


ORIGINAL



Fever control in critically ill adults. An individual patient data meta-analysis of randomised controlled trials

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Abstract

Purpose: One potential way to protect patients from the physiological demands that are a consequence of fever is to aim to prevent fever and to treat it assiduously when it occurs. Our primary hypothesis was that more active fever management would increase survival among patient subgroups with limited physiological reserves such as older patients, patients with higher illness acuity, and those requiring organ support.

Methods: We conducted an individual-level patient data meta-analysis of randomised controlled trials to compare the outcomes of ICU patients who received more active fever management with the outcomes of patients who received less active fever management. The primary outcome variable of interest was the unadjusted time to death after randomisation.

Results: Of 1413 trial participants, 707 were assigned to more active fever management and 706 were assigned to less active fever management. There was no statistically significant heterogeneity in the effect of more active compared with less active fever management on survival in any of the pre-specified subgroups that were chosen to identify patients with limited physiological reserves. Overall, more active fever management did not result in a statistically significant difference in survival time compared with less active fever management [hazard ratio 0.91; (95% CI 0.75–1.10), $P=0.32$].

Conclusions: Our findings do not support the hypothesis that more active fever management increases survival compared with less active fever management overall or in patients with limited physiological reserves.

Keywords: Sepsis, Fever, Septic shock, Paracetamol, Non-steroidal anti-inflammatory drugs, Physical cooling

Introduction

Fever occurs commonly in intensive care (ICU) patients and increases metabolic demand [1]. Increasing metabolic demand has important physiological consequences on oxygen consumption and cardiac output [1]. One

potential way to protect patients from the physiological demands that are a consequence of fever is to aim to prevent fever and to treat it assiduously when it develops [2]. This strategy is an attractive candidate intervention to improve outcomes in the ICU setting because patients with a range of critical illnesses including major trauma, infection, acute myocardial infarction, and pancreatitis develop fever [3–5], and many such patients have limited physiological reserves.

Body temperature can be manipulated in ICU patients with medicines [6, 7] and physical cooling devices [8] allowing for more or less active approaches to fever

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management. In a recent systematic review and aggregate data meta-analysis evaluating the effect of fever management on all-cause mortality in ICU patients, we found that more active fever management neither increased nor decreased mortality in critically ill adults compared with less active fever management [9]. However, despite these findings, it is plausible that the balance of risks and benefits of active fever management in ICU patients varies based on the physiological reserves of the patients being treated and the nature of their illness [10]. In this context, we submit that physiological reserves are reasonably defined as the capacity of a patient to cope with the physiological demands associated with fever and depend on patients' physiology, illness severity, and the organ support they require.

Our primary hypothesis was that more active fever management would increase survival among patient subgroups with limited physiological reserves such as older patients, patients with higher illness acuity, and those with very high body temperature (≥ 39.5 °C). Because fever is part of the adaptive host response to infection [11], we further hypothesised that more active fever management would improve survival in the absence of infection but not in the presence of infection.

Methods

Study design

To address our hypotheses, we conducted an individual-level patient data meta-analysis (IPDMA) using available data from randomised controlled trials identified in our recent systematic review and aggregate data meta-analysis [9]. We contacted lead investigators for all randomised controlled trials identified in the recent systematic review and requested access to individual patient-level data (see ESM for details). The search strategy used in our systematic review has been published previously [9]; however, in brief, we searched major databases for randomised controlled trials evaluating fever management in adult ICU patients excluding trials where the intervention involved therapeutic hypothermia. We included trials that evaluated any treatment administered commonly to febrile patients to reduce body temperature. The protocol for this IPDMA was posted online on 29 June 2018 at <http://wellingtonicu.com/PubResPres/Protocols/> in advance of analyses being undertaken.

Data extraction and cleaning for analysis

Pre-randomisation (baseline) data points were extracted from individual study databases. These were age, gender, invasively ventilated (yes or no), receiving inotropes and/or vasopressors at baseline (yes or no), suspected infection at baseline (yes or no), Acute Physiology And Chronic Health Evaluation (APACHE) II score [12],

Take-home message

We conducted an individual level patient data meta-analysis of randomised controlled trials to compare the outcomes of ICU patients who received more active fever management with the outcomes of patients who received less active fever management. Our findings do not support the hypothesis that more active fever management increases survival compared with less active fever management overall, or in patients with limited physiological reserves.

mean arterial pressure (mmHg), heart rate (beats per min), serum creatinine ($\mu\text{mol/l}$), and body temperature (°C).

We sought to compare the outcomes of patients who received more active fever management with the outcomes of patients who received less active fever management. Accordingly, where studies compared an antipyretic drug with placebo, the patients allocated to the antipyretic drug were considered to have received more active fever management. Where studies compared different thresholds for temperature treatment, patients allocated to the group with the lowest body temperature target were considered to have received more active fever management.

Time to death after randomisation was defined as the difference between time zero (T0) and the date and time of death. T0 was generally defined as the date and time of randomisation. In one study, where the date and time of randomisation were not recorded, the date and time of administration of the first dose of study medication defined T0. Where no time, only a date, was available to define either T0 or the time of death, the time(s) were assumed to be 12:00 p.m. The time for censored participants (those who did not die) was defined as the last time of observation in relation to the time of randomisation as described above. All patients who died on or before the date of ICU discharge were defined as dead for the purposes of evaluating the end point 'mortality at ICU discharge'. ICU and hospital length of stay were defined as the difference between T0 as described above and ICU and hospital discharge, respectively. Where no time, only a date, was available to define either T0 or the time of discharge, the time(s) were assumed to be 12:00 p.m. Body temperature at 6, 12, 24, 48, and 72 h after randomisation were included in the IPDMA database. One study reported temperature data at 4 h and 8 h after randomisation [7]. For this study, the 6-h temperature data point was calculated by averaging the values from the 4–8 h time points.

Outcomes

The primary outcome variable of interest was the time to death after randomisation. This outcome was chosen

Table 1 Baseline characteristics

Characteristic	More active fever control (n = 707)	Less active fever control (n = 706)
Age (years)	56.7 ± 17.2 (n = 705)	56.5 ± 17.2 (n = 705)
Male sex, n/N (%)	415/707 (58.7)	397/706 (56.2)
Intensive care support, n/N (%)		
Invasive mechanical ventilation	498/707 (70.4)	500/706 (70.8)
Receiving inotropes and/or vasopressors	358/707 (50.6)	377/706 (53.4)
APACHE-II score ^a	17.1 ± 7.1 (n = 605)	17.3 ± 7.4 (n = 605)
SAPS score ^b	76.9 ± 13.9 (n = 101)	78.3 ± 14.4 (n = 99)
Biochemistry and physiology		
Heart rate (beats per min)	106 ± 22 (n = 703)	107 ± 23 (n = 705)
Mean arterial pressure (mmHg)	78 ± 15 (n = 704)	77 ± 14 (n = 705)
Temperature (°C)	38.5 ± 1.0 (n = 703)	38.5 ± 0.9 (n = 706)
Serum creatinine (µmol/l)	134 ± 128 (n = 536)	129 ± 123 (n = 535)
Study, n/N (%)		
Bernard et al.	224/707 (31.7)	231/706 (32.7)
Niven et al.	14/707 (2.0)	12/706 (1.7)
Saxena et al.	21/707 (3.0)	20/706 (2.8)
Schortgen et al.	101/707 (14.3)	99/706 (14.0)
Young et al.	347/707 (49.1)	344/706 (48.7)
Suspected infection at baseline	672/707 (95.1)	673/706 (95.3)

Plus/minus values are mean ± SD

APACHE Acute Physiology and Chronic Health Evaluation, ICU intensive care unit, SAPS Simplified Acute Physiology Score

^a Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death. APACHE II scores were not collected for participants in the Schortgen et al. trial

^b Scores on the SAPS III range from 0 to 263, with higher scores indicating more severe disease and a higher risk of death. SAPS III was only collected for participants in the Schortgen et al. trial

as the primary outcome because it allowed multiple trials with different durations of follow-up to be combined without loss of data. Secondary outcomes were mortality at ICU discharge, ICU and hospital length of stay, and body temperature at 6, 12, 24, 48, and 72 h following randomisation.

Statistical analyses

Data summaries by treatment group are frequency and proportions expressed as percentages for categorical data and mean ± standard deviation for continuous data.

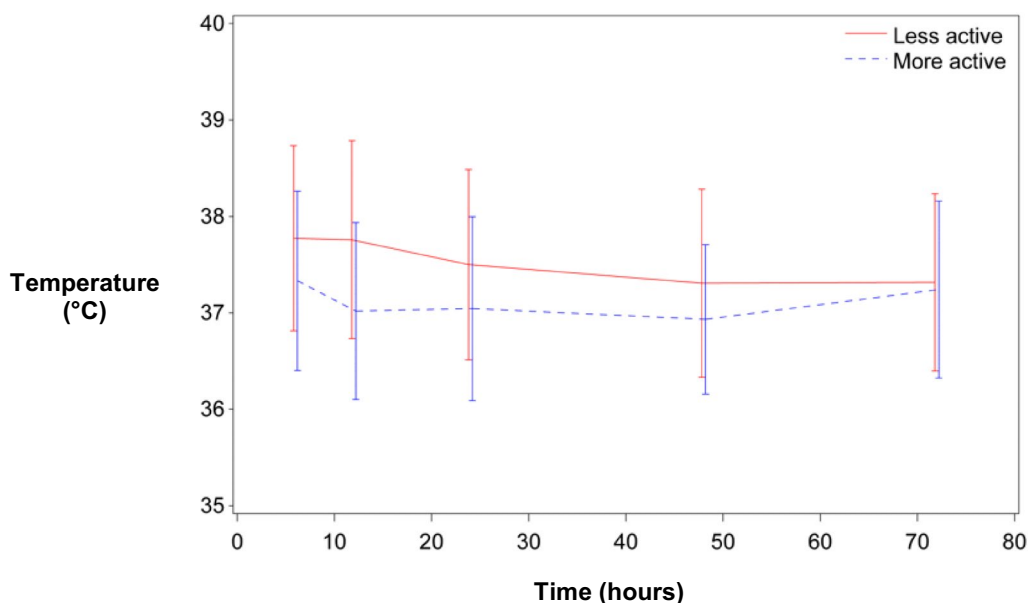
Survival times use log-rank tests and are shown as Kaplan-Meier curves and relative survival estimated with a Cox proportional-hazards model. The primary analysis model was adjusted for study as fixed effect; however, a sensitivity analysis adjusted for baseline covariates of age, sex, and APACHE-II score was also performed incorporating individual study as a fixed effect. Because the APACHE-II score was not available for one study [8] two post hoc sensitivity analyses were used: one in which the APACHE-II score was not included in the adjusted model and another in which illness severity scores based on Simplified Acute Physiology Score (SAPS3) [13] were

used in place of APACHE-II scores for the study that did not include APACHE-II data (see ESM for details).

ICU mortality was compared by treatment group using logistic regression with analyses performed in a similar fashion to those performed for survival. Mortality data by treatment group are reported as frequencies with proportions expressed as percentages with treatment effects reported as odds ratios.

ICU and hospital length of stay were highly skewed and were analysed on the logarithm transformed scale. These variables are summarised as geometric mean with treatment effects expressed as a ratio of geometric means. A post hoc analysis evaluating whether ICU length of stay differed in relation to randomised treatment for patients who did or did not die in the ICU used an ANCOVA-based interaction model.

Interaction analyses were also used to explore whether survival, ICU mortality, ICU length of stay, or hospital length of stay varied in pre-specified subgroups based on pre-randomisation characteristics. The subgroups of interest were: invasively ventilated or not; receiving inotropes and/or vasopressors or not; both invasively ventilated and receiving inotropes and/or vasopressors



Time point	Mean difference, °C (95% CI)	P value*
6 hours	-0.49 (-0.60 to -0.38)	<0.001
12 hours	-0.73 (-0.83 to -0.63)	<0.001
24 hours	-0.33 (-0.46 to -0.2)	<0.001
48 hours	0.33 (-0.46 to -0.2)	<0.001
72 hours	-0.04 (-0.15 to 0.08)	0.52

Fig. 1 Body temperature over time with more active fever management vs. less active fever management. *P value for the interaction term evaluating temperature difference by time from randomisation was <0.001 indicating a statistically significant variation in the temperature difference by treatment over time

or not; infection present or not; high fever (≥ 39.5 °C or < 39.5 °C); age (≥ 75 years or < 75 years); APACHE-II score ≥ 25 or < 25 ; and physical cooling included in the study intervention or physical cooling not included in the study intervention.

Temperature was analysed using a mixed linear model with a power exponential structure for the correlation between repeated measurements and the time by randomisation interaction term used to estimate temperature differences between randomised treatments at each time point.

A two-sided *P* value < 0.05 was considered to indicate statistical significance and estimates are shown with 95% confidence intervals (CI). No adjustment was made for multiple comparisons.

SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for analyses.

Results

Data sources

Individual-level patient data were obtained for 5 [6–8, 14, 15] of 13 randomised controlled trials identified in

the systematic review conducted for our aggregate data meta-analysis [9]. This included the three largest trials [6–8] and resulted in data from 1413 of 1780 (79.4%) of the participants in the original trials being included in this analysis. Details of included trials and those trials from which data could not be obtained are shown in the ESM.

Patient characteristics

Of the 1413 participants included in this analysis, 707 were assigned to more active fever management and 706 were assigned to less active fever management. The study groups had similar characteristics at baseline (Table 1). More than 95% of participants were suspected to have an infection at baseline.

Effects of fever management on body temperature

Patients assigned to more active fever management had statistically significantly lower body temperature than patients assigned to less active fever management (Fig. 1). The effect of study treatment on body temperature varied with time with a maximum temperature difference

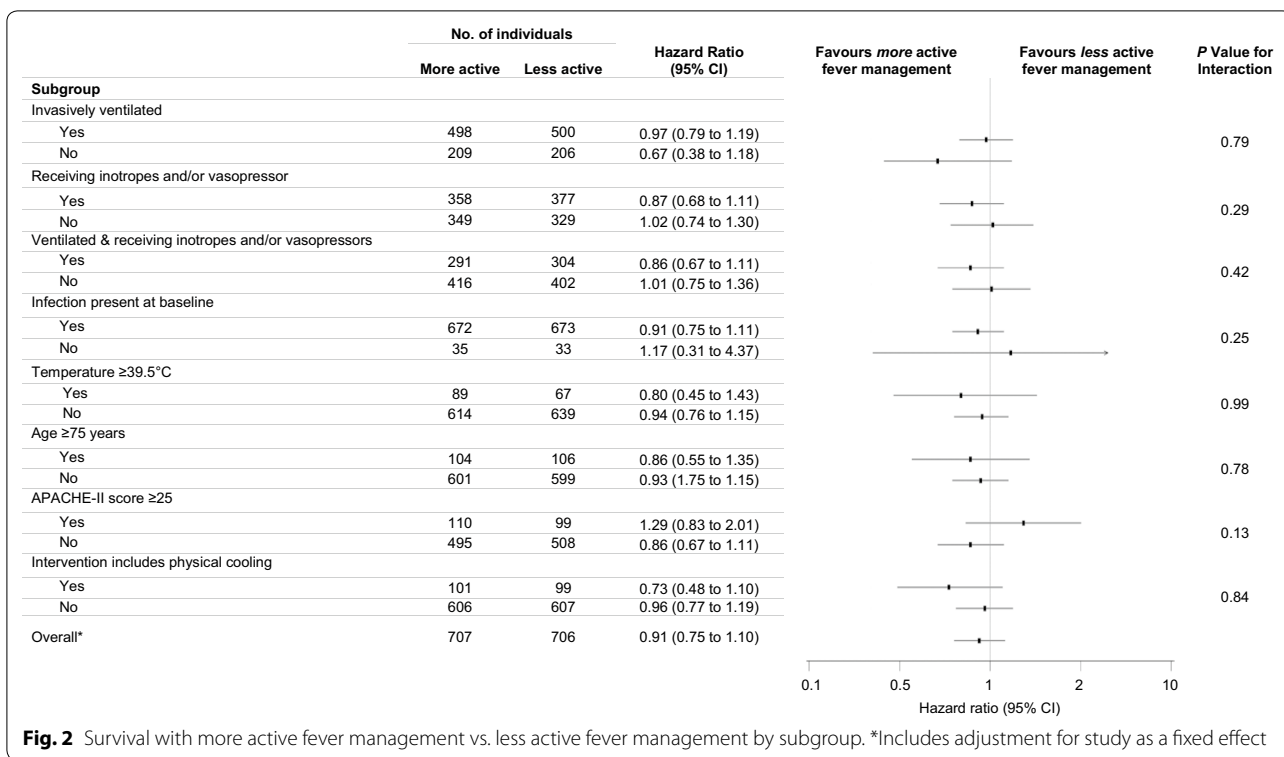


Fig. 2 Survival with more active fever management vs. less active fever management by subgroup. *Includes adjustment for study as a fixed effect

Table 2 Outcomes

	More active fever control (n = 707)	Less active fever control (n = 706)	Treatment effect estimate ^a (95% CI)	P value
Outcomes				
Survival (days), median (95% CI)				
	202 (146–N/A)	212 (143–390)	Hazard ratio 0.91 (0.75–1.10)	0.32
			Adjusted hazard ratio ^b 0.96 (0.77–1.19)	0.69
ICU mortality—n/N (%)				
	98/707 (13.9)	121/706 (17.1)	Odds ratio 0.78 (0.58–1.04)	0.09
			Adjusted odds ratio ^a 0.76 (0.52–1.09)	0.13
ICU length of stay (days), geometric mean (95% CI)				
	5.7 (5.2–6.2)	5.6 (5.2–6.2)	Ratio of geometric means (95% CI) 1.01 (0.89–1.14)	0.92
			Ratio of geometric means (95% CI) 1.08 (0.96–1.23)	0.19

IQR interquartile range, CI confidence interval

^a The hazard ratio from the primary survival analysis includes an adjustment for study as a fixed effect. The widths of the confidence intervals for secondary analyses have not been adjusted for multiplicity and the intervals should not be used to infer definitive differences between the groups

^b Adjusted for age, sex, study, and APACHE-II score; APACHE-II data were not available for the Schortgen et al. trial. Additional adjusted analyses are presented in the ESM

of 0.73 °C (95% CI 0.63–0.83 °C) between temperature groups evident at 12 h post randomisation.

Survival and mortality

In the analysis addressing the primary hypothesis that more active fever management would increase survival among patient subgroups with limited physiological

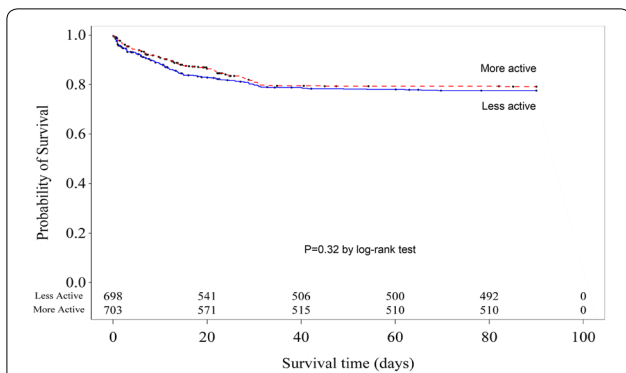


Fig. 3 Kaplan-Meier survival estimates of the probability of survival. Because the number of observations beyond day 90 is small, this figure is truncated at day 90 with data censored at day 90 if death had not occurred by then. An expanded Kaplan-Meier survival plot including all available data points is provided with the electronic supplementary material

reserves such as older patients, patients with higher illness acuity, and those requiring organ support, we found no statistically significant heterogeneity of treatment effect in any of the pre-specified subgroups (Fig. 2). Similarly, there was no heterogeneity of survival response by treatment allocation in patients with and without infections (Fig. 2). Overall, more active fever management did

not result in a statistically significant difference in survival time compared with less active fever management [hazard ratio; 0.91; (95% CI 0.75–1.10), $P=0.32$] (Table 2, Fig. 3, Fig. S1 ESM). Findings were similar in analyses adjusting for pre-specified baseline covariates (Table 2 and Fig. 3) and in sensitivity analyses (ESM). Moreover, the estimates of the hazard ratios related to survival from the sensitivity analyses were more-or-less identical treating the studies as fixed effects (as was pre-specified) or as random effects.

There was no statistically significant heterogeneity in the effect of more active compared with less active fever management on ICU mortality in any of the pre-specified subgroups (Fig. 4). A total of 98 of 707 patients (13.9%) assigned to more active fever management and 121 of 706 patients (17.1%) assigned to less active fever management died in the ICU [absolute mortality difference, -3.3% points (95% CI -7.1 to 0.5% points); odds ratio, 0.78 (95% CI 0.58–1.04), $P=0.09$] (Table 2). Findings were similar in analyses adjusting for pre-specified baseline covariates (Table 2) and in sensitivity analyses (ESM).

Length of stay

Overall, ICU length of stay and hospital length of stay were similar between treatment groups (Table 2).

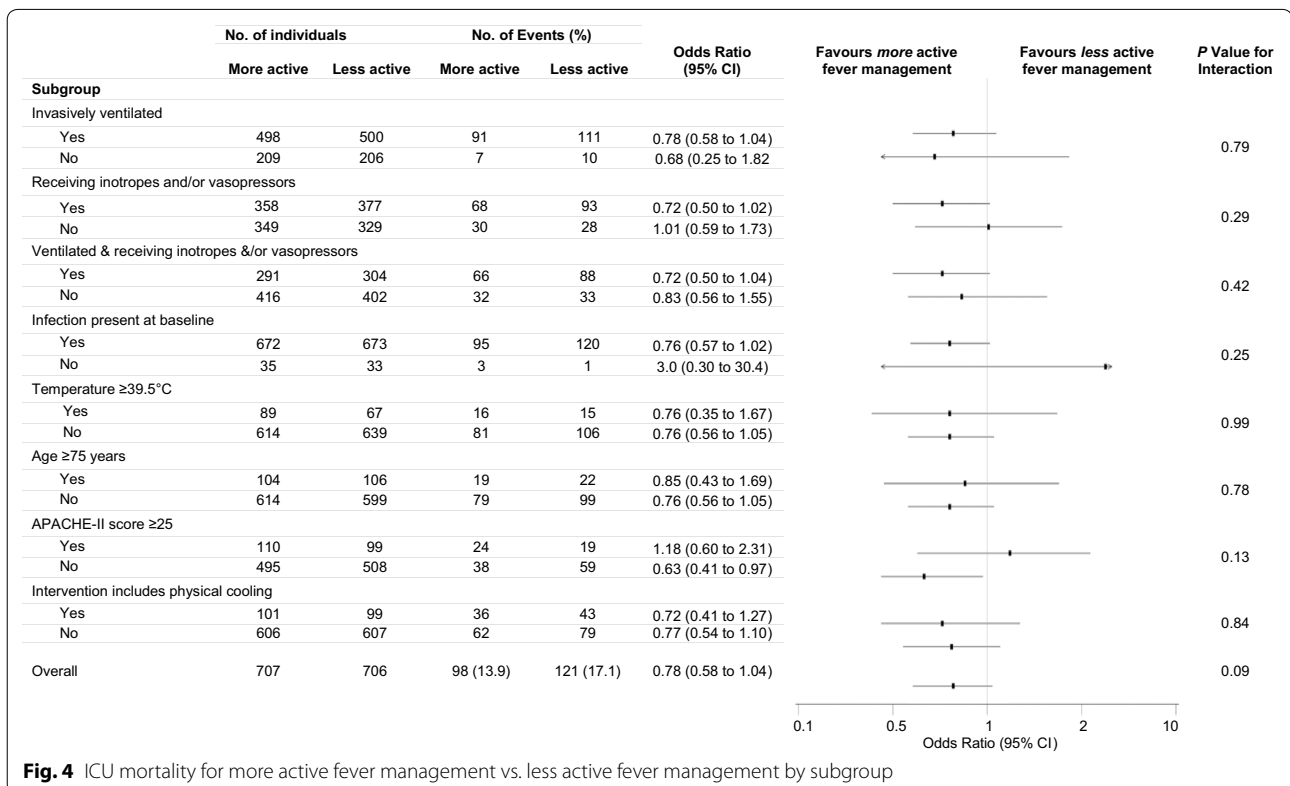
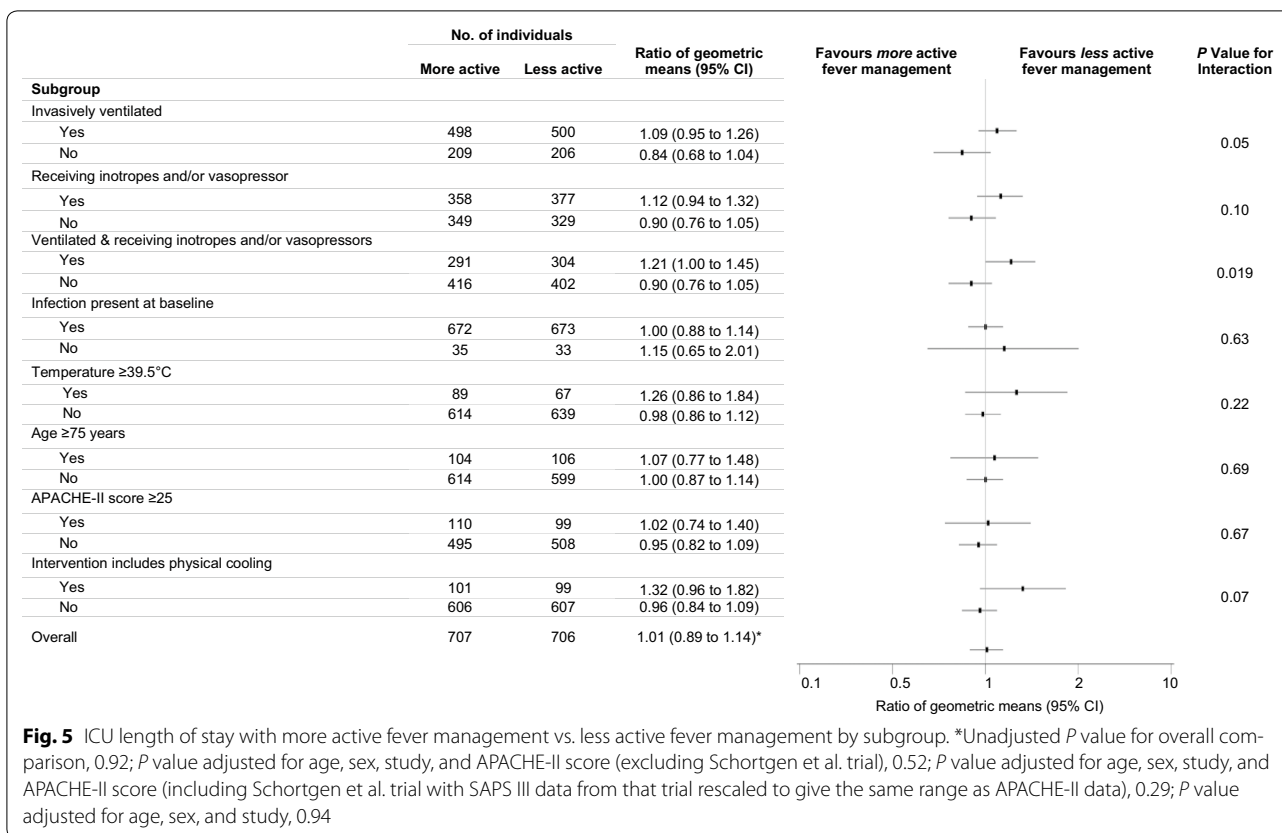


Fig. 4 ICU mortality for more active fever management vs. less active fever management by subgroup



However, there was statistically significant heterogeneity of response to treatment in relation to length of stay variables in some subgroups (Fig. 5 and Fig. S2, ESM). In each case where significant heterogeneity in response to treatment was observed, the length of stay was statistically significantly shorter in a subgroup where the point estimate for ICU mortality risk favoured more active fever management. In a post hoc interaction analysis of ICU and hospital length of stay by treatment allocation, there was statistically significant heterogeneity in response in survivors compared with non-survivors (ESM). Compared with less active fever management, more active fever management was associated with longer ICU and hospital length of stay in patients who died in ICU and with shorter ICU and hospital length of stay in patients who survived ICU.

Discussion

In this individual-level patient data meta-analysis of randomised controlled trials, more active fever management did not increase survival compared with less active fever management in critically ill adults either overall or in those with limited physiological reserves. Survival by treatment group was similar in a range of subgroup pairs that divided the study population into groups based on

age, illness severity, on receipt of specific organ supports, and in the presence or absence of high fever at baseline.

Overall, effect size estimates in relation to ICU mortality based on the 95% CI were consistent with an absolute effect on ICU mortality with active fever management ranging from a decrease of 7.1% points to an increase of 0.5% points. Although we observed statistically significant heterogeneity of treatment effect in relation to ICU and hospital length of stay effects, the interpretation of these findings is complicated because length of stay can be reduced by more rapid recovery or by early death. Moreover, a reduction in mortality, even a non-statistically significant one, can be associated with a statistically significant increase in length of stay when survivors have longer average lengths of stay than non-survivors. In patients who were receiving invasive mechanical ventilation, those receiving inotropes and/or vasopressors, or those receiving both of these, a relative increase in hospital length of stay was associated with lower ICU mortality based on point estimates. We also found that, compared with less active temperature management, more active temperature was associated with reduced ICU and hospital length of stay in patients who survived ICU and with increased length of stay in patients who died in ICU.

Our study is consistent with two recent aggregate data metaanalyses [9, 16] evaluating fever control in adult ICU patients; however, it extends their findings because the use of individual-level patient data allowed us to conduct analyses adjusting for important baseline covariates and to accurately evaluate subgroups of interest defined based on pre-randomisation characteristics.

Our study has a number of limitations. Because our analyses were not adjusted for multiple comparisons, they should be considered exploratory and should not be used to infer definitive treatment effects. Although we did not demonstrate statistically significant heterogeneity of treatment effect on survival for subgroups of interest, confidence intervals around hazard ratios were generally wide and the possibility of clinically important differences in survival responses by subgroup cannot be excluded. In particular, as nearly all patients were suspected of having an infection at baseline, our findings effectively neither confirm nor refute the hypothesis that the presence of infection is an important factor in determining the efficacy of active fever management [17]. We were only able to obtain data from 5 out of 13 trials identified in our recent systematic review. However, the three largest trials [6–8] conducted were included in our analysis and 79.4% of all potential data from prior randomised controlled trials were analysed. Most of the studies where data were not available were small single-centre studies. The studies included in our analysis used a variety of different therapies and it is not known whether these therapies have equivalent effects on patient outcomes. Nevertheless, as all therapies evaluated are given to patients to treat fever, we submit that combining trials in an IPDMA has both face validity and clinical relevance.

In conclusion, our findings do not support the hypothesis that more active fever management increases survival compared with less active fever management in patients with limited physiological reserves. However, as point estimates for the effect of active fever management on ICU mortality encompass potentially clinically important effects, further clinical trials are justified. The significant heterogeneity in treatment effects on length of stay in subgroups based on the receipt of organ support, combined with the finding that more active fever management increases ICU and hospital length in patients who die in ICU, and reduces length of stay in patient who survive ICU, suggests that further research in patients receiving organ support may be of interest.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s00134-019-05553-w>) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest

Dr. Paul Young and Dr. Manoj Saxena report receiving speaker's fees from Bard Medical Pty. Dr. Gordon Bernard reports having an equity stake and is on the Board of Directors for Cumberland Pharmaceuticals, Nashville, TN, makers of intravenous ibuprofen (Caldolor).

Ethical approval

An approval by an ethics committee was not applicable.

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