

RESEARCH ARTICLE

Targeted temperature management evolving over time—A local process analysis

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Abstract

Background: Post-resuscitation care of comatose survivors from cardiac arrest includes target temperature management (TTM) to mitigate cerebral reperfusion injury. High-quality TTM requires protocols enhancing good precision. This study explored how the quality of TTM may have evolved with increasing experience from clinical trial protocols and standard operating procedures. We hypothesized that there would be a positive effect over time, detectable between trial periods and between trial periods and later everyday practice.

Methods: Three TTM quality parameters were defined: time to target, temperature variability, and fever incidence. Data from 181 patients treated during three different time periods in a tertiary center were analyzed; 45 from Period 1 (local trial cohort 2011–2013) targeting 33°C or 36°C; 76 from Period 2 (local trial cohort 2018–2020) targeting 33 or <37.5°C; 60 from Period 3 (current standard operating procedure 2020–2021) targeting 36°C. Groups of similar target temperatures from different time periods were compared using ordinary group statistics.

Results: TTM quality in all three parameters increased between trial periods. There were no differences in TTM quality as to temperature variability or fever incidence between the <37.5°C Period 2 and the 36°C Period 3 groups. A 33°C target temperature was associated with lower fever incidence than 36°C and <37.5°C target regimes.

Conclusion: The observed increase in TTM quality in this single-center study may be a result of increased competence through learning and training in different strict TTM protocols. If so, the results of this study further support the protocolization of post-cardiac arrest intensive care.

KEYWORDS

fever, hypothermia, intensive care, out-of-hospital cardiac arrest, post-resuscitation, precision, quality, targeted temperature management, temperature, time to target

Editorial Comment

In this study, three quality parameters of targeted temperature management were compared during three time periods where substantial evolution and large trials of targeted temperature

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management of comatose survivors from cardiac arrest were being conducted. Findings demonstrated improvement in all three parameters, supporting an interpretation that the clinical staff were able to increase their competence in delivering high-quality temperature management as time progressed. This could be due to increased focus on this patient population, participation in trials, or both.

1 | INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) represents a major health concern with more than 350,000 cases each year in Europe.¹ Since almost two decades, the recommended management of unconscious survivors to OHCA includes targeted temperature management (TTM). TTM aiming for hypothermia was introduced after the publication of two randomized controlled trials (RCT) in 2002 which demonstrated beneficial effects on survival and neurologic outcome from OHCA with target temperatures of 32–34°C and 33°C.^{2,3} More recently, the TTM1 and TTM2 trials have failed to demonstrate superior effects from TTM at 33°C when compared to 36°C and normothermia <37.5°C, respectively.^{4,5} However, the outcomes in all groups of these trials supersede those of the control groups in the earlier trials, indicating that scientifically founded, rigorous standard operating procedures (SOP) are important.⁶ Animal studies with protocols resembling post-arrest clinical practice TTM have demonstrated that a short time from ROSC to a hypothermic target temperature is beneficial.⁷ It has been concluded that TTM of high quality assumes a good performance in several aspects promoting beneficial but avoiding negative effect on outcome.⁸

During the last decade, our institution took part in two major trials and introduced an updated SOP for TTM in patients remaining comatose after OHCA. We designed the present study to analyze the quality of the local TTM management of these patients in our current clinical practice and explore whether it has changed over time with an increasing experience from TTM management. We hypothesized that there would be a positive effect over time, detectable between trial periods and between trial periods and later SOP in everyday practice.

2 | METHODS

This retrospective analysis of prospectively registered data was approved by the Swedish Ethical Review Authority (Dnr 2021-03749). Individual consent from the patients was waived because the information was retrieved from databases of which the patients had already been informed and offered to withdraw from in compliance with the General Data Protection Regulation. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology statement.⁹

The patients were recruited from three cohorts with survivors of cardiac arrest, treated in our university hospital tertiary intensive care unit (ICU) with different regimes of TTM during three different time periods. The first two cohorts were treated during trial periods

(randomization to 33°C or 36°C TTM between March 2011 and January 2013 [Period 1] and randomization to 33°C or normothermia <37.5°C TTM between March 2018 and January 2020 [Period 2]) whereas the third clinical cohort was treated according to an SOP targeting 36°C between February 2020 and June 2021 (Period 3). Full eligibility and exclusion criteria, as well as detailed protocols, are described in the original publications.^{4,5} The Period 3 cohort was not subjected to specific exclusion criteria, but clinicians were advised that TTM was of uncertain value or contraindicated in patients resuscitated from cardiac arrest (CA) secondary to trauma or massive bleeding or with an initial rhythm of asystole in unwitnessed cases. For temperature management, a core temperature feedback surface cooling device was used (Arctic Sun 5000, Bard, Inc.) during the entire period of this study.

Demographics, medical history, and treatment data were retrieved from medical records, including emergency medical support records and ICU charts. Three elements of TTM were used as measures of quality: time to target temperature (in the hypothermic groups), temperature variability, and incidence of fever.⁸ A schematic TTM timeline with outcome variables is visualized in Figure 1.

The time from ROSC to reaching the specified target temperature was reported in three subdivisions; time from ROSC to ICU admission, time from ICU admission to initiation of cooling, and time from initiation to target temperature. Hourly temperature registrations were collected from ICU admission. Because patients with OHCA normally present with a subnormal temperature, this analysis was limited to the 33°C groups with the timepoint for reaching the target temperature defined by the first temperature registration at 33.0°C or below.

Temperature variability was defined as the standard deviation (SD) of temperature registrations in line with a previous similar study.¹⁰ A high variability was arbitrarily defined as an SD $\geq 0.5^\circ\text{C}$. The variability was measured during the maintenance phase defined as

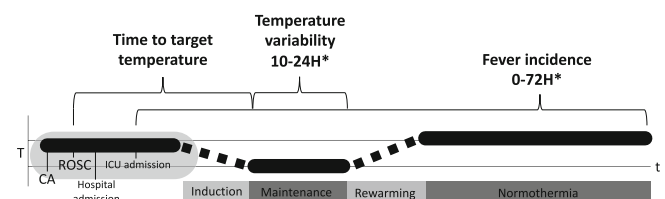


FIGURE 1 TTM timeline. Schematic TTM timeline with a hypothermic target temperature and quality measures in bold. *After ICU admission. Y-axis T is temperature and X-axis t is time. CA, cardiac arrest; ICU, intensive care unit; ROSC, return of spontaneous circulation; TTM, targeted temperature management

TABLE 1 Baseline characteristics

Number	Baseline characteristics						
	Period 1	Period 1	Period 1	Period 2	Period 2	Period 2	Period 3
	Total	33°C	36°C	Total	33°C	<37.5°C	36°C
	45	23	22	76	35 ^a	38 ^a	60
Demographics							
Age, mean (SD)	64 (12)	66 (11)	62 (13)	68 (12)	67 (12)	68 (12)	60 (15)
Male sex, no. (%)	38 (84)	19 (83)	19 (86)	61 (80)	30 (86)	29 (76)	51 (85)
BMI, mean (SD)	27 (6)	27 (4)	28 (5)	27 (6)	28 (5)	27 (7)	28 (6)
Medical history, no. (%)							
Previous AMI	12 (27)	8 (35)	4 (18)	12 (16)	4 (11)	8 (21)	7 (12)
Previous CHF	3 (7)	2 (9)	1 (5)	15 (20)	8 (23)	6 (16)	8 (13)
Hypertension	36 (47)	13 (57)	9 (41)	22 (49)	18 (51)	18 (47)	18 (30)
Diabetes	6 (13)	5 (22)	1 (5)	9 (12)	6 (17)	2 (5)	8 (13)
Previous neurological disorder	9 (20)	5 (22)	4 (18)	17 (22)	6 (17)	10 (26)	7 (12)
Previous PCI	6 (13)	4 (17)	2 (9)	6 (8)	2 (6)	4 (11)	6 (10)
Previous CABG	8 (18)	4 (17)	4 (18)	8 (11)	4 (11)	4 (11)	1 (2)
Previous arrhythmia	9 (20)	4 (17)	5 (23)	10 (13)	5 (14)	5 (13)	8 (13)
Characteristics, no. (%)							
Location							
Home	30 (67)	16 (70)	14 (64)	43 (57)	17 (49)	23 (61)	36 (60)
Public place or work	13 (29)	6 (26)	7 (32)	30 (39)	16 (46)	14 (37)	15 (25)
Other	2 (4)	1 (4)	1 (4)	3 (5)	2 (6)	1 (3)	9 (15)
Initial rhythm VF/VT	33 (75) ^b	15 (65)	18 (86) ^b	54 (74) ^c	27 (79) ^b	25 (69) ^d	32 (55) ^d
Witnessed arrest	41 (91)	21 (91)	20 (91)	68 (90)	31 (89)	34 (90)	50 (83)
Bystander CPR	37 (82)	31 (91)	27 (75)	61 (84)	20 (87)	17 (77)	47 (83) ^c
Mechanical device CPR	29 (64)	15 (65)	14 (64)	53 (72)	26 (77)	25 (66)	31 (53) ^d
Cooling device used	45 (100)	23 (100)	22 (100)	64 (84)	35 (100)	26 (68)	60 (100)
Time to event, min							
CA to ALS, median (IQR)	12 (9–15)	12 (9–18)	12 (7–14) ^b	10 (5–12)	10 (5–14)	8 (6–11)	9 (5–12)
CA to ROSC, median (IQR)	29 (20–39)	30 (24–52)	25 (18–35)	26 (17–49)	26 (17–40)	26 (16–40)	23 (12–30)
Admission							
Admission temp, mean (median)	35.2 (35.5)	34.9 (35.4)	35.5 (35.5)	35.5 (35.7)	35.6 (35.7)	36.1 (35.5)	35.7 (35.7)
Angiography, no (%)	21 (47)	13 (57)	8 (36)	39 (51)	24 (69)	15 (40)	32 (53)
Discharge							
Extubation prior to 40 h ^e , no (%)	2 (4)	0 (0)	2 (9)	3 (4)	1 (3)	2 (5)	6 (10)
ICU stay (days), median (IQR)	3 (3–4)	3 (2–5)	3 (3–4)	4 (2–6)	4 (3–6)	3 (2–5)	4 (2–7)
Hospital stay (days), median (IQR)	7 (3–12)	5 (3–12)	8 (5–13)	9 (4–17)	10 (4–24)	8 (3–14)	9 (4–18)
ICU mortality, no (%)	16 (36)	12 (52)	4 (18)	26 (34)	11 (31)	13 (34)	17 (29) ^b
Hospital mortality, no (%)	28 (62)	15 (65)	13 (59)	42 (55)	18 (51)	22 (58)	33 (56) ^b
CPC at hospital discharge							
CPC1–2, no. (%)	16 (36)	7 (30)	9 (42)	29 (39) ^c	14 (42) ^d	14 (38) ^b	25 (42) ^b
CPC 3–5, no. (%)	29 (64)	16 (70)	13 (59)	44 (60) ^c	19 (58) ^d	23 (62) ^b	34 (58) ^b

Abbreviations: ALS, advanced life support; AMI, acute myocardial infarction; BMI, body mass index; CA, cardiac arrest; CABG, coronary arterial bypass graft; CHF, congestive heart disease; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; IQR, interquartile range; ICU, intensive care unit; PCI, percutaneous coronary intervention; SD, standard deviation; VF, ventricular fibrillation; VT, ventricular tachycardia.

^a33°C group missing two subjects' data and <37.5°C group missing one subjects data due to treatment at 36°C despite randomization to 33°C/<37.5°C.

^bOne missing data.

^cThree missing data.

^dTwo missing data.

^eAfter ICU admission.

10–24 h following ICU admission. This time span was chosen to include patients at target temperature regardless of the time spent on reaching it, which varied between targets and cohorts.

Fever was defined as an hourly temperature registration $\geq 38.5^{\circ}\text{C}$. Its incidence was measured during the first 72 h of ICU care and was

subdivided into an early phase and a normothermia phase. The early phase was defined as 0–39 h after ICU admission representing induction, maintenance, and rewarming while the normothermia phase was defined as 40–72 h after ICU admission. The analysis was limited to temperature registrations obtained while patients were still comatose

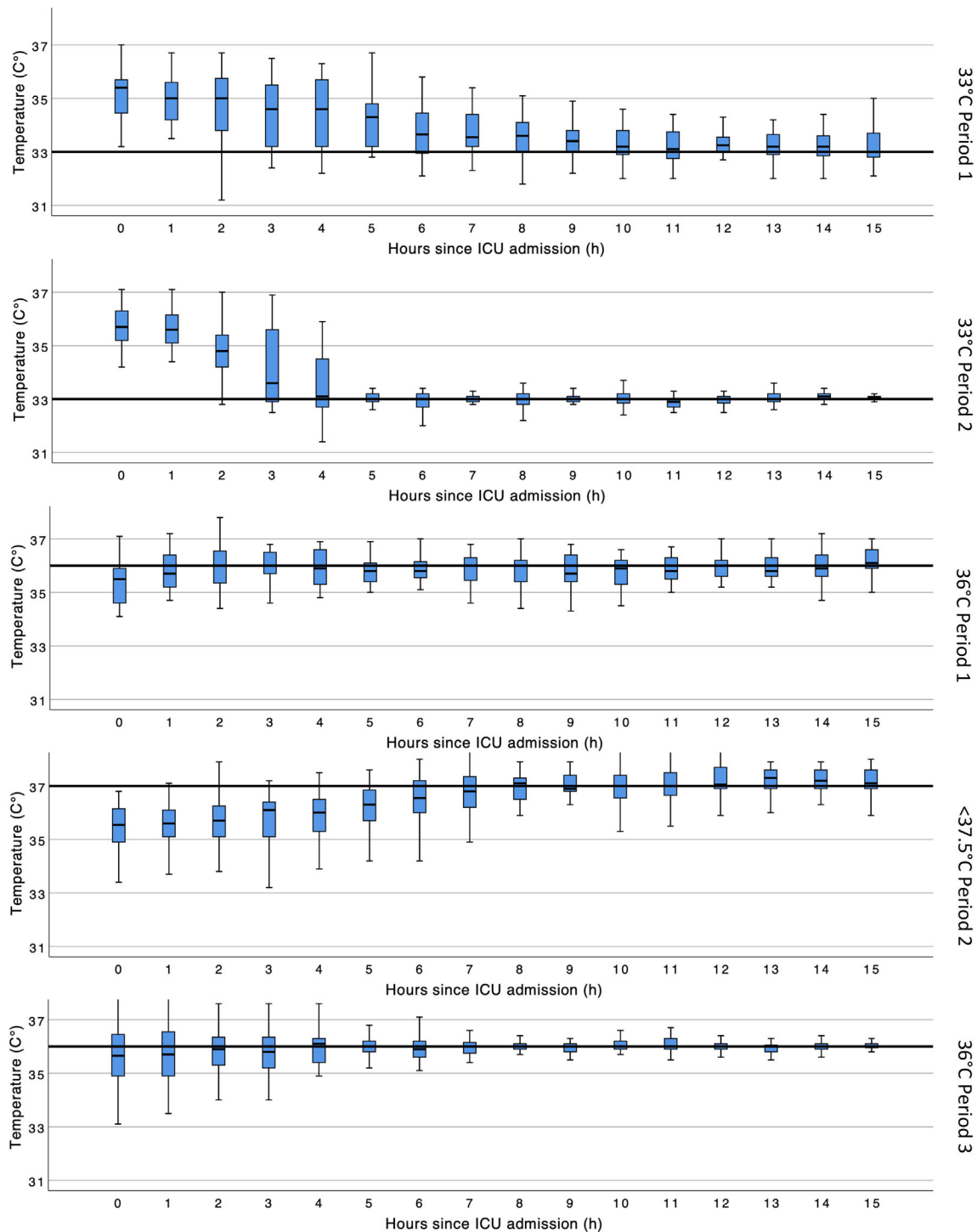


FIGURE 2 Progression of core temperature during the initial 15 h in the ICU. Boxes represent interquartile range (IQR), the marked line is the median, and the T-bars are maximum and minimum temperatures within 1,5 IQR from the box. Time from ICU admission to target temperature was shorter ($p < .001$) and temperature variability was lower ($p < .001$) in the 33° Period 2 group compared to the 33° Period 1 group. ICU, intensive care unit; SOP, standard operating procedure

TABLE 2 Mean (SD) time (h:min) to 33°C target temperature from ROSC with subdivisions

	ROSC to target	ROSC to ICU	ICU to initiation	Initiation to target
33°C Period 1 (n = 23)	10:06 (04:17)	01:55 (01:05)	02:21 (01:42)	05:50 (03:24)
33°C Period 2 (n = 35)	06:38 (01:41)*	01:55 (00:59)	01:36 (01:05)	03:07 (01:36)*

Note: Student's *t* test was used for comparison between groups where *Statistical significance $p < .05$.

Abbreviations: ICU, intensive care unit; n, number of subjects; ROSC, return of spontaneous circulation; SD, standard deviation.

and intubated. As different rates of early extubations were identified as a potential confounder, the proportion of patients extubated prior to 40 h after ICU admission in each group is reported in Table 1. Comparison over time was made between patient groups with similar target temperatures.

We hypothesized that there would be a positive effect on TTM quality over time, detectable between trial periods and between trial periods and later everyday practice.

For statistical analysis, the respective Student's *t* test and Mann-Whitney *U* test were applied to normally and non-normally distributed continuous variables and the Fisher's exact test was used for categorical variables. All tests were two-sided with a *p* value $< .05$ considered to indicate statistical significance. No imputations were performed for missing values. For all computations, the software SPSS (v26, IBM Statistics, IBM Corp.) was used.

3 | RESULTS

There were 47 patients eligible from Period 1, 78 patients from Period 2, and 60 patients from Period 3. Of these 185 eligible patients, two from the Period 1 cohort and two from the Period 2 cohort were excluded: from the Period 1 cohort, one patient due to early awakening and one patient due to CA secondary to multi-organ failure and from the Period 2 cohort, one patient due to early awakening and one patient due to dismissal of CA diagnosis. The final study population consisted of 181 patients who were assigned to temperature target groups for comparison as per protocol. Three patients during Period 2 were treated at 36°C despite being randomized to 33°C and $<37.5^\circ\text{C}$ TTM. These patients were excluded from all analyses comparing these specific subgroups. However, they were included in the per protocol exploratory analysis of fever incidence, comparing 33°C target to the combined group of 36°C and $<37.5^\circ\text{C}$ target patients.

The three main groups had similar baseline characteristics (Table 1). The progression of core temperature toward targets during the first 15 h in the ICU is shown in Figure 2.

3.1 | Time to target temperature

The time from ROSC to target temperature 33°C was shorter in the 33°C Period 2 group as compared to the 33°C Period 1 group. This difference was limited to the time from initiation to target temperature. As for the other subdivisions, time from ROSC to ICU admission and time from ICU admission to initiation did not differ (Table 2).

TABLE 3 Temperature variability

	SD $\geq 0.5^\circ\text{C}$ during maintenance phase n/total (%)
33°C Period 1	16/23 (70%)
33°C Period 2	5/35 (14%)*
36°C Period 1	9/22 (41%)
$<37.5^\circ\text{C}$ Period 2	7/38 (18%)
$<37.5^\circ\text{C}$ Period 2	7/38 (18%)
36°C Period 3	9/60 (15%)

Note: Variability was defined as SD $> 0.5^\circ\text{C}$ during 10–24 h after ICU admission. Fischer's exact test was used for comparison between groups of similar temperature targets in paired rows where * indicates statistical significance $p < .05$.

3.2 | Variability

The proportion of patients with high temperature variability (SD $\geq 0.5^\circ\text{C}$) during the maintenance phase was lower in the 33°C Period 2 group as compared to the 33°C Period 1 group. There were no differences between the other groups (Table 3).

3.3 | Fever

During the early phase, the incidence of fever did not differ between the groups with similar temperature targets. During the normothermia phase, it was lower in the 33°C Period 2 and $<37.5^\circ\text{C}$ Period 2 group compared to the 33°C Period 1 and 36°C Period 1 group, respectively. There was no difference between the $<37.5^\circ\text{C}$ Period 2 group and the 36°C Period 3 group (Table 4). In an exploratory analysis including all patients, a 33°C target temperature was associated with a lower fever incidence during the total 72 h of ICU stay as compared to any other target temperature, 6 of 58 patients (10%) versus 32 of 123 patients (26%) ($p = .018$).

4 | DISCUSSION

The primary objective of the present study was to explore how the quality of TTM at our institution evolved over time with different TTM protocols. Our main findings were that TTM quality increased between Period 1 and Period 2 cohorts targeting 33°C; quality defined as short time to target, low temperature variability, and low

TABLE 4 Fever incidence during target temperature management (TTM)

	Early phase 0–39 h n/total (%)	Normothermia 40–72 h n/total (%)	Total 72 h n/total (%)
33°C Period 1	0/23 (0%)	6/23 (26%)	6/23 (26%)
33°C Period 2	0/35 (0%)	0/34 (0%)*	0/35 (0%)
36°C Period 1	3/22 (14%)	7/20 (35%)	9/22 (41%)
<37.5°C Period 2	5/38 (13%)	3/36 (8%)*	8/38 (21%)
<37.5°C Period 2	5/38 (13%)	3/36 (8%)	8/38 (21%)
36°C Period 3	5/60 (8%)	10/54 (19%)	14/60 (23%)

Note: Fever incidence ($\geq 38.5^\circ\text{C}$) during active TTM during the initial 72 h in the ICU. Patients extubated prior to 40 h were excluded from fever analysis during normothermia phase. Any temperature registrations after extubation prior to 72 h were excluded from analysis. Fischer's exact test was used for comparison between groups with similar temperature targets in paired rows. *Statistical significance $p < .05$.

fever incidence. No significant decline in TTM quality was observed in the 36°C Period 3 group (2020–2021) as compared to the <37.5°C Period 2 group. Additionally, a target temperature of 33°C was associated with lower fever incidence during the initial 72 h in the ICU as compared to 36°C and <37.5°C target regimes.

The timing of TTM has been debated with a prolonged initiation time and a slow rate of cooling identified as negative factors and potential weaknesses of earlier studies.^{11,12} Very short time to target temperature and even intra-arrest initiation of cooling have been positively associated with favorable neurologic outcome and survival in animal models,^{13,14} but not yet reproduced in human clinical trials.^{15–17} Conversely, observational human studies have often found shorter times to target to be associated with worse outcome, possibly confounded by low admission temperatures and fast cooling among the patients prone to worse outcome, hypothesized to have a complete loss of thermoregulatory function.^{18–20} However, when studying time to initiation, shorter times have been associated with better outcome.²¹

Our finding that the time from ROSC to target temperature was shorter in the second of the two groups targeting 33°C in the respective TTM trials could be attributed entirely to the shorter time interval between initiation of cooling and reaching target temperature. This period represents an internal intensive care process that supports our hypothesis that managing patients according to strict trial protocols infers training and better performance.

The inclusion interval was longer in the first of the two trial periods (240 min as opposed to 180), which is a potential confounder. However, as displayed in Table 2, there was no difference between groups in neither time from ROSC to ICU admission, nor time from ICU admission to initiation of cooling, suggesting limited influence. The surface cooling device used was similar during both study periods with the same temperature settings for cooling to 33°C. During the entire study period, there were no changes to local SOP treatment recommendations of sedation, neuromuscular blockade, or antibiotic protocols. Staffing numbers and CA admission frequency did not differ between the study periods, nor did time-consuming procedures (such as angiography) before initiation. In our opinion, the evolutive

factors related to shorter induction times are awareness of its importance and training of equipment handling among ICU staff. Also, intensified information prior to Period 2, as well as years of similar TTM protocols and SOPs in everyday practice may be other contributing factors. With the observed shortening, the achieved average induction time in our institution is comparable to the upper middle range of reported induction times in the current literature.²²

Our finding that the temperature variability during the maintenance phase had decreased over time may be attributed to purported training factors like those discussed above for the shorter times to target temperature. Furthermore, temperature variability was similar in the 36°C Period 3 and the <37.5°C Period 2 groups as compared to the 33°C Period 2 group, suggesting that a normothermic target can be maintained with as good a precision as a low temperature target. This was also found in a previous study in which altering the SOP target temperature from 34°C to 36°C was associated with less temperature deviations $>0.5^\circ\text{C}$ over target during the maintenance phase.²³ Conversely, another retrospective observational study reported lower compliance to target temperature among 36°C TTM patients compared with 33°C TTM patients.²⁴ However, a meta-analysis of different cooling methods presented better outcome with devices able to maintain a strict target temperature, suggesting that lower variability is favorable.²⁵ All the while, high temperature variability has not been associated with worse clinical outcome in temperature variability studies.^{10,26,27} In spite of these conflicting outcome results, we advocate that an acquired reduction of temperature variability is a sign of increased quality and precision of TTM management.⁸

Our finding that fever incidence decreased over time may also be attributed to a learning effect as previously mentioned. Rates of extubations prior to 40 h in the ICU were $\leq 10\%$ in all groups, limiting potential confounding by skewed exclusion of temperature data following early extubation and termination of TTM treatment. Furthermore, a 33°C target temperature was associated with lower fever incidence as compared to 36°C or <37.5°C target regimes. The necessary use of a cooling device in patients with a 33°C target temperature makes temperature fluctuations unlikely to ever reach fever during the intervention period but cannot account for differences

during the normothermia phase. Utilization of a cooling device was documented in 100% of the patients with 33°C and 36°C targets and in 68% of the patients with the <37.5°C temperature target. Notwithstanding, the <37.5°C targeted patients exhibited a lower fever incidence than the 36°C target groups, making the degree of device usage an unlikely explanation. Whether this difference can be attributed to unidentified medical mechanisms or increased staff temperature adherence during a low-temperature protocol remains uncertain. Still, staff training is important as early fever within the first 48 h and post-hypothermia fever >38.5°C is associated with worse neurological outcome and lower survival^{28,29} and should be avoided and actively treated according to international post-resuscitation guidelines.³⁰

4.1 | Limitations

The inherent difficulties to comparing different patient cohorts from different periods in time is an important limitation. The cohorts differed to some inclusion criteria and treatment recommendations of the study protocols and the SOP which may have influenced the results. These include inclusion of only presumed cardiac cause-arrests in Period 1 and presumed cardiac cause or unknown in Period 2, while no such criterion was used in Period 3. Also, a rewarming rate of $\frac{1}{2}^{\circ}\text{C h}^{-1}$ was used in Periods 1 and 3, instead of $\frac{1}{3}^{\circ}\text{C h}^{-1}$ as in Period 1. Comparisons over time may be confounded by unidentified factors embedded in the evolution of treatment in general. Trial periods during which strict intervention protocols are implemented do not perfectly represent everyday practice. Indirect effects on staff adherence to protocols may also be exerted by the presence of stakeholders such as trial and clinical leaders which may not be sustained for long after the study periods.

A limitation of data precision potentially contributing to a slight overestimation of time to target temperature was the moderate resolution of temperature registrations with only one data point per hour. Consequently, if patient's target temperature was 33.1°C after 4 h, the first registration with a temperature on or below the target of 33°C would be after 5 h, overestimating the true time to target temperature. By trivial calculation, if reaching target temperatures was evenly distributed from minute 1 to 60 every hour, this overestimation would be around 30 min. Furthermore, there are principal technical limitations to the measurement of core temperature via a urinary bladder probe. Bladder probes do not provide accurate temperatures in anuric or oliguric patients. Also, when catheters are flushed, the injected solution might alter bladder temperature. However, it was pre-specified by the applied study protocols that temperature in oliguric patients should be measured via esophageal or intra-vascular probes.

Furthermore, the retrospective and single-center study design limit internal and external validity, respectively. While strict TTM protocols and well-established SOPs based on international guidelines should minimize treatment discrepancies both internally and externally the study design is susceptible to unidentified biases. While our

institution frequently handles OHCA patients enabling individual ICU staff members to acquire training in TTM protocols, a smaller institution with a lesser volume of such patients may not have this opportunity to increase its quality in TTM practice.

5 | CONCLUSION

In summary, our hypothesis that the observed increase in TTM quality, as assessed by the three elements in this study, stemmed from an increasingly acquired competence through learning and training is in line with the Cochrane systematic review demonstrating that similar patients treated within and outside RCT protocols attain similar results.³¹ Regardless of the underlying mechanism for learning, the results of this study further support protocolization of post-cardiac arrest care.

AUTHOR CONTRIBUTION

AS and CR conceived the study. AS retrieved and analysed the data. AS and LL drafted the manuscript. CR and MT revised the manuscript. All authors read and approved the final submission.

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