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Quality of Targeted Temperature Management and Outcome of out-of-hospital cardiac arrest patients:

A *post hoc* analysis of the TTH48 study

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Abstract

Background: Several studies have investigated the effectiveness of targeted temperature management (TTM) after out-of-hospital cardiac arrest (OHCA). However, there are not data on the quality of TTM provided to these patients and its association with outcome.

Methods: We performed a *post hoc* analysis of data from the TTH48 study (NCT01689077), which compared the effects of prolonged TTM at 33°C for 48 hours to standard 24-hour TTM on neurologic outcome (i.e. unfavorable neurological outcome, UO, was defined by Cerebral Performance Category of 3-5 at 6 months). Admission temperature, speed of cooling and rewarming rates were collected in each patient. Precision was assessed by measuring temperature variability (TV), i.e. the standard deviation (SD) of all temperature measurements in the cooling phase. Overcooling and overshoot were defined at least one measured temperature <32°C or >35°C during the cooling phase, respectively. Post-cooling fever was defined as a body temperature exceeding 38.5°C. A specific score, ranging from 1 to 9, was assessed to define the "quality of TTM".

Results: A total of 352 patients were analyzed in this study; of those, 175 (50%) were treated with TTM for 48 hours. Most of patients had a moderate quality of TTM (n=217; 62% - score 4-6), while 80 (23%) patients had a low quality of TTM (score 1-3) and only 52 (16%) a high quality of TTM (score 7-9). The proportion of patients with UO was similar between the different quality of TTM groups (p=0.90); similar results were observed for mortality. Although a shorter time from arrest to target temperature and a lower proportion of time outside the target ranges in the TTM 48-h than in the TTM 24-h group, quality of TTM was similar between groups. Also, the proportion of patients with UO was similar between the different quality of TTM groups when TTM 48-h and TTM 24-h were compared; similar results were also observed for mortality.

Conclusions: In this study, high quality of TTM was provided to a small proportion of patients. However, quality of TTM was not associated with patients' outcome. Prolonged TTM duration during 48 hours did not significantly affect the quality of TTM when compared to standard TTM 24-hour duration.

Introduction

Patients who are successfully rescued from out-of-hospital cardiac arrest (OHCA) are at high risk of death and severe neurological sequelae despite the intensity of therapies that are initiated after the admission to the Intensive Care Unit [1]. In order to improve the chances of survival and neurologic recovery, international guidelines recommend use of target temperature management (TTM) as the only available neuroprotective strategy to mitigate the development and extension of anoxic brain injuries occurring after reperfusion [2]. Nevertheless, the effectiveness of such intervention has been largely questioned and several issues have been raised on the optimal implementation of TTM in the clinical management of comatose OHCA survivors. As an example, current recommendations stated that target temperature during the cooling phase should be kept constant in a target between 32°C and 36°C [3, 4]; however, other TTM characteristics, such as the patients' selection, timing and duration of cooling, remain undefined. The Time-differentiated Therapeutic Hypothermia (TTH48) trial showed that prolonged duration (i.e. 48 hours) of TTM at 33°C after adult OHCA did not improve the proportion of patients achieving favorable neurological outcome when compared to the standard 24-hour duration [5].

Several clinical studies have suggested that deviations from the target temperature during TTM, such as overcooling, rewarming episodes and higher temperature variability during the cooling phase and post-TTM, may potentially influence brain function and reduce the neuroprotective effects of TTM [6-10]. Recently, the concept of "high-quality TTM" was proposed [11] as a way to increase the effectiveness of TTM after CA. Still, whether this optimized TTM delivery actually impacts on patients' outcome remains unknown. Moreover, there is lack of data on whether a prolonged TTM can provide a higher precision, slower rewarming and less post-TTM fever, which would result more frequently in "high quality TTM", when compared to standard TTM duration.

Thus, the primary aim of this study was to evaluate the quality of TTM provided into a randomized trial evaluating TTM in OHCA patients. Secondary outcomes included the association

of quality of TTM with neurological outcome (with the hypothesis the high quality of TTM would be associated with a better neurological outcome) and the differences in quality of TTM between 48-h and 24-h TTM duration (with the hypothesis that longer duration of TTM may be associated with a better TTM delivery).

Methods

Study design and population

This is a *post hoc* analysis of data from the Time-differentiated Therapeutic Hypothermia (TTH48) trial (NCT01689077), a multicenter, randomized clinical trial conducted in Europe, which compared whether prolonged TTM at 33°C for 48 hours results in better neurologic outcome compared with standard 24-hour duration [5]. The study protocol was approved by the Ethics Committees in each participating center, with written informed consent obtained from the next of kin or a legal surrogate before randomization. The study recruited 355 patients between February 2013 and June 2016 and demonstrated no significant difference in favorable neurologic outcome at 6 months for those treated during 48 or 24 hours (69% vs. 64%) of TTM.

Adult patients resuscitated from OHCA of a presumed cardiac cause, older than 17 years and younger than 80 years, with sustained return of spontaneous circulation for more than 20 consecutive minutes, and Glasgow Coma Scale (GCS) score less than 8, were included in the TTH48 trial. Exclusion criteria have been reported in the main manuscript [5]; for this study, we excluded those patients without recording of hourly body temperature over the study period and missing outcome. All patients were sedated and treated with invasive mechanical ventilation. Other aspects of patient management were decided by the attending physician according to standard local practices.

Targeted Temperature Management

During TTM, three periods were identified: 1) achievement of target temperature (time from initiation of cooling to first temperature < 34.0°C); 2) maintenance of target temperature (time from target temperature to first temperature ≥ 34.0°C); and 3) rewarming to 37.0 °C. Core temperature was mainly measured using urinary, esophageal or intravascular probes. Temperature was managed with either surface or intravascular methods [12], according to center preference, in combination with cold

fluids to initiate TTM and rapidly reach target temperature. After randomization, duration of cooling (i.e. 24 or 48 hours) was considered from the time core temperature was 34°C or lower. At the end of the 24-hour or 48-hour period, rewarming was performed at a maximal rate of 0.5°C/h until a core temperature of 37.0°C was reached. Sedation was discontinued at 37.0°C; the decision to keep devices on patients to avoid or minimize the occurrence of post-TTM fever according was performed according to local practices.

Targeted Temperature Management variables

The two study groups were assessed for: 1) time from arrest to target temperature (i.e. < 34.0°C); 2) time to target temperature (i.e. time from initiation of cooling to first body temperature < 34.0°C); 3) cooling rate (i.e. changes in temperature from initiation of cooling to first body temperature < 34.0°C, expressed as °C/h); 4) number of patients achieving the target temperature; 5) overcooling (i.e. at least one body temperature < 32.0°C); 6) time spent outside targets (i.e. target is within 32 and 34°C since the first body temperature < 34.0°C until the initiation of rewarming; time outside target is expressed as number of hours or the percentage of hours according to the duration of cooling); 7) overshoot (i.e. body temperature during cooling > 35.0°C; 8) rewarming rate (i.e. changes in temperature between the initiation of rewarming to the first temperature > 37.0°C, expressed as °C/h); 9) post-TTM fever (i.e. number of patients with at least one body temperature measurement after rewarming exceeding 38.0°C, until a maximum of 72 hours after normothermia). Precision was assessed by measuring temperature variability (TV), i.e. the standard deviation (SD) of all temperature measurements in the cooling phase (i.e. from first body temperature < 34.0°C to temperature > 34°C after the initiation of rewarming) [13]. To correct for duration and cooling and the number of available data on temperature, some of the TTM variables (i.e. overcooling, time spent outside targets, overshoot and precision) were calculated only on the first 24 hours for the two groups. No imputation for missing value was performed.

Quality of TTM assessment

Quality of TTM was quantified using a score which was arbitrarily developed for each of the main variables included considered (Appendix 1), varying from a minimum (i.e. very low quality) of 0 to a maximum of 9 (i.e. very high quality). Using this score, quality of TTM was therefore defined as "low" (i.e. score 0-3), "moderate" (i.e. score 4-6) and "high" (i.e. score 7-9).

Study outcomes

The quality of TTM (i.e. primary outcome) was analyzed as the proportion of patients for each item of the score as well as the proportion of patients receiving low, moderate and high quality of TTM. Unfavorable neurological outcome (UO) at 6 months was defined a Cerebral Performance Categories score (CPC) of 3-5 (i.e. CPC 1 = alert, able to work and lead a normal life; CPC 2 = moderate cerebral disability and sufficient cerebral function for part-time work; CPC 3 = severe cerebral disability, dependent on others, and impaired brain function; CPC 4 = coma and vegetative state; CPC 5 = dead or certified brain dead). The proportion of patients with UO across different quality of TTM categories was analyzed. Main adverse events were collected throughout the hospital stay and reported as defined in the main trial [5]. Hyperglycemia was defined as a blood glucose > 150 mg/dL; hypernatremia was defined as serum sodium > 145 mEq/L; hypokalemia was defined as a serum potassium < 3.5 mEq/L.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics 24.0 for Windows. Descriptive statistics were computed for all study variables. A Kolmogorov–Smirnov test was used, and histograms and normal-quantile plots were examined to verify the normality of distribution of

continuous variables. Data are presented as count (percentage) or median [25th–75th percentiles]. Differences between groups (i.e. 48-hour vs. 24-hour; low vs. moderate vs. high quality TTM) were assessed using a Fisher's exact test for categorical variables and a Wilcoxon rank test for continuous variables. Data from repeated measures were analyzed using a two-way Friedman ANOVA and differences at each time point explored by the Dunn's test. No multivariate regression analysis was performed to adjust outcome to predefined covariates (i.e. trial site, age, gender, initial cardiac arrest rhythm, time to return of spontaneous circulation, bystander-initiated life support, duration of cooling), as this was already performed in the main trial [5]. A $p < 0.05$ was considered as statistically significant.

Results

Study population

Of the 355 randomized to the trial, 3 were excluded because of lack of data on body temperature, leaving 352 (99%) patients for the final analysis. Of those, 175 (49%) were treated in 48-hours and 177 (51%) in 24-hour groups. The proportion of patients treated with intravascular catheter was similar between 48-hour and 24-hour groups (65% vs. 59%; p=0.22). Main characteristics of the study population are reported in Table 1. The number of patients with at least one adverse event was similar between groups (Supplemental Table 1).

Quality of TTM and neurological outcome

The number of patients within the different quality of TTM score are shown in Table 2; most of patients had a moderate quality of TTM (n=217; 62%), while 80 (23%) patients had a low quality of TTM and only 52 (16%) a high quality of TTM (Figure 1). The components of the score with the highest number of "low quality" value were rewarming rate (n=154, 44%) and post-TTM fever (n=204, 58%). The proportion of patients with UO was 29/80 (36%) in the low-quality group, 70/217 (32%) in the moderate quality group and 21/55 (38%) in the high-quality group (p=0.90 – Figure 2). Similar results were observed for mortality (25/80, 31% vs. 61/217, 28% vs. 21/55, 38%, respectively; p=0.34). Also, mortality and UO was similar across different quality of TTM ranges (Figure 3).

Quality of TTM and duration of cooling

Main characteristics of TTM are presented in Table 3, according to the duration of TTM. Time from arrest to target (≤34°C) was significantly shorter for patients treated with TTM for 48 hours (5.2 [3.9-6.9] vs. 6.0 [4.4-8.4] hours, p=0.02), despite similar body temperature on admission

(35.2 [34.3-35.8] vs. 35.0 [34.4-35.7] °C; p=0.44) than the 24-hour group. Cooling rate was higher, although not statistically significant, in the 48-hour when compared to the 24-hour group (0.5 [0.2-0.8] vs. 0.4 [0.2-0.6] °/hours, p=0.11). Temperature variability was similar between the 48-hour and 24-hour TTM groups (0.66 [0.46-0.90] °C vs. 0.60 [0.49-0.90] °C; p=0.59), as was rewarming rate (0.34 [0.24-0.46] °C/hour vs. 0.35 [0.22-0.47] °C/hour; p=0.96). The number of patients with overcooling (11% vs. 14%) or overshoot (60% vs. 55%) was also similar between groups. However, the proportion of time outside the target ranges was lower in the 48-hour than in the 24-hour group (13 [5-32] % vs. 18 [8-37] %, respectively - p=0.049). The proportion of patients with fever was significantly lower in the 48-hour group (52% vs. 64%; p=0.03). When analyzing only the first 24 hours of cooling, the hours outside TTM ranges were predominantly observed in this phase for the 48-hour group, with an increased percentage of temperature values outside the ranges when compared to the 24-hour group (p=0.056). Similarly, most of the overshoot in TTM observed in the 48-hour group were reported in the first 24 hours of cooling.

The median quality of TTM score was 5 [4-6] and 5 [3-6] in the 48-hour and 24-hour TTM group, respectively (p=0.51). There was no statistically significant difference in mortality (48-hour = 48/175, 27% vs. 24-hour = 60/177, 34%; OR 0.77 [95% CIs 0.46-1.16], p=0.22) or UO (48-hour = 55/175, 31% vs. 24-hour = 65/177, 37%; OR 0.79 [0.51-1.21], p=0.31) between the two groups. Also, mortality and UO was similar across different quality of TTM ranges within the 48-hour and 24-hour groups (Figure 4).

Discussion

In this *post hoc* analysis of a randomized clinical trial, we evaluated the characteristics and the quality of TTM provided to OHCA patients. We observed that the only a small proportion of patients received high quality of TTM, as defined by a score based on the combination of several relevant items. However, quality of TTM was not associated with patients' outcomes. The proportion of time outside the target ranges and the incidence of fever were significantly lower in patients treated at 48-hour duration of TTM than the others. However, the quality of TTM was similar between groups and no differences in mortality or UO were observed between different quality of TTM scores when analyzed according to the duration of TTM.

To our knowledge, this is the first time "quality of TTM" according to some relevant TTM characteristics has been evaluated using a specific score. Despite that randomized trials should provide the most accurate TTM according to specific recommendations reported in the study protocol, we observed that only 16% of the study cohort received high quality TTM. This finding is important as it suggests that the exposure to this therapy might be significantly heterogenous among treated patients, with large variability in precision, temperature values outside the ranges and post-TTM fever. Moreover, as trial participants usually receive an enhanced oversight above usual care, which is ensured by data and safety monitoring and protocol compliance [14], one may argue that the quality of TTM would be ever poorer in "real life" settings, at least in the absence of a specific and well-described TTM protocol [15, 16]. Future studies should more frequently also report the quality of TTM and large randomized trials should address this issue into the study protocol in order to maximize the effectiveness of such therapy. However, as the quality of TTM score was arbitrarily developed using relevant TTM items which have been described in the literature, larger cohorts are needed to better quantify the weight of each reported item on TTM performance.

In this study, no differences in outcome between patients with low-, moderate- and high-quality scores of TTM were observed. There are some possible explanations to our findings. First of

all, the lack of heat generation (i.e. resulting in rapid cooling, low temperature variability, slow rewarming) is a probably a sign of extended brain damage [17]. Secondly, the cut-offs of time to target temperature, TV and rewarming rate were selected *a priori* and whether other cut-offs would be more relevant to assess the quality of TTM needs to be retested in larger databases. Third, we did not specifically correct for potential differences among patients receiving low-, moderate- and high-quality TTM; however, it would be unlikely that such difference would have significantly changed the overall conclusions of this study, as UO rates were very similar among groups. Finally, it is possible that the quality of TTM would not influence at all patients' outcome or, if relevant, might be determinant only on specific subgroup of patients, who remain still undefined. Despite the lack of evidence for an association with outcome in our study, quality of TTM remains an important issue in cardiac arrest patients [11]; the implementation of such therapeutic strategy using the most effective approach in terms of rapid cooling, constant temperature control, slow rewarming and avoidance of fever should be used in all patients, whenever possible.

The optimal duration of cooling during TTM after OHCA is still debated. The Time-differentiated Therapeutic Hypothermia (TTH-48) trial showed that 48-hour duration of TTM did not improve the proportion of patients surviving with a favorable neurological outcome when compared to the standard 24-hour duration [5]. Interestingly, no data on how duration of the cooling phase might influence the characteristics and the quality of TTM have been reported so far. In our study, 48-hour duration was associated with a more rapid time to target temperature; however, this phase precedes the intervention phase (i.e. cooling for 24 or 48 hours) and should be considered as related to the treating healthcare professionals, time to initiation of cooling, administration of cold fluids or differences in the cooling method [12], rather than an effect of the duration strategy. In our study, TV was similar between the 48-hour and 24-hour TTM groups; however, the percentage of time outside temperature ranges was lower in the 48-h group, in whom most of outlier temperature values (i.e. in particular overshoot) occurred in the first 24 hours of TTM. Deviations from the target temperature during TTM may potentially influence brain function and reduce the

neuroprotective effects of TTM [6-10]. Shinozaki et al. observed that TTM over a longer period during the first days after CA was an important determinant of patients' outcome, suggesting that the inflammatory response following the ischemia and reperfusion injury might be more potently minimized with a prolonged control of core temperature [18]. However, Nobile et al. [13] did not find a correlation between the temperature variability, an index of precision of the TTM, and the neurologic impairment, suggesting that TV might be more a sign of intact thermoregulatory mechanisms (i.e. brain function) rather than a marker of poor outcome. Whether our findings suggest that prolonged TTM might provide a more precise therapy or just reflect a less accurate initial protocol compliance in the 48-h group remains an unanswered question. Previous report has suggested a potential anti-inflammatory effect of prolonged hypothermia on the systemic inflammatory response after rewarming in patients after cardiac arrest [19], which could also result in a lower heat generation and reduced temperature variability. However, as TTM requires sedation to allow reduction of body temperature and avoid shivering, drug accumulation has been reported in cardiac arrest patients undergoing TTM [20] and one may argue that prolonged TTM would be associated with more drug accumulation and, therefore, with a less reactive thermoregulatory mechanisms to hypothermia, which would translate into more time within target temperature ranges. Future studies addressing the duration of TTM in OHCA patients should better consider this issue and describe temperature variability according to the phase (i.e. early vs. late) of cooling.

Development of fever after cardiac arrest is frequent, probably related to an adaptive response to cell damage and activation of inflammatory cascades; fever has previously been found to be associated with unfavorable outcome [6-8]. In our analysis the incidence of early fever was significantly lower in the 48-hour than in the 24-hour group. Preclinical studies demonstrate hyperthermia after 24 hours from the arrest, but not at 48 hours, could worsen post-anoxic brain injury, suggesting a time-dependence of neuronal vulnerability to hyperthermia [21]; while an early fever is generally associated with poor outcome, the ability to thermoregulate and generate a fever may indicate a neurologically intact subject.

This study has several limitations. First, the study was not powered to detect differences in clinical outcome across different levels of quality of TTM. Second, the accuracy of intervals, such as time to cooling or target temperature, might be unreliable since this information may be subject to reporting or measurement errors. Third, different sites of temperature measurement were used, which may have led to a measurement bias when assessing absolute temperature values. Also, these values do not directly reflect brain temperature, which might exceed body temperature by 0.5 to 2.0°C after an acute brain injury [22]. Fourth, temperature data were recorded at various intervals in different centers and the total number of available data on body temperature was different among patients; variation in temperature within interval gaps may influence outcome and was not evaluated in this study.

Conclusions

In this study, high quality of TTM was provided to 16% of OHCA patients. Although quality of TTM was not associated with patients' outcome, future studies should more accurately report the quality of TTM provided to cardiac arrest patients. Prolonged TTM duration during 48 hours did not significantly affect the quality of TTM when compared to standard TTM 24-hour duration.

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Table 1. Characteristics of included patients, according to the cooling method. Data are expressed as count (%) or median (25^{th}-75^{th} percentiles).

`	48-hour (n=175)	24-hour (n=177)
Demographic characteristics		
Age, years	62 [54-69]	62 [54-69]
Male gender, n (%)	144 (82%)	149 (84%)
Weight, kgs	85 [75-93]	85 [75-93]
Previous Neurologic disability, n (%)	3 (2%)	7 (4%)
Medical history		
Previous myocardial infarction, n (%)	28 (16%)	26 (15%)
Previous PCI or CABG, n (%)	26 (15%)	29 (16%)
Previous cardiac arrest, n (%)	0 (0%)	3 (2%)
Chronic heart failure, n (%)	13 (7%)	9 (7%)
Chronic obstructive pulmonary disease, n (%)	13 (7%)	11 (6%)
Liver cirrhosis, n (%)	3 (2%)	0 (0%)
Chronic renal failure with dialysis, n (%)	1 (1%)	1 (1%)
Diabetes mellitus, n (%)	35 (20%)	28 (16%)
Immunocompromised, n (%)	2 (1%)	1 (1%)
Previous stroke, n (%)	11 (6%)	15 (8%)
Arrest characteristics		
Witnessed, n (%)	160 (91%)	163 (92%)
Bystander initiated CPR, n (%)	147 (84%)	146 (82%)
Shockable rhythm, n (%)	152 (86%)	160 (91%)
Time to return of spontaneous circulation, min	20 [15-30]	21 [16-27]
Mechanical chest compression, n (%)	47 (27%)	43 (24%)
Adrenaline, n (%)	110 (63%)	111 (63%)
Amiodarone, n (%)	77 (44%)	68 (38%)
Pre-ICU orotracheal intubation, n (%)	168 (96%)	168 (95%)
Pre-ICU cooling, n (%)	64 (37%)	83 (47%)
Coronary angiography, n (%)	146 (83%)	145 (82%)
PCI, n (%)	76 (43%)	69 (39%)
Characteristics on ICU admission		
Sedation, n (%)	175 (100%)	174 (98%)
Mean arterial pressure, mmHg	78 [67-93]	78 [66-90]
Lactate, mEq/L	2.6 [1.4-4.5]	2.7 [1.5-5.0]

PCI = percutaneous coronary intervention; CABG = coronary artery bypass graft; ICU = intensive care unit; CPR = cardiopulmonary resuscitation - $^{\$}$ $p<0.001$; * $p < 0.05$; $^{\epsilon}$ $p<0.1$

Table 2. The proportion of patients for each item defining the quality of targeted temperature management (TTM) score.

	+2	+1	0
Time from arrest to target temperature, hours	75 (21%)	190 (54%)	87 (25%)
Overcooling		308 (87%)	44 (13%)
Overshoot		261 (74%)	91 (26%)
Temperature Variability, °C	95 (27%)	178 (51%)	79 (22%)
Rewarming Rate, °C/hour	62 (18%)	136 (39%)	154 (44%)
Fever		148 (42%)	204 (58%)

Table 3. Characteristics of targeted temperature management (TTM) between the two groups. Data are expressed as count (%) or median (25^{th}-75^{th} percentiles). Number of hourly available temperature at normothermia = number of hourly recorded body temperature available after normothermia has been reached.

	48-hour (n=175)	24-hour (n=177)
Admission Temperature, °C	35.2 [34.3-35.8]	35.3 [34.4-35.7]
Time from Arrest to Temperature < 34°C, hours	5.2 [4.0-6.9]	6.0 [4.4-8.4] *
Time from Randomization to Temperature < 34°C, hours	2.5 [1.4-4.8]	3.5 [1.9-6.0]
First recorded Temperature < 34°C, °C	33.7 [33.3-33.9]	33.6 [33.1-33.9]
Cooling Rate, °C/h	0.5 [0.2-0.8]	0.3 [0.2-0.6] *
Duration of cooling, hours	50 [48-51]	26 [24-27]
Mean temperature during cooling, °C		
- *All temperature*	33.4 [33.1-33.7]	33.4 [33.2-33.9]
- *First 24 hours*	33.6 [33.3-34.3]	33.4 [33.2-33.9]
Minimum temperature during cooling, °C		
- *All temperature*	32.7 [32.4-33.0]	32.8 [32.4-33.0]
- *First 24 hours*	32.9 [32.5-33.1]	32.8 [32.4-33.0]
Maxima temperature during cooling, °C		
- *All temperature*	35.3 [34.6-36.0]	35.2 [34.5-35.8]
- *First 24 hours*	35.3 [34.6-35.9]	35.2 [34.5-35.8]
Temperature Variability during cooling, °C		
- *All temperature*	0.66 [0.46-0.90]	0.68 [0.49-0.90]
- *First 24 hours*	0.67 [0.39-0.89]	0.68 [0.49-0.90]

Patients never achieving target temperature, n (%)	10 (6)	12 (7)
Temperature outside targets, hours - *All temperature* - *First 24 hours*	 6 [2-14] 5 [2-12]	 6 [2-13] 6 [2-13]
Temperature outside targets, % - *All temperature* - *First 24 hours*	 13 [5-32] 25 [8-50]	 18 [8-36] * 18 [8-36]
Patients with overcooling, n (%) - *All temperature* - *First 24 hours*	 19 (11) 11 (6)	 25 (14) 25 (14)
Patients with overshoot, n (%) - *All temperature* - *First 24 hours*	 105 (60) 102 (58)	 97 (55) 41 (55)
Time to Normothermia, hours	8.0 [6.3-12.0]	8.2 [6.5-12.3]
Rewarming Rate, °C/h	0.34 [0.24-0.46]	0.35 [0.22-0.47]
Number of hourly available temperature at normothermia, hours	41 [18-68]	45 [25-74]
Max temperature reached during normothermia, °C	38.1 [37.6-38.5]	38.2 [37.8-38.6]
Post-TTM Fever, n (%)	91 (52)	113 (64) *

TTM = targeted temperature management - $ p<0.001; * p < 0.05; € p<0.1

Figure 1: Number of patients for each score of targeted temperature management (TTM) quality.

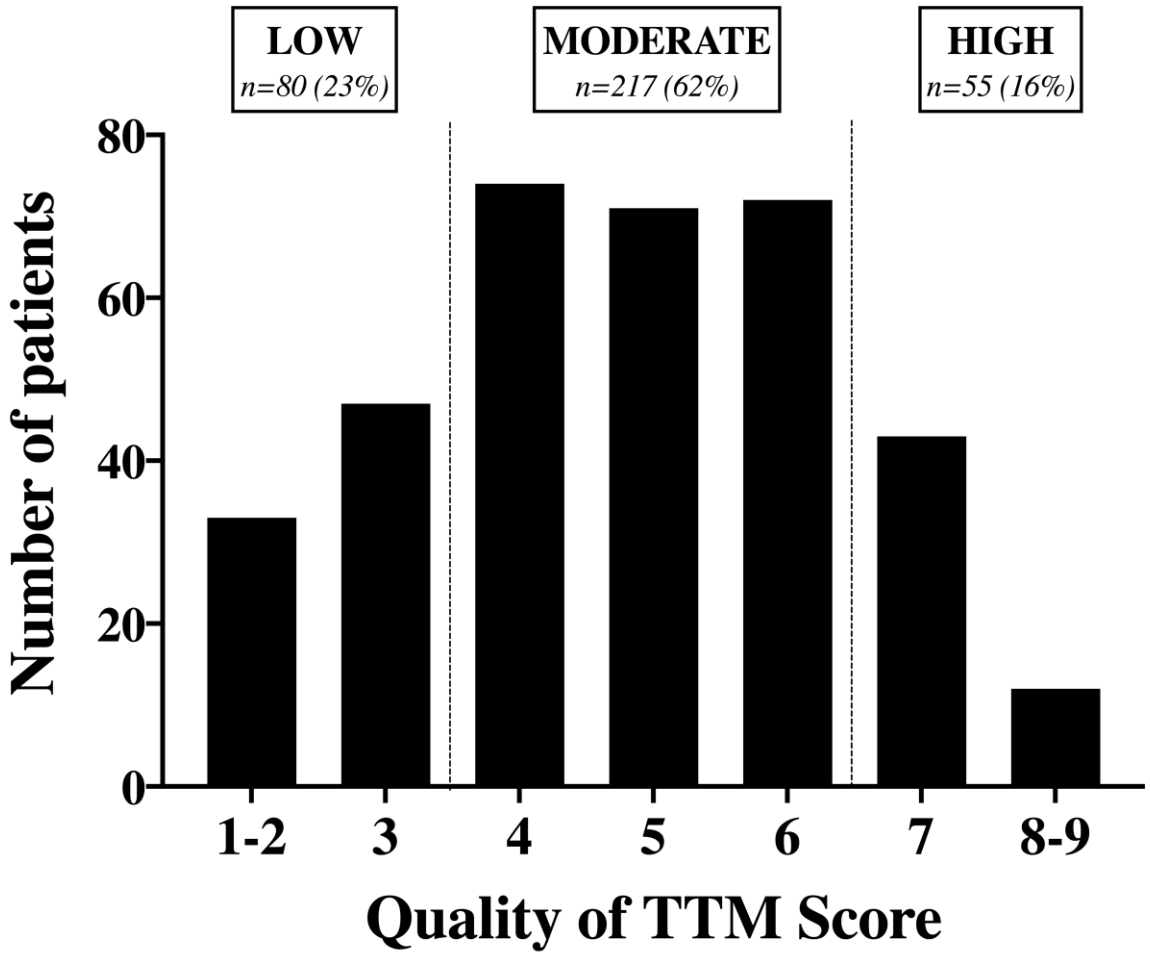


Figure 2: Mortality and unfavorable neurological outcome (UO) according to the different degree of quality of targeted temperature management (TTM).

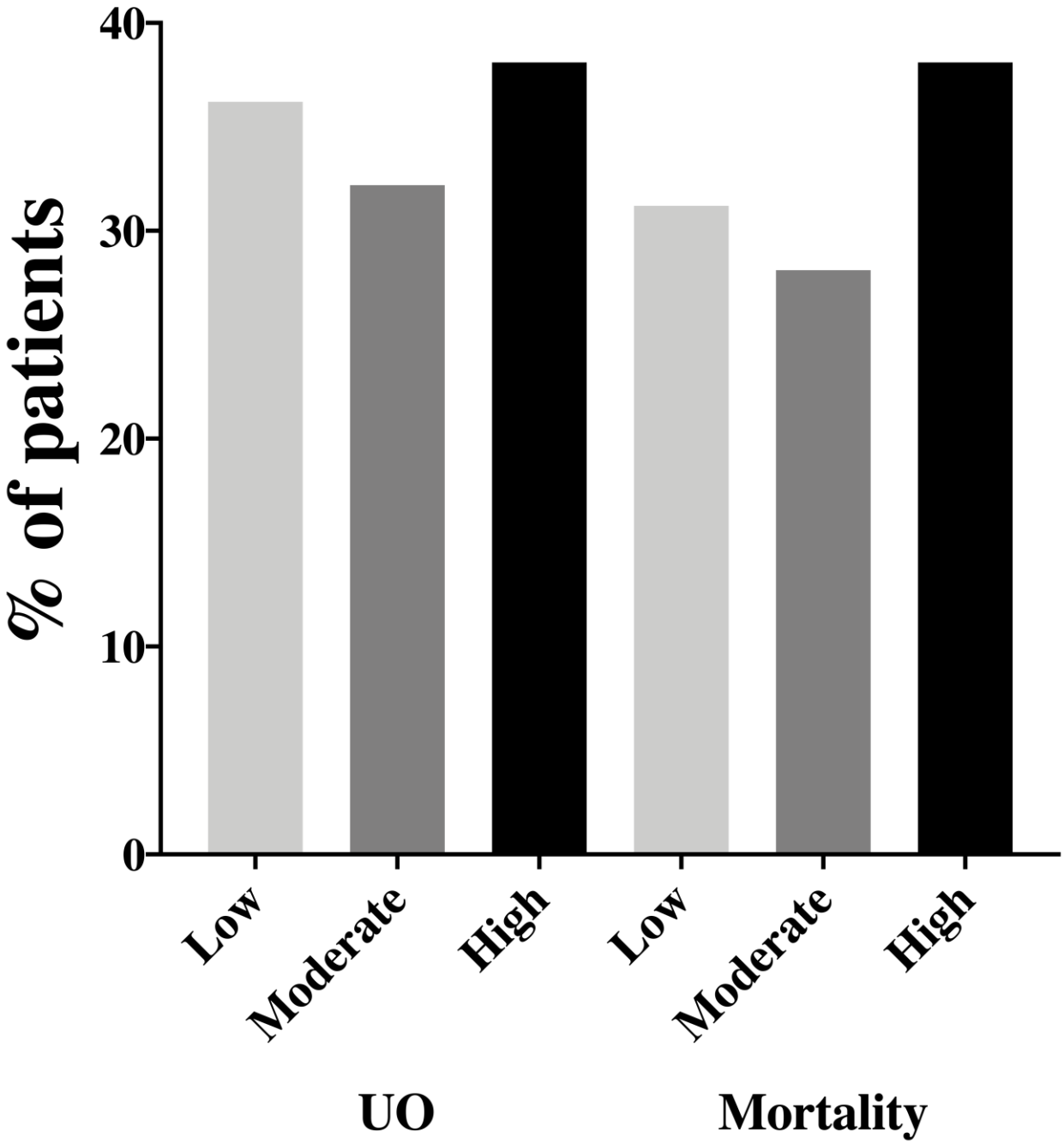


Figure 3: Mortality and unfavorable neurological outcome (UO) according to different quality of targeted temperature management (TTM) scores. Score 1 and 2, as well as 8 and 9, were combined because of the small number of patients in each group.

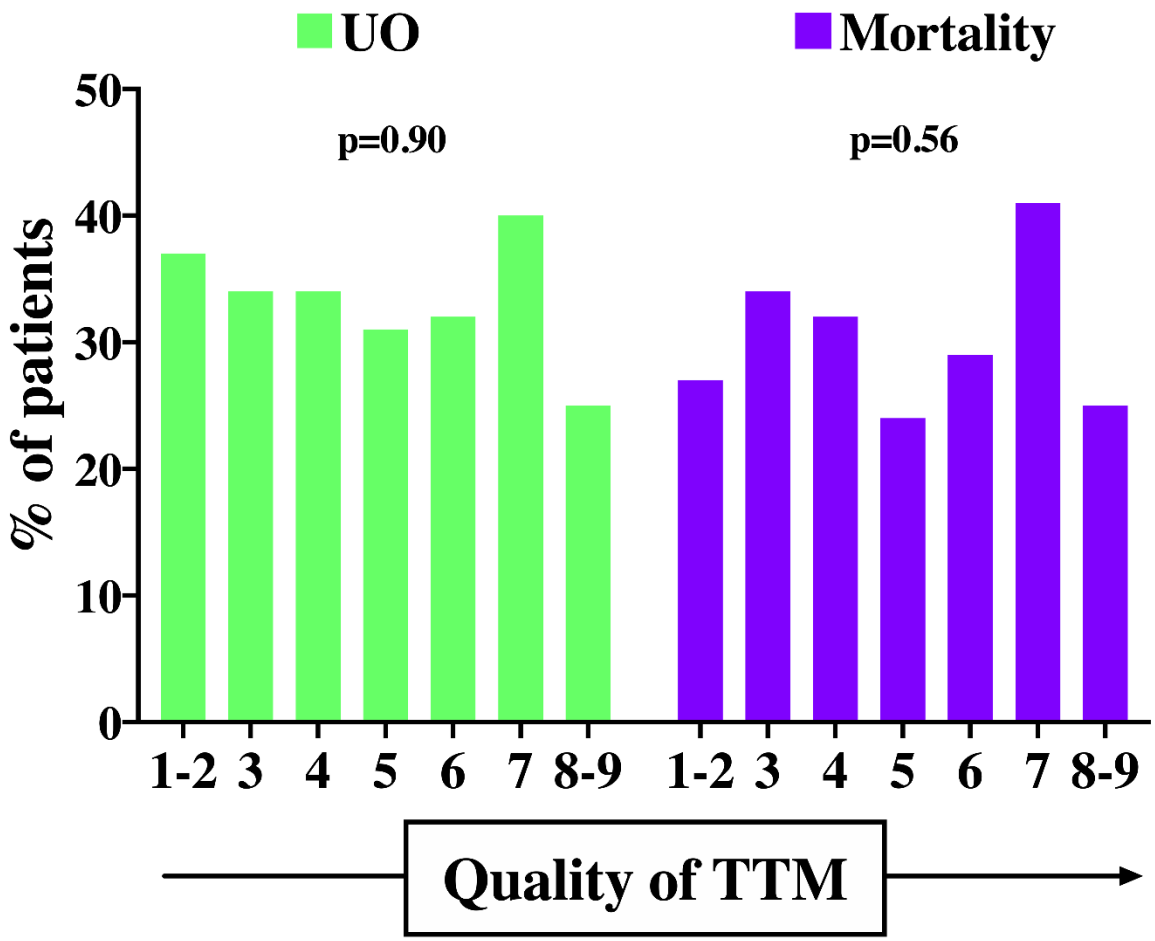
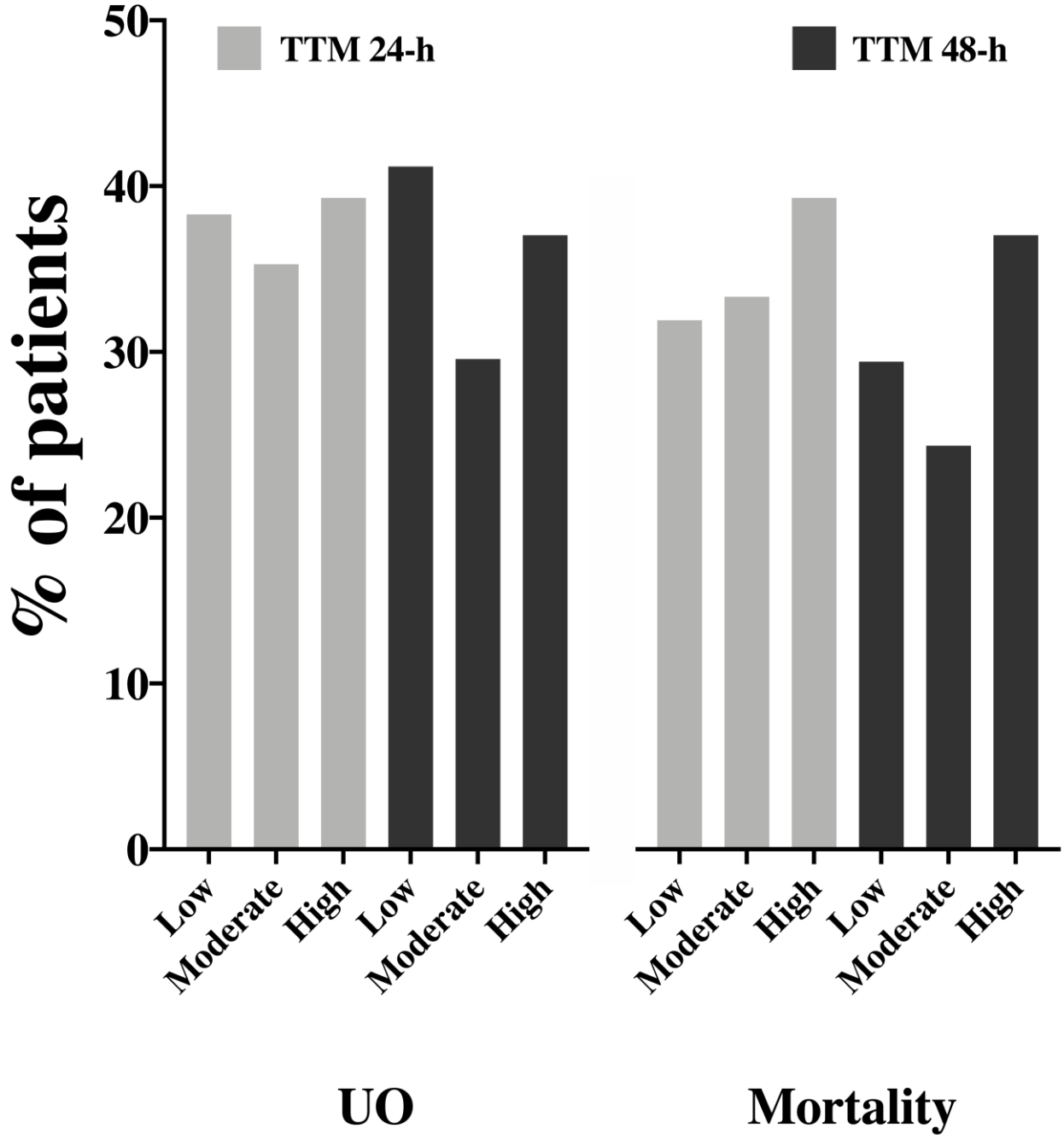


Figure 4: Mortality and unfavorable neurological outcome (UO) according to different quality of targeted temperature management (TTM) scores, within the two study groups (TTM during 48 hours vs TTM during 24 hours).



Appendix 1. Score to assess the quality of targeted temperature management (TTM).

	+2	+1	0
Time from arrest to target temperature, hours	<4	4-8	>8
Overcooling		Absent	Present
Overshoot		Absent	Present
Temperature Variability, °C	<0.5	0.5-1.0	>1.0
Rewarming Rate, °C/hour	<0.2	0.2-0.4	>0.4
Fever		Absent	Present

Supplemental Table 1. Temperature analyses and outcomes of included patients, according to the duration of cooling. Data are expressed as count (%) or median (25^{th}-75^{th} percentiles).

	48-hour (n=175)	24-hour (n=177)
Primary outcome		
UO at six months	55 (31%)	65 (37%)
Secondary outcomes		
Mortality at six months	48 (27%)	60 (34%)
Adverse Events		
Any adverse event	171 (98%)	174 (98%)
Pneumonia	86 (49%)	76 (43%)
Other infections	73 (42%)	56 (32%)
Any bleeding	17 (10%)	23 (13%)
RBC Transfusion	15 (9%)	20 (11%)
Seizure/myoclonus localized	27 (15%)	18 (10%)
Seizure/myoclonus globalized	39 (18%)	29 (16%)
Severe Circulation Failure	17 (10%)	11 (6%)
Arrhythmias	80 (46%)	75 (42%)
Severe (VT/VF or unstable despite treatment)	20 (11%)	20 (11%)
New cardiac arrest requiring CPR	5 (3%)	7 (4%)
Renal replacement therapy	12 (7%)	15 (8%)
Hyperglycemia	141 (81%)	141 (80%)
Hypernatremia	22 (13%)	23 (13%)
Hypokalemia	66 (38%)	60 (34%)
Resource use		
ICU length of stay (days)	6 [4-8]	5 [3-7]

CPC = Cerebral Performance Category; ICU = intensive care unit; RBC = red blood cells; VT/VF = ventricular tachycardia / ventricular fibrillation; UO = unfavorable neurological outcome