneous circulation indexed by survival and good neurological outcome at six months.

FIGURE 2B Total hypothermia time indexed by survival and good neurological outcome at six months.

FIGURE 2C The hypothermic to ischemic ratio indexed by survival and good neurological outcome at six months.

FIGURE 3 Scatterplot depicting the relationship between ischemia time and total hypothermia time (time until patients reached 37°C) with mortality. The lines represent from left to right HI ratio 200, 100 and 50 respectively.

FIGURE 4 Receiver operating characteristic curve of time to return of spontaneous circulation, hypothermia duration and hypothermia to ischemia duration for predicting mortality at 180 days.

TABLE 1 Patient characteristics, factors at resuscitation and on admission indexed by survival at six months.

Baseline characteristics	**Survivors (n=237)**	**Non-survivors (n=101)**	**P-value**
Age (years)	59 (51-68)	66 (58-72)	<0.001
Male sex no. (%)	202 (85.2%)	78 (77.2%)	0.074
Weight (kg)†	85 (75-93)	85 (75-95)	0.758
Neurological function pre-arrest Normal (CPC 1) – no. (%) Some disability (CPC 2) – no. (%)	 230 (97%) 7 (3%)	 98 (97%) 3 (3%)	 0.993
Medical history – no. (%)1			
Previous myocardial infarction	35 (14.8%)	18 (18.2%)	0.443
Previous PCI or CABG	35 (14.8%)	19 (18.0%)	0.457
Previous cardiac arrest	2 (0.8%)	1 (1.0%)	0.896
Chronic heart failure (NYHA IV)	10 (4.2%)	8 (7.9%)	0.165
Chronic obstructive pulmonary disease	15 (6.3%)	8 (7.9%)	0.595
Liver cirrhosis	1 (0.4%)	2 (2.0%)	0.156
Chronic renal failure with dialysis	0 (0%)	1 (1%)	0.125
Diabetes mellitus	28 (11.9%)	33 (32.7%)	<0.001
Immunosuppression	0 (0%)	3 (3%)	0.008
Previous stroke	14 (5.9%)	12 (11.9%)	0.059
Cardiac arrest location – no. (%)			
Home	114 (48%)	69 (68%)	

Public place	108 (46%)	25 (25%)	0.001
Other out-of-hospital	15 (6%)	7 (7%)	
Arrest witnessed – no. (%)			
Bystander	206 (86.9%)	84 (83.2%)	0.496
EMS	13 (5.5%)	4 (8.9%)	
Unwitnessed	18 (7.6%)	8 (7.9%)	
Resuscitation factors			
Bystander initiated CPR, n (%)	207 (87.3%)	75 (74.3%)	0.003
Shockable rhythm, n (%)	221 (93.2%)	78 (77.2%)	<0.001
Time to basic life support (minutes)[1]	1 (0-2)	0 (0-2)	0.544
Time to advanced life support (minutes)[1]	8 (5-11)	9 (5-11)	0.202
Time to return of spontaneous circulation[2]	19 (15-25)	26 (20-34)	<0.001
Mechanical chest compression used, no. (%)	49 (20.9%)	34 (34.7%)	0.008
Prehospital treatment - no. (%)			
Epinephrine (yes)	129 (54.4%)	83 (82.2%)	<0.001
Amiodarone (yes)	96 (40.5%)	42 (41.6%)	0.854
Temperature variables on admission			
Temperature °C[3]	35.1 (34.4-35.8)	34.9 (34.0-35.6)	0.165
Time to target temperature	292 (229-390)	307 (214-393)	0.956

[1]Data missing in two patients

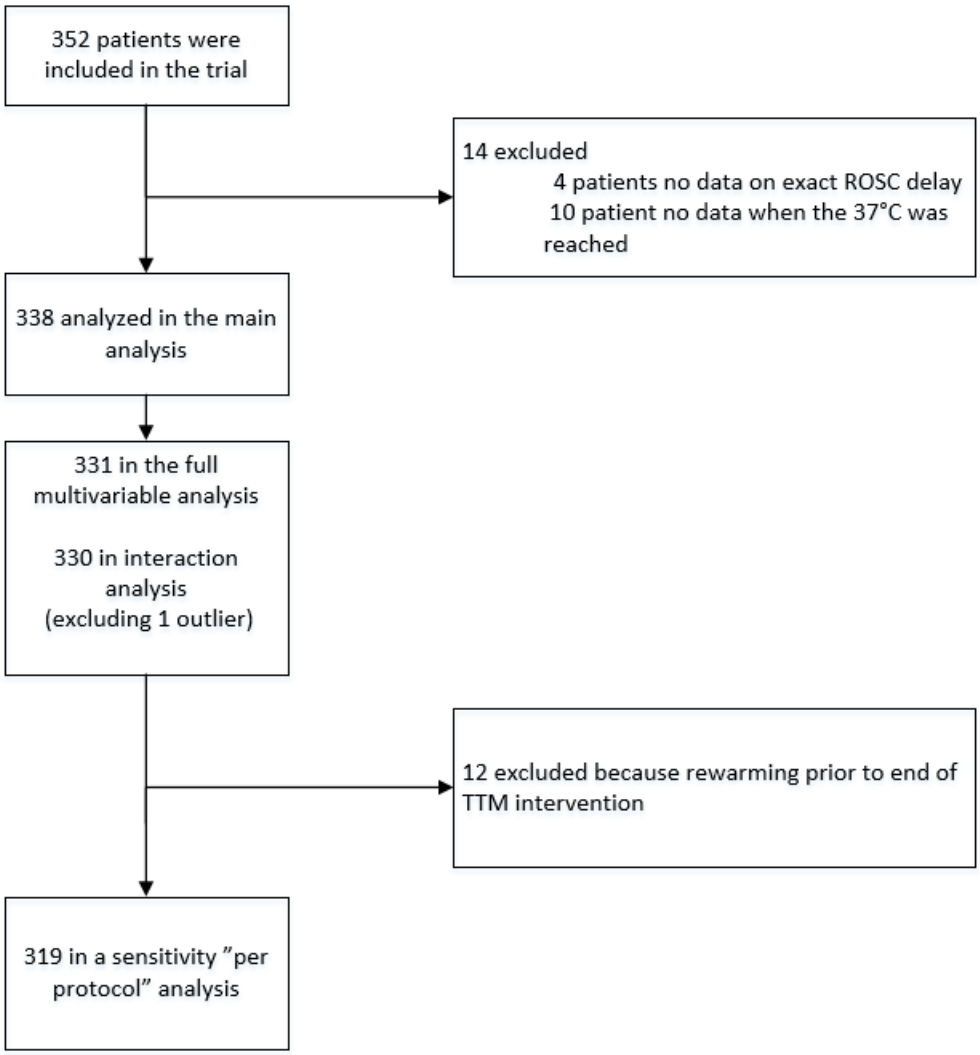
[2]Data missing in three patients

[3]Data missing in seven patients

TABLE 2 Univariate and Multivariate analysis of factors associated with time death.

Variable	**Univariate HR (95% CI)**	**p-value**	**Multivariate HR (95% CI)**	**p-value**
Age (per year increase)	1.05 (1.03-1.07)	<0.001	1.03 (1.01-1.06)	0.004
Male gender	0.66 (0.42-1.05)	0.08	0.70 (0.42-1.16)	0.17
Diabetes	2.68 (1.79-4.0)	<0.001	1.84 (1.17-2.94)	0.01
Immunosuppression	4.67 (1.48-14.76)	0.009	3.17 (0.85-11.83)	0.09
Previous stroke	1.71 (0.94-3.12)	0.08	1.49 (0.81-2.77)	0.20
Cardiac arrest at home	1.94 (1.29-2.91)	0.001	1.55 (0.98-2.45)	0.06
Bystander CPR	0.51 (0.33-0.78)	0.002	0.84 (0.51-1.4)	0.50
Shockable rhythm	0.35 (0.22-0.55)	<0.001	0.56 (0.34-0.92)	0.02
Mechanical chest compression used	1.89 (1.27-2.81)	0.002	1.4 (0.9-2.17)	0.14
Epinephrine used	3.29 (2.0-5.39)	<0.001	2.16 (1.26-3.7)	0.005
Coronary angiography	1.88 (1.22-2.9)	0.004	0.56 (0.35-0.91)	0.02
Log HI ratio	0.4 (0.31-0.55)	<0.001	0.52 (0.37-0.72)	<0.001

331 patients were included in this multivariable model. A HR lower than 1 denotes decreased mortality and a HR larger than 1 denotes increased mortality.



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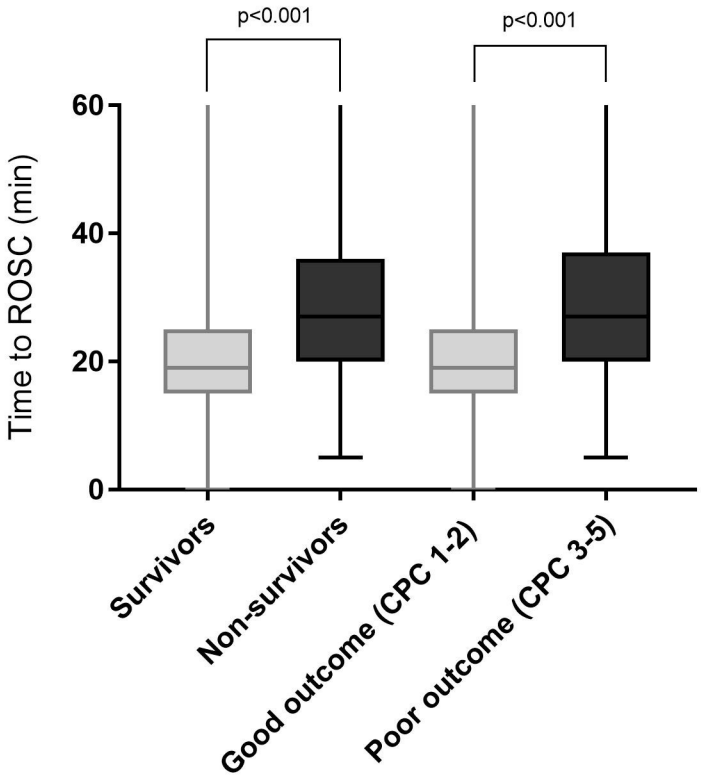

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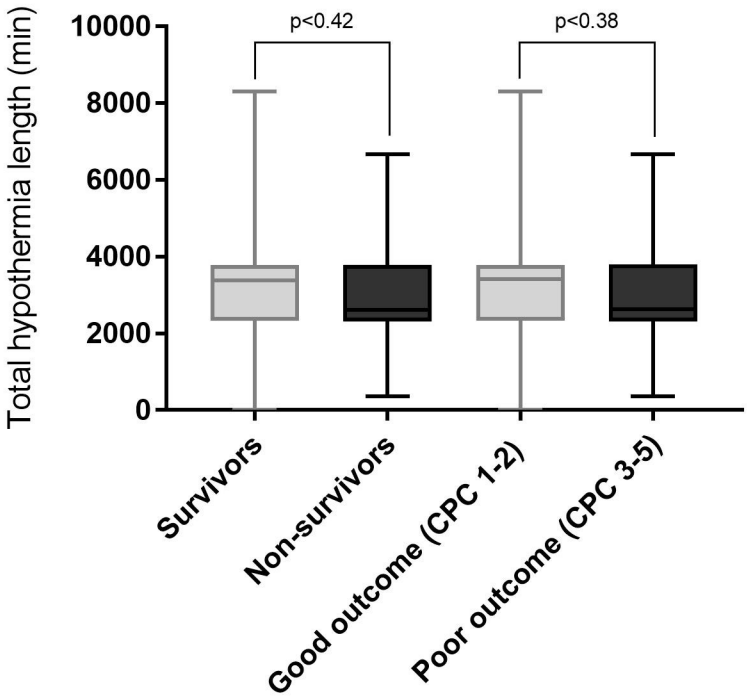

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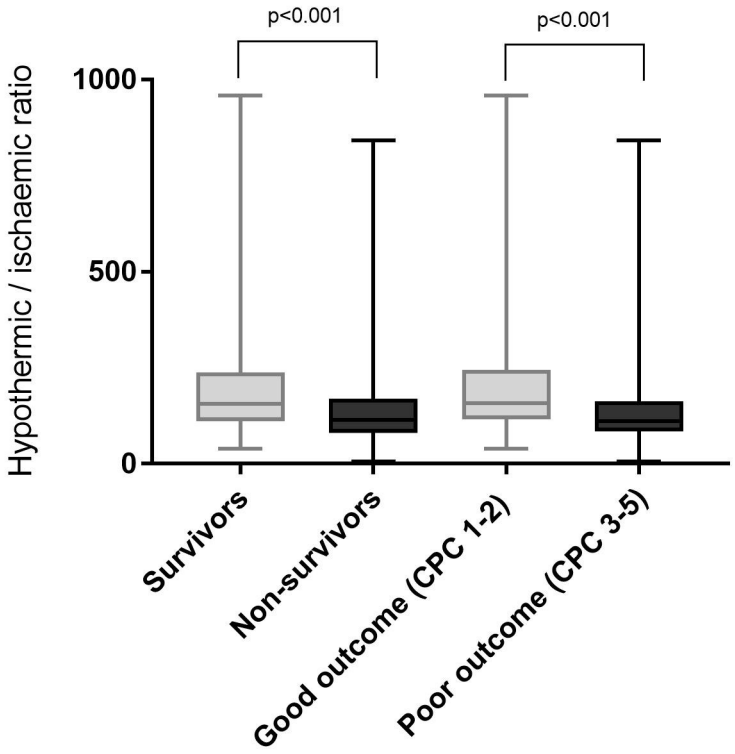

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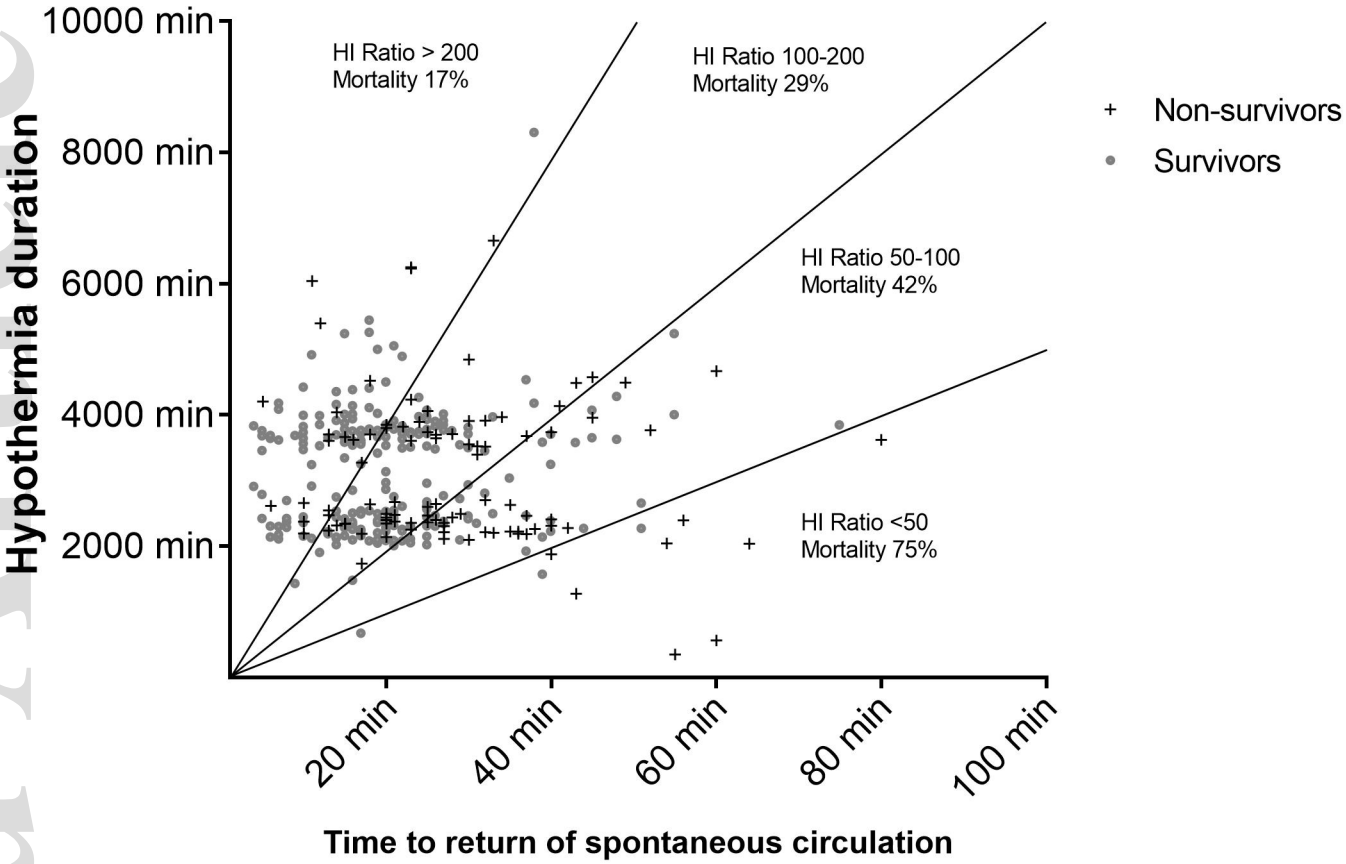

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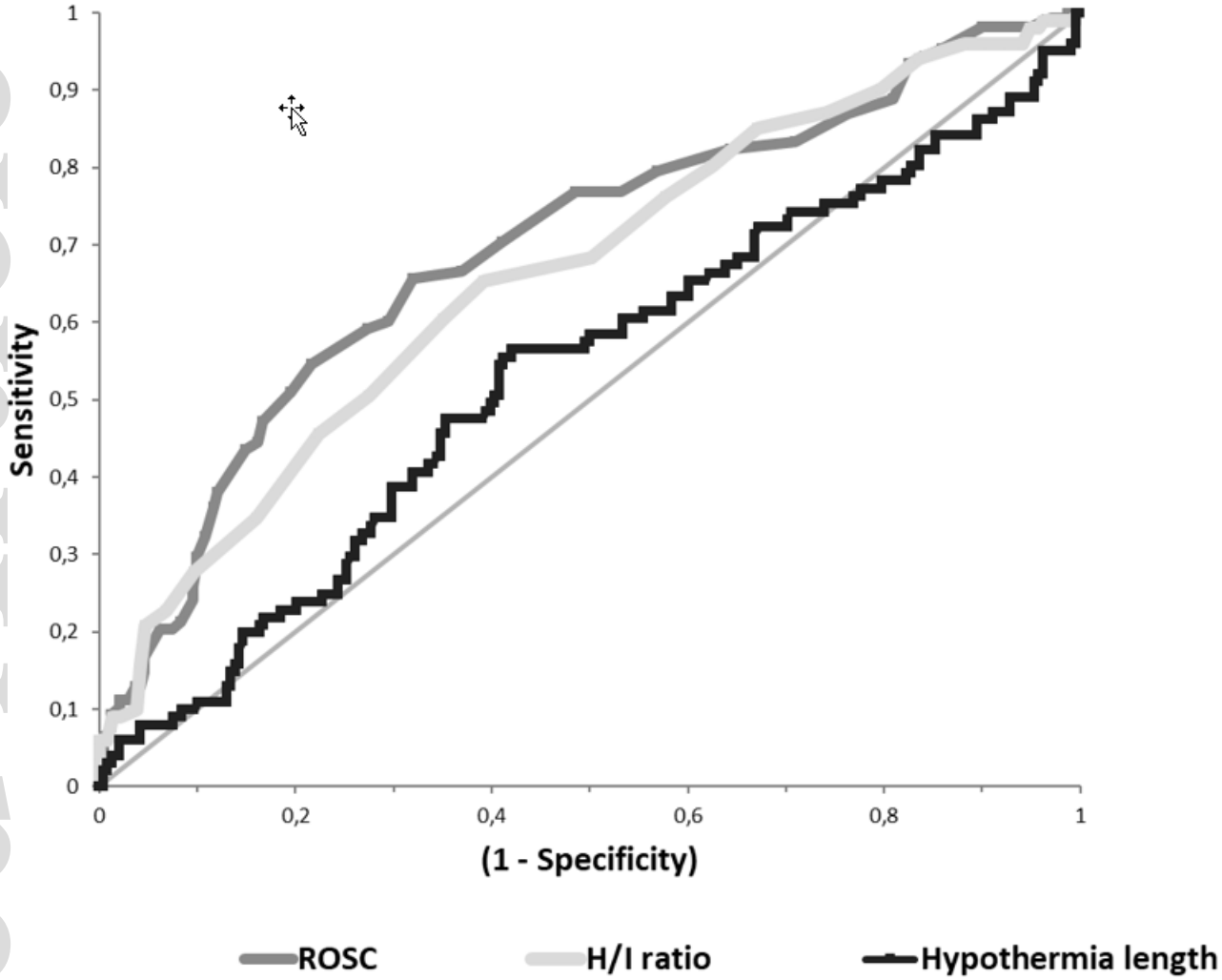

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