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RESEARCH ARTICLE

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Factors associated with fever after cardiac arrest: A post-hoc analysis of the FINNRESUSCI study

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Abstract

Background: Fever after cardiac arrest may impact outcome. We aimed to assess the incidence of fever in post-cardiac arrest patients, factors predicting fever and its association with functional outcome in patients treated without targeted temperature management (TTM).

Methods: The FINNRESUSCI observational cohort study in 2010–2011 included intensive care unit (ICU)-treated out-of-hospital cardiac arrest (OHCA) patients from all five Finnish university hospitals and 14 of 15 central hospitals. This post hoc analysis included those FINNRESUSCI study patients who were not treated with TH. We defined fever as at least one temperature measurement of ≥37.8°C within 72 h of ICU admission. The primary outcome was favourable functional outcome at 12 months, defined as cerebral performance category (CPC) of 1 or 2. Binary logistic regression models including witnessed arrest, bystander cardiopulmonary resuscitation (CPR), initial rhythm and delay of return of spontaneous circulation were used to compare the functional outcomes of the groups.

Results: There were 67,428 temperature measurements from 192 patients, of whom 89 (46%) experienced fever. Twelve-month CPC was missing in 7 patients, and 51 (28%) patients had favourable functional outcome at 12 months. The patients with shockable initial rhythms had a lower incidence of fever within 72 h of ICU admission (28% vs. 72%, $p < .01$), and the patients who experienced fever had a longer median return of spontaneous circulation (ROSC) delay (20 [IQR 10–30] vs. 14 [IQR 9–22] min, $p < .01$). Only initial non-shockable rhythm (OR 2.99, 95% CI 1.51–5.94) was associated with increased risk of fever within the first 72 h of ICU admission. Neither time in minutes nor area (minutes × degree celsius over threshold) over 37°C, 37.5°C, 38°C, 38.5°C, 39°C, 39.5°C or 40°C were significantly different in those with favourable functional outcome compared to those with unfavourable functional outcome within the first 24, 48 or 72 h from ICU admission. Fever was not associated with favourable functional outcome at 12 months (OR 0.90, 95% CI 0.44–1.84).

Conclusions: Half of OHCA patients not treated with TTM developed fever. We found no association between fever and outcome.

KEYWORDS

cardiac arrest, fever, hyperthermia, resuscitation, targeted temperature management, therapeuric hypothermia

Editorial Comment

How temperature in different ranges can effect recovery after cardiac arrest is still the subject of intense study. In this secondary analysis of a out-of-hospital cardiac arrest cohort in Finland, the outcomes for those not actively treated for temperature management were analyzed along with other case factors. For this cohort, no association was observed between temperature levels and early or later outcomes, favorable or unfavorable.

1 | INTRODUCTION

Fever may occur after out-of-hospital cardiac arrest (OHCA), and the European Resuscitation Council (ERC) recommends avoiding temperature of >37.7°C for 72 h after return of spontaneous circulation (ROSC) in comatose OHCA patients.[1] Initial studies showed that targeted temperature management (TTM) at 33°C increased the rate of favourable neurologic outcome in OHCA patients with an initial shockable rhythm,[2,3] but a recent large randomised controlled trial including 1850 patients showed that TTM at 33°C does not improve the functional outcome compared to targeted normothermia and may increase the risk of arrythmia with haemodynamic compromise.[4] No randomised trials have compared early controlled normothermia to no temperature control, but observational studies have shown an association between fever and unfavourable functional outcome.[1,5–7] Furthermore, it is not known if fever in these patients functions as an independent factor causing worse functional outcome or merely reflects a more severe ischaemic brain injury.[1]

Understanding risk factors of fever and its effects on functional outcome in patients not treated with TTM could eventually lead to better identification of patients at risk for fever and ultimately more focused treatment. We aimed to determine the occurrence of fever and factors associated with it in OHCA patients not treated with TTM. The observational FINNRESUSCI study was conducted when post-cardiac TTM targeted a temperature of 33°C and there were few other recommendations. In Finland, many hospitals focused on treating patients with similar characteristics as those included in the Hypothermia After Cardiac Arrest (HACA) trial.[2] This analysis gives the opportunity to study the development of fever when there were few recommendations on fever avoidance beyond TTM at 33°C.

2 | METHODS

2.1 | Study population and setting

This study is a post hoc analysis of FINNRESUSCI study patients who were not treated with TTM.[8] The FINNRESUSCI study was an observational prospective cohort study including OHCA patients from all Finnish university hospital intensive care units (ICU) and 14 of 15 central hospital ICUs during 2010–2011. The referral areas of the participating hospitals cover approximately 98% of the Finnish adult population. The inclusion criteria for the original study were OHCA, successful resuscitation, age over 18 years and post-resuscitation care in a participating ICU. The study did not have a specific protocol for TTM, but at the time, Finnish intensive care guidelines recommended TTM only if the OHCA was witnessed, the initial rhythm was shockable and the patient was unconscious at hospital or ICU admission.[9] However, some patients with non-shockable initial rhythms were also treated with TTM, as the 2010 European Resuscitation Council (ERC) guidelines suggested.[10] Baseline and resuscitation characteristics of the included patients were compared with patient population of the original FINNRESUSCI study. The neurological outcome was evaluated with cerebral performance category (CPC) scores at 12 months after OHCA. The living patients were telephoned by an experienced neurologist blinded to treatment in the ICU and the aetiology of the OHCA. CPC was assessed based on a structured interview. Patients with missing CPC scores at 12 months were included in the fever incidence calculations but excluded from further outcome analysis.

2.2 | Temperature data and outcomes

The temperature data were examined for coherence, and clearly faulty temperature measurements were excluded from the analysis.

No specific temperature measurement frequency or fever management protocol was applied. Core temperatures were measured with rectal or bladder probes. We defined fever as the occurrence of temperatures exceeding 37.7°C up to 72 h after ICU admission.[1,4,11] The a priori-decided resuscitation factors of witnessed cardiac arrest (yes/no), initial rhythm (shockable/non-shockable), ROSC delay and bystander cardiopulmonary resuscitation (CPR) were compared between the patients with and without fever.

The primary outcome was favourable functional outcome, which we defined as a CPC of 1 or 2 at 12 months. The association of the duration, timing, and magnitude of fever with functional outcome was studied with time and area, defined as time spent over the threshold multiplied by the difference between the threshold and measured values. We studied temperature thresholds in increments of 0.5°C from 37°C to 40°C. Analyses were performed separately for the first 24, 48 and 72 h from ICU admission to adjust for the timing of the fever. In addition, the incidence of sepsis, pneumonia and clinically reported infections was compared between the groups with and without fever. Additionally, we compared the characteristics of favourable and unfavourable functional outcome groups.

We further investigated the effect of the mean temperature of the first 48 h using binary logistic regression by modelling the temperature with restricted cubic splines, a statistical method for transforming the variable to allow nonlinear relationships towards the outcome while ensuring smooth and stable estimates. We show the effect of the mean temperature in the unadjusted model and when adjusted with acute physiology and chronic health evaluation (APACHE) without temperature, sequential organ failure assessment (SOFA) and non-shockable rhythm.

2.3 | Statistical analyses

We assessed continuous variables for normality with the Shapiro–Wilk test. As all the data were non-normally distributed, we compared them using the Mann–Whitney *U* test. Data is presented as medians with interquartile ranges (IQR) and we included the mean and maximum values in the threshold analysis. Categorical data was compared with the chi-square test and we present them as numbers and percentages. We developed multivariable binary logistic regression models to study whether the a priori-decided resuscitation factors were associated with fever. These variables were selected based on previous evidence. A second binary logistic regression analysis was conducted to determine the association of fever with functional outcome at 12 months; this model included the same factors as in the a priori-defined mortality model (i.e. witnessed arrest, initial rhythm, ROSC delay and bystander CPR).

We visualised temperatures using scatterplots with locally weighted scatterplot smoothed (loess) curves separately for the patients with favourable and unfavourable functional outcomes. We considered a *p* value <.05 as significant. The statistical analyses were conducted with IBM SPSS Statistics for Windows, Version 28.0 (IBM Corporation, Armonk, NY, USA) and R: A language and environment for statistical computing, Version 4.2.2 and 4.3.1. (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

3.1 | Study population

A total of 504 patients were included in the original FINNRESUSCI study (Figure S1). Of these patients, 192 were not treated with TTM and were included in this study. The differences between patients included in this study and the original FINNRESUSCI study are described in Table S1. A total of 67,428 temperature measurements at the ICU from the first 72 h of admission were included in the study (i.e. a median of 17 [IQR 5–488] measurements per patient). Of the 192 patients, data on long-term outcomes were missing for seven patients; therefore, 185 patients were included in the functional outcome assessments. Of these patients, 51 had favourable functional outcome and 134 had unfavourable functional outcome at 12 months. The initial rhythms of the patients not selected for TTM treatment and the analysis of the general characteristics of the whole patient population have been published previously.[8]

3.2 | Fever incidence

Of the 192 patients included, 89 (46%) experienced fever of over 37.7°C within 72 h of ICU admission. High temperatures of over 38.5°C, 39°C, 39.5°C and 40°C were experienced by 23 (12%), 11 (6%), 5 (3%) and 2 (1%) patients, respectively. A total of 57 patients had initially shockable rhythms, and most did not experience fever (41 [72%] vs. 16 [28%], $p < .01$). The patients who experienced fever had a younger median age (63 [IQR 51–75] vs. 69 [IQR 59–78] years, $p = .01$) and less hypertension (25 [28%] vs. 42 [41%], $p = .046$) and chronic renal failure (2 [2%] vs. 9 [9%], $p = .048$) in their medical histories. In addition, the patients who experienced fever had a longer median ROSC delay (20 [IQR 10–30 min] vs. 14 [IQR 9–22 min], $p = .02$) and were less commonly awake at ICU arrival (12 [13%] vs. 29 [28%], $p = .01$). The length of ICU stay was longer for the febrile patients (41 [IQR 24–64] vs. 25 [IQR 15–70] h). Of the 192 patients included, 124 (65%) were in the ICU at 24 h, 66 (34%) at 48 h and 42 (22%) at 72 h following admission. Of the discharged patients 50 (74%) had died at 24 h, 66 (52%) at 48 h and 79 (53%) at 72 h following ICU admission. The patients' demographic characteristics, resuscitation factors and ICU treatments are compared in Table 1.

The only factor that was significantly associated with fever was non-shockable rhythm, both in univariable analysis (OR 3.02, 95% CI 1.54–5.89, $p = .01$) and in multivariable analysis (OR 2.45, 95% CI 1.15–5.21, $p = .02$) (Table 2). The results did not change in a sensitivity analysis of the patients who were alive at 72 h after admission.; these results are presented in Table S2. In a second sensitivity analysis of patients who were still in the ICU at 24 h after admission none of the tested factors were significantly associated with fever.; these results are presented in Table S3.

TABLE 1 Demographic characteristics and resuscitation factors.

Variable	All patients (*n* = 192)	Fever experienced (*n* = 89)	No fever experienced (*n* = 103)	*p*
Patient characteristics				
Age (years), median (IQR)	67 (54–77)	63 (51–75)	69 (59–78)	.01
Male, *n* (%)	131 (68)	67 (75)	64 (62)	.31
Hypertension, *n* (%)	67 (35)	25 (28)	42 (41)	.046
Coronary artery disease, *n* (%)	58 (30)	26 (29)	32 (31)	.69
Diabetes, *n* (%)	38 (20)	15 (17)	23 (22)	.30
Heart failure, *n* (%)	31 (16)	18 (20)	13 (13)	.18
Chronic renal failure, *n* (%)	11 (6)	2 (2)	9 (9)	.048
SAPS II, 24 h median (IQR)	59 (47–71)	60 (52–66)	59 (41–76)	.91
APACHE II, median (IQR)	30 (24–36)	31 (25–34)	29 (21–38)	.52
SOFA, median (IQR)	9 (7–11)	9 (7–10)	9 (6–12)	.76
Resuscitation				
Bystander CPR, *n* (%)	77 (40)	34 (38)	43 (42)	.89
Witnessed arrest, *n* (%)	168 (88)	78 (88)	90 (87)	.85
Shockable rhythm, *n* (%)	57 (30)	16 (18)	41 (40)	<.01
Non-shockable rhythm, *n* (%)	135 (70)	73 (82)	62 (60)	<.01
ROSC delay (min), median (IQR)[a]	15 (10–25)	20 (10–30)	14 (9–22)	.02
Awake at ICU arrival, *n* (%)	41 (21)	12 (13)	29 (28)	.01
Treatment during ICU stay				
Sedation length (*h*), median (IQR)	16 (9–24)	18 (11–33)	14 (7–21)	.10
Coronary angiography, *n* (%)	20 (10)	9 (10)	11 (11)	.85
PCI, *n* (%)	8 (4)	2 (2)	6 (6)	.20
Renal replacement therapy, *n* (%)	6 (3)	3 (3)	3 (3)	.88
Infection				
Pneumonia, *n* (%)	49 (26)	27 (30)	22 (26)	.16
Sepsis, *n* (%)	10 (5)	4 (4)	6 (6)	.68
Any infection, *n* (%)	55 (29)	27 (30)	28 (27)	.63
Outcome				
ICU LOS (h), median (IQR)	35 (18–66)	41 (24–64)	25 (15–70)	.01
ICU mortality, *n* (%)	57 (30)	24 (27)	33 (32)	.44
Hospital mortality, *n* (%)	106 (55)	54 (61)	52 (50)	.16
1-year mortality, *n* (%)[b]	129 (70)	66 (65)	63 (75)	.09
1-year CPC 1–2, *n* (%)[b]	51 (28)	20 (23)	31 (32)	.19
1-year CPC 3–5, *n* (%)[b]	134 (72)	67 (77)	67 (68)	.19

Abbreviations: APACHE, acute physiology and chronic health evaluation II score; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; IQR, interquartile range; PCI, percutaneous coronary intervention; ROSC, return of spontaneous circulation; SOFA, sequential organ failure assessment.
[a]Data missing for one patient.
[b]Data missing for 7 patients.

The incidence of sepsis (4 [4%] vs. 6 [6%], $p = .68$), pneumonia (27 [30%] vs. 22 [21%], $p = .16$) or any reported infection (27 [30%] vs. 28 [27%], $p = .63$) did not differ between the patients who experienced fever and those who did not. However, the patients with fever had higher median c-reactive protein (CRP) concentration in plasma within the first 72 h of ICU admission (86 [IQR 43–134] vs. 49 [IQR 17–95], $p = .001$) and higher median white blood cell (WBC) count (14.5 [IQR 11.4–17.4] vs. 11.4 [IQR 9.1–16.4]) within the first 72 h of ICU admission.

3.3 | Temperature threshold analysis

The median times spent over all the studied thresholds were comparable across both functional outcome groups. This result remained when considering separately the first 24, 48 and 72 h after ICU admission. The results of the time over thresholds analysis are presented in Table 3. Including the magnitude in addition to the length in minutes, the minutes × degrees over

TABLE 2 Logistic regression model predicting the odds of fever within 72 h of ICU admission.

Independent variable	OR[a] in univariable analysis in all patients (95% CI)	*p*	AIC of reduced model	OR[a] in multivariable analysis in all patients (95% CI)	*p*	AIC of reduced model
Witnessed arrest	1.02 (0.43–2.42)	.68	11.2	1.24 (0.50–3.06)	.65	202.9
Non-shockable rhythm	3.02 (1.54–5.89)	.01	22.9	2.45 (1.15–5.21)	.02	208.2
ROSC delay (min)	1.00 (0.99–1.01)	.73	114.0	1.00 (0.98–1.01)	.90	202.7
Bystander CPR	0.86 (0.48–1.54)	.62	12.2	0.93 (0.51–1.70)	.81	202.7
Awake at ICU arrival	0.40 (0.19–0.84)	.02	17.8	0.60 (0.25–1.41)	.24	204.1

Abbreviations: CA, cardiac arrest; CI, Confidence interval; CPR, cardiopulmonary resuscitation; OR, odds ratio; ROSC, return of spontaneous circulation.
[a]A higher OR represents a higher probability for fever within 72 h of ICU admission.

TABLE 3 Threshold comparison results.

Threshold	*n*	All patients (*n* = 192)**	CPC 1–2 at 12 months (*n* = 51)	CPC 3–5 at 12 months (*n* = 134)	*p*
Minutes spent over threshold, median (IQR)/mean (max.) within 24 h of ICU arrival	CPC1-2/CPC3-5				
37°C	36/80	263 (0–776)/419 (1438)	262 (0–748)/428 (1425)	256 (0–779)/414 (1437)	.72
37.5°C	23/59	0 (0–278)/254 (1349)	0 (0–258)/203 (1349)	0 (0–547)/276 (1310)	.23
38°C	12/33	*/119 (1204)	*/91 (1202)	0 (0–39)/134 (1204)	.35
38.5°C	6/17	*/47 (1099)	*/21 (901)	*/60 (1099)	.47
39°C	2/9	*/17 (740)	*/3 (106)	*/23 (740)	.42
39.5°C	0/5	*/6 (740)	*/0 (0)	*/9 (740)	.16
40°C	0/2	*/2 (350)	*/0 (0)	*/4 (350)	.38
Minutes spent over threshold, median (IQR)/mean (max.) within 48 h of ICU arrival					
37°C	42/91	571 (0–1353)/783 (2850)	720 (25–1645)/945 (2850)	501 (0–1260)/723 (2646)	.10
37.5°C	29/73	111 (0–712)/464 (2774)	78 (0–720)/506 (2774)	206 (0–737)/454 (2625)	.95
38°C	16/43	0 (0–215)/228 (2565)	0 (0–327)/246 (1845)	0 (0–200)/231 (2565)	.93
38.5°C	11/23	*/91 (1710)	*/60 (900)	*/107 (1710)	.81
39°C	5/12	*/25 (975)	*/11 (285)	*/32 (975)	.65
39.5°C	0/7	*/11 (750)	*/0 (0)	*/16 (750)	.10
40°C	0/3	*/3 (350)	*/0 (0)	*/5 (350)	.28
Minutes spent over threshold, median (IQR)/mean (max) within 72 h of ICU arrival					
37°C	42/91	624 (0–1610)/950 (4200)	920 (25–1963)/1112 (4200)	551 (0–1511)/892 (4080)	.20
37.5°C	29/73	250 (0–851)/554 (4065)	78 (0–720)/600 (3662)	272 (0–893)/547 (4065)	.76
38°C	16/43	0 (0–235)/277 (3810)	0 (0–356)/292 (2590)	0 (0–239)/283 (3810)	.69
38.5°C	11/23	*/107 (2310)	*/64 (901)	*/129 (2310)	.89
39°C	5/12	*/29 (975)	*/12 (285)	*/37 (975)	.82
39.5°C	0/7	*/11 (750)	*/0 (0)	*/16 (750)	.10
40°C	0/3	*/3 (0–350)	*/0 (0)	*/5 (350)	.28

Note: * = 0 (0–0); **CPC missing from 7 patients.
Abbreviations: CPC, cerebral performance category; ICU, intensive care unit; IQR, interquartile range.

thresholds results were also comparable in both functional outcome groups (Table S4). No identifiable level of fever was clearly associated with functional outcome in either of the threshold analyses.

3.4 | Outcomes

We found no statistically significant difference in the incidence/occurrence of fever between the functional outcome groups;

20 patients (39%) experienced fever in the favourable outcome group and 67 patients (50%) in the unfavourable functional outcome group ($p = .19$). However, the length of ICU stay was longer for the febrile patients (41 [IQR 24–64] vs. 25 [IQR 15–70] h), $p = .01$. Although statistically not significant, non-febrile patients had more commonly favourable functional outcomes (31 [32%] vs. 20 [23%], $p = .19$).

In the binary logistic regression model, fever was not significantly associated with functional favourable outcome at 12 months (OR 0.65, 95% CI 0.34–1.24, $p = .19$). In the univariate analysis, initial shockable rhythm (OR 3.82, 95% CI 2.05–7.12, $p < .01$) and shorter ROSC delay in minutes (OR 0.97, 95% CI 0.95–1.00, $p = .04$) were significantly associated with favourable functional outcome. In a multivariable binary logistic regression model that included fever, initial rhythm, witnessed OHCA, ROSC delay and bystander CPR, only initial shockable rhythm was associated with favourable functional outcome at 12 months (OR 5.64, 95% CI 2.65–12.01, $p < .01$), while fever remained statistically non-significant (OR 0.90, 95% CI 0.44–1.84, $p = .77$). A sensitivity analysis was conducted with all 7 patients missing with data for functional outcome dead and alive, but results remained unchanged. The regression model results are presented in Table 4 and log odds for mean and maximum temperature predicting favourable functional outcome are modelled in Figure 2. Furthermore, maximum temperature within 72 h of ICU admission was not associated with favourable functional outcome in a binary logistic regression model (OR 1.11, 95% CI 0.89–1.39, $p = .36$). We conducted a sensitivity analysis of the patients who were still in the ICU after 24 h of admission, and the results remained unchanged. In another sensitivity analysis that excluded all patients awake at the ICU arrival, the initially shockable rhythm was not associated with favourable functional outcome (OR 1.81, 95% CI 0.66–4.94, $p = .25$) while other results remained unchanged. The results of the above-mentioned analysis are presented in Table S5. When awake patients were excluded from the functional outcome analysis, the initial shockable rhythm was no longer significantly associated with favourable functional outcome (OR 1.81, 95% CI 0.66–4.94, $p = .25$), but other results remained unchanged (Table S6). Patients with unfavourable functional outcomes had lower SAPS II, APACHE II, and SOFA scores, delayed ROSC, and more initially non-shockable rhythms. In the group with favourable outcomes, angiography or PCI was performed more commonly, but there were no significant differences in infections or medical history between the two groups (Table S7).

All the measured temperatures of the included patients are presented in scatterplots with loess smoothed trend lines in Figure 1. Median and IQR of temperatures for first 72 h from ICU admission are presented separately for favourable and unfavourable functional outcome groups in Figures S1 and S2. As the statistical analysis also showed, the temperature trends remained comparable in both the favourable and unfavourable functional outcome groups.

The effect of mean and max temperatures on outcome was tested using binary logistic regression by modelling the temperature using restricted cubic splines to allow for a non-linear effect. We conducted separate models adjusting for APACHE score, initial rhythm and SOFA score, and the results are shown in Figure 2A,B. The association of mean and max temperatures with outcome tended to form U-shaped curves in all the models. While comparing the models with the temperature to models without it using likelihood ratio tests, adding temperature to the models improved them in all cases ($p < .05$) apart from mean temperature and APACHE score. However, when patients who died at the ICU were excluded, the U-shape vanished, and the inclusion of temperature did not significantly improve the model. The results are presented in Figure S4.

4 | DISCUSSION

In this post hoc analysis of the FINNRESUSCI study,[8] we studied the incidence of fever, factors associated with the risk of developing fever and the association of fever with functional outcome in a selected population of ICU-treated OHCA patients who were not treated with TTM. Half of the patients developed fever (≥37.8°C) during the first 72 h of ICU admission. In most cases fever was mild, and temperatures above 39°C were uncommon. Fever was more commonly found in younger patients, in those with no history of hypertension or chronic renal failure and in those with an initially non-shockable rhythm. No association between fever and functional outcome at 12 months was found even though the point estimated suggested harm from fever. No specific threshold for fever was found to be significantly associated with functional outcome at 24, 48 or 72 h from ICU admission.

Fever is common in critically ill patients, with incidence varying in different populations. In ICU patients, the incidence ranges from 26%

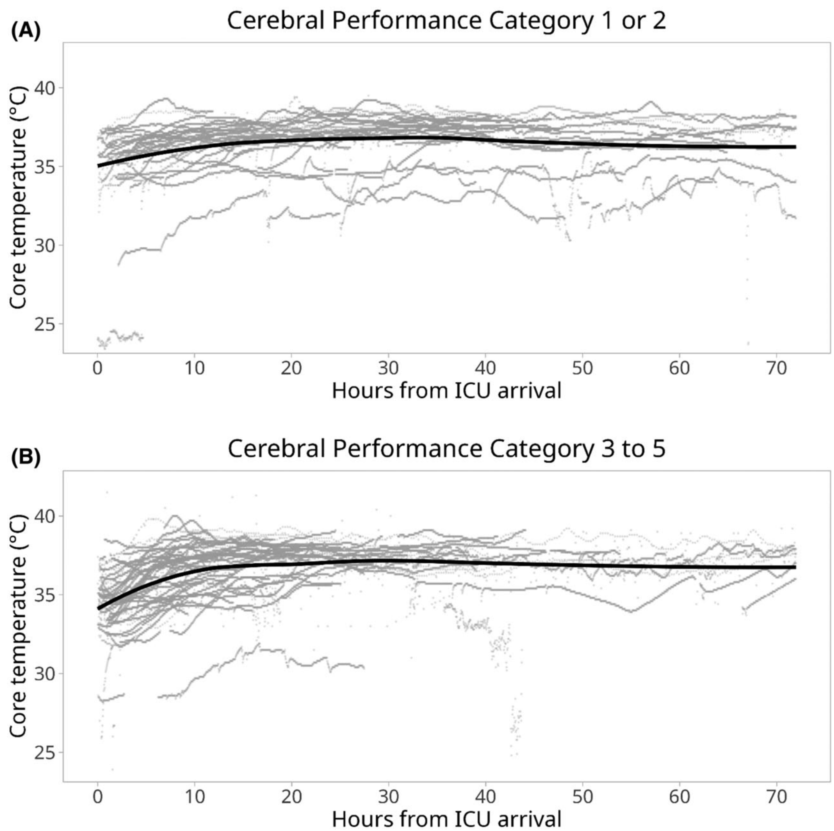
TABLE 4 Logistic regression model predicting the favourable functional outcome at 12 months.

Independent variable	OR[a] in univariate analysis (95% CI)	p	OR[a] in multivariate analysis (95% CI)	p
Fever >37.7°C	0.65 (0.34–1.24)	.19	0.90 (0.44–1.84)	.77
Witnessed arrest	0.91 (0.36–2.35)	.85	0.56 (0.20–1.60)	.28
Bystander CPR	1.12 (0.61–2.03)	.72	0.73 (0.35–1.51)	.73
Shockable rhythm	3.82 (2.05–7.12)	<.01	5.64 (2.65–12.01)	<.01
ROSC delay (min)	0.97 (0.95–1.00)	.04	0.99 (0.98–1.01)	.65

Abbreviations: CI, Confidence interval; CPR, cardiopulmonary resuscitation; OR, odds ratio; ROSC, return of spontaneous circulation.

[a]A higher odds ratio (OR) represents a higher probability for favourable functional outcome at 12 months.

FIGURE 1 Loess smoothed temperature scatterplot for (A) favourable functional outcome patients and (B) unfavourable functional outcome patients.



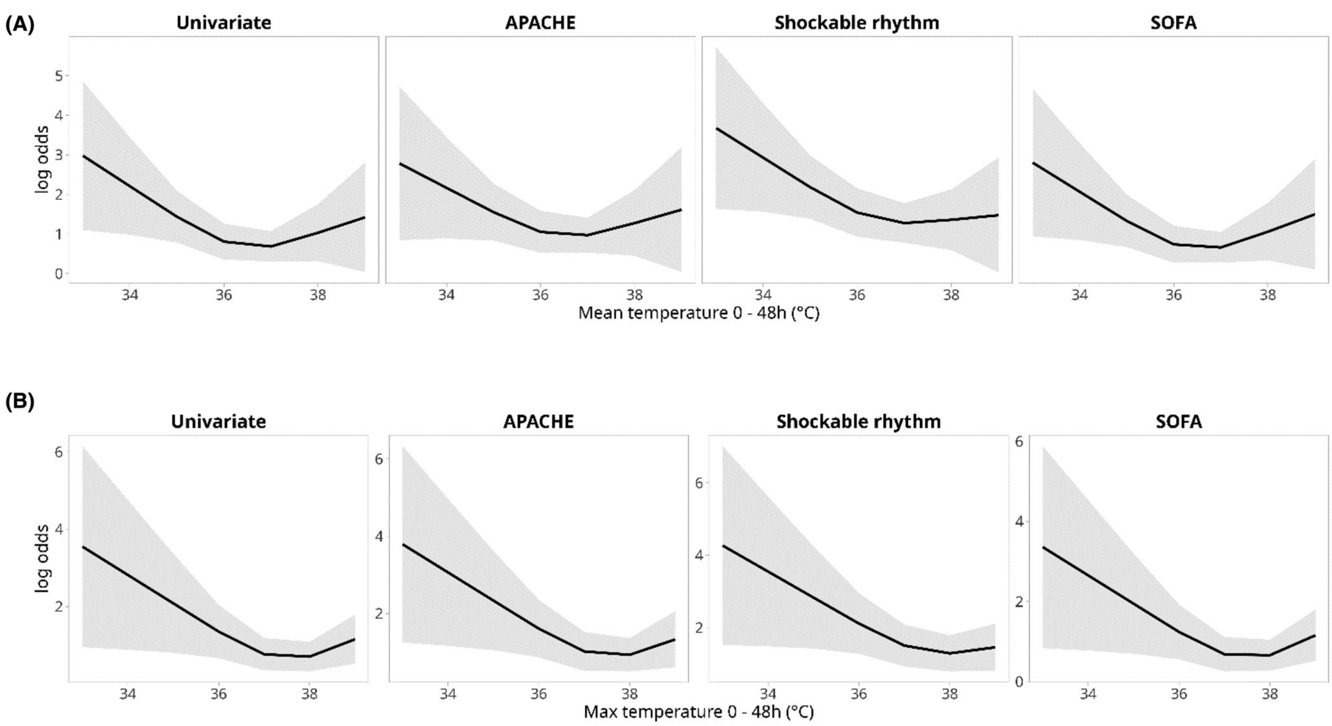


FIGURE 2 Log odds values for mean (A) and maximum (B) temperature predicting unfavourable functional outcome (CPC 3–5) at 12 months, univariate model and adjusted for the APACHE score, initial rhythm, and the SOFA score.

to 70%.[12] In a large study with over 100,000 patients, Saxena et al. reported peak temperature incidences of 38.0°C–38.4°C in 15%, 38.5°C–38.9°C in 7%, 39.0°C–39.4°C in 3%, 39.5°C–39.9°C in 1% and ≥40.0°C in <1% of patients with traumatic brain injury or stroke.[13] Our findings on the incidence of fever after cardiac arrest in patients not treated with TTM appear comparable. These data indicate that mild fever is common but high fever much less so.[6,7,12,14–19] However, we acknowledge that the cardiac arrest population may differ from the general ICU population.

Previously, two theories for fever after OHCA have been put forward. One possible cause is that fever is related to a concomitant bacterial infection. Gaussorgues et al.[20] and Gueugniaud et al.[21] found that two or more blood cultures positive for infection within 12 h after resuscitation increased the likelihood of fever. Moreover, fever after OHCA could be a physiologic result of ischaemic injury and due to systemic inflammatory response.[7,16,22,23] This theory also seems plausible, as studies have shown elevated inflammatory markers after OHCA without clinically identified infections.[7,18]

Whether fever impacts outcome is a complex question and likely relates to both the underlying illness and the reason for the fever. Young et al. found that in ICU patients, fever in patients without infections was associated with increased in-hospital mortality, and fever in patients with infections was associated with decreased in-hospital mortality.[24] The association between fever and outcomes vary in different populations.[13,25] In a study by Langhelle and colleagues a median temperature of 37.8°C was found in a study of over 400 patients and temperatures above this were associated with mortality.[26] Some previous studies before the TTM era did not find association between fever and functional outcome.[27–29] In the current study, the strongest predictor of fever was a non-shockable initial rhythm. This supports the possibility that fever may be the result of ischaemic injury, as an initially non-shockable rhythm is a factor for unfavourable functional outcome.[30]

Previous studies have shown associations between fever and unfavourable functional outcome for patients treated in the ICU.[7,19,31–33] In 2002, Zeiner and colleagues, in a study including 151 patients not treated with TH, found that a maximum temperature >37°C increased the risk of unfavourable functional outcome. In their study, a lower minimum temperature within 4 h and a higher maximum temperature within 48 h of ROSC were associated with unfavourable functional oucome.[7] We were unable to replicate these findings but acknowledge that the sample size and non-invasive treatment methods for fever (i.e. paracetamol and/or uncovering of the patient's body) may have impacted our results, and as seen in Figures S2 and S3, there was a slight trend towards lower temperatures in unfavourable functional outcome patients for first hours from ICU admission.

Whether treating fever improves outcome is unknown. Fever as a protective mechanism in sepsis has been indicated, and it appears that spontaneous normothermia or mild hypothermia may be an ominous sign.[31,32,34,35] A recent meta-analysis by Holgersson and colleagues concluded that fever therapy does not seem to affect mortality, and does not have serious adverse events.[36] The effects of commonly used antipyretics, such as nonsteroidal anti-inflammatories (NSAID) and paracetamol, on fever and functional outcome seem to be modest or non-existent, whereas NSAIDs are associated with increased bleeding risks and renal toxicity, and paracetamol in high doses can cause liver toxicity.[25,37,38] Furthermore, a recent study by Hassager and colleagues showed that prolonged device-based prevention of fever for 72 h did not improve the functional outcome compared to 36-h treatment.[39] However, a large trial by Lascarrou and colleagues concluded that TTM was associated with favourable functional outcomes compared with targeted normothermia.[40] Nevertheless, recent studies do not show a clear consensus of the effects of TTM on functional outcome.[1–4,7,40]

Our findings should be interpreted keeping in mind some strengths and limitations. Our study sample included a substantial amount of temperature data collected from multiple centres from a real-life setting. We had extensive data on factors at resuscitation, and long-term outcome was determined prospectively by a person unaware of the ICU treatment. We do, however, recognise some limitations. First, the sample size was limited, and some patients may have died or been discharged from the ICU before fever could have occurred. Second, we did not have data on what means were used to non-invasively treat fever, such as antipyretics, and, if so, what types were given.[10] Third, the means and frequencies of temperature measurements varied between treatment centres, and we do not have temperature data after transfers to non-ICU wards. Fourth, this dataset is more than a decade old, and it is possible that ICU treatment practices have changed. Fifth, Given the low likelihood of high fever, our sample size may be too small to identify associationsselc between high fever and patient outcome. Sixth, it is likely that our patient sample included patients perceived to have either too good or too poor prognoses, which was why TTM targeting 33°C was not used. There was no nationally used specific protocol bundle for post-arrest care at the time, but commonly treatment was based on available literature. Seventh, no statistical correction for multiple testing was used due to the exploratory nature of the study. Finally, this cohort of patients is selected as the guidelines at the time of the original study mainly recommended TTM for unconscious patients with an initial shockable rhythm. In addition, the aetiology of cardiac arrest may differ from general OHCA patients and thus this population may not be representative of cardiac arrest patients treated in the ICU.

5 | CONCLUSIONS

Half of OHCA patients not treated with TTM developed fever. In most cases, fever was mild, and very high fever was uncommon. Fever was more common in patients with a non-shockable initial rhythm. Although fever timing, duration and magnitude were not associated with patient outcome, the point estimate suggested an association between fever and unfavourable outcome.

AUTHOR CONTRIBUTIONS

AH, MR and MSK designed this post-hoc study. MR, JK, JV, MT, TV planned and conducted the original FINNRESUSCI study. AH, MSK and ML prepared a statistical analysis plan that was approved by all authors. AH and ML conducted the statistical analysis. AH and MSK prepared a first draft of the paper. All authors critically reviewed the draft and approved the final version.

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CONFLICT OF INTEREST STATEMENT

Markus Skrifvars reports speaker fees in 2021 and 2022 from BARD Medical. All other authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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