

Control of Fever in Septic Patients: the Results of a Randomised Controlled Trial

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Abstract

Background: Fever is a defence against infection. However, its benefit might be masked by cardiorespiratory maladaptation to thermal stress. The aim of this study was to evaluate the effect of fever control on the outcomes of septic patients who were presumed to have a sufficient cardiorespiratory reserve.

Methods: Septic patients with a presumed sufficient cardiorespiratory reserve and fever ($>38.3^{\circ}\text{C}$) of infectious etiology were randomised to one of the two study arms. In the aggressive arm, the antipyretic intervention was started immediately when the body temperature rose above 38.3°C , in the conservative arm only when it exceeded 39.5°C . Both pharmacological (ibuprofen) and physical antipyretic methods were used. The total SOFA score on day 7 was selected as the primary endpoint. Non-parametric tests were used for statistics when comparing variables between the study arms.

Results: A total of 5998 patients were screened for fever of infectious etiology. 609 patients met inclusion criteria, of whom 154 patients were randomised. A significantly higher body temperature and longer duration of febrile episode was reached in the conservative arm. The SOFA score was significantly lower on day 7 when the conservative approach was applied. In-hospital mortality did not differ between the arms. When analysing a subgroup of patients with ICU stay < 4 days, a significantly lower SOFA score on day 3 and a tendency for lower in-hospital mortality was observed in the aggressive arm. In contrast, among patients with ICU stay ≥ 6 days, a significantly lower SOFA score on day 7 and significantly lower in-hospital mortality was found in the conservative arm.

Conclusions: The conservative approach to the treatment of fever in septic patients with sufficient cardiorespiratory reserve was associated with a lower total SOFA score on day 7 compared to the aggressive approach. However, both approaches may positively influence outcome of septic patients: the aggressive approach seems to be beneficial in the early stage of sepsis, and the conservative approach in the stage of sepsis remission.

Trial registration: The study was retrospectively registered at <http://www.clinicaltrials.gov> (Ref. No. NCT04227652).

Background

Treatment of fever in critically ill patients with sepsis is still a hot topic (1). In experimental studies of animals with viral and bacterial infections, suppression of fever using antipyretics is associated with higher mortality (2, 3). In observational studies of patients with infections, in-hospital mortality was found higher if a febrile response to infection was missing (4-8). The administration of antipyretics is also connected with a higher mortality in septic patients (9), though one study has somewhat challenged this conclusion (10). Two large randomised controlled trials (RCTs) in septic patients showed that the treatment of fever delays early deaths, but neither study proved any decrease in in-hospital mortality (11,12). Furthermore, a recent meta-analysis of RCTs on the benefits of antipyretic interventions in septic

patients did not provide any evidence that these interventions would lead to better survival (13). Despite the uncertainty as to whether the treatment of fever in septic, neurologically intact patients is beneficial, the use of antipyretic interventions in these patients remains common clinical practice (9, 14, 15).

Fever is considered an important tool in helping the body fight infection (16). Temperature in the range of the physiological fever response inhibits the growth and viability of microorganisms; stimulates the maturation, mobility, and phagocytic capacity of immunocompetent cells; and potentiates the killing effect of antibiotics (17-19). Through these mechanisms, fever accelerates microbial clearance and may shorten the duration of a disease. The second way fever can be helpful during infection is by inducing the expression of heat-shock proteins (HSPs). HSPs represent a natural protection of cells against various forms of stress appearing during the host's response to infection. In addition, HSPs have immunomodulatory properties: they inhibit the activation of nuclear factor kappa beta (NF- κ B), leading to a decrease in the release of pro-inflammatory cytokines (20, 21). As follows, fever may contribute to reducing the extent of dysregulation of the inflammatory response to infection and thus improve the patient's prognosis (22).

Proponents of reducing fever in patients with sepsis often argue by its high metabolic cost. An increase in body temperature from 37°C to 39°C results in a 25% increase in metabolic rate and, subsequently, in increased oxygen consumption, carbon dioxide production, minute ventilation, heart rate and cardiac output (23). Critically ill patients with limited cardiorespiratory reserve might not adequately compensate for such increased metabolic demands. In these patients, fever could cause severe hemodynamic instability and hypoxic tissue injury, which may worsen their prognosis (24).

The dual effect of fever described above (i.e., the enhancement of the host's defences against infection on one hand and the induction of cardiorespiratory stress on the other) may also have a dual effect on the results of RCTs looking at the benefits of fever control in critically ill septic patients. For example, if most randomised patients have sufficient cardiorespiratory reserve, then the benefit of fever will be fully reflected in the results of the study. Conversely, if individuals with limited cardiorespiratory reserve represent a significant percentage in the cohort of randomised patients, then the beneficial effect of fever will be masked by the induction of cardiorespiratory stress. This consideration is indirectly supported by the results of one RCT that was terminated prematurely due to a significant trend towards higher mortality in critically ill patients enrolled in the arm with aggressive fever control (25). Notably, the mean age of patients in this study (47 years) is lower than in other studies of critically ill patients with sepsis (~60 years). Due to their younger age, it can be assumed that the patients in this study had sufficient cardiorespiratory reserve to compensate for the increased metabolic demands caused by fever. This phenomenon apparently created a space for clinical manifestation of the protective effect of elevated body temperature, as evidenced by lower mortality of patients in the arm with a permissive approach to the treatment of fever.

Hence the aim of the present study was to evaluate the effect of antipyretic treatment on the outcome of critically ill patients with sepsis who were presumed to have a sufficient cardiorespiratory reserve. Our

hypothesis was that a sufficient cardiorespiratory adaptation to increased body temperature will create a precondition for making apply the benefit of fever, resulting in better outcome in patients with conservative approach to the treatment of fever.

Methods

The study was performed at the University Hospital in Ostrava, the Czech Republic, in four intensive care units of the Department of Anaesthesiology and Intensive Care.

Patient screening and randomisation

During the study period, all adult patients admitted to the intensive care units (ICU) of our department were screened for fever of infectious etiology except those after planned orthopedic surgery. We considered a body temperature $>38.3^{\circ}\text{C}$ for at least 60 minutes to be a fever. If fever of infectious etiology was suspected or infection was already confirmed, then the patient was considered eligible for inclusion to the study.

In the next step, while assessing the eligibility for randomisation, we considered intactness of central nervous system, pregnancy, previous antipyretic medication, length of stay in another ward and informed consent. Moreover, to meet the aim of our study, a special attention was given to the assessment of the risk of cardiorespiratory maladaptation to the increased metabolic demands caused by fever. Patients with a history of chronic heart failure, myocardial infarction, or coronary artery bypass grafting (CABG), heart valve defects, cardiac arrhythmias, or an increased predisposition to cardiac arrhythmias, chronic obstructive or restrictive lung disease, or who underwent lung surgery (lung resection) were excluded from the study. Patients with acute respiratory distress syndrome (ARDS) were also excluded since our department considers the maintenance of body temperature in the range of normothermia to be the standard care in such patients. Age was not a predefined criterion for the exclusion. The inclusion of an elderly patient was based on an ad-hoc decision of the attending physician after having evaluated the patient's biological reserves. Patients found to be eligible for randomisation were randomised to one of the study arms using a simple envelope method.

Body temperature monitoring

During patient screening, body temperature was monitored using an axillary temperature sensor. After randomisation, body temperature was monitored using a bladder temperature sensor.

Antipyretic interventions in the study arms

Pharmacological and physical antipyretic methods were used in both arms of the study. Ibuprofen was administered orally or by nasogastric tube for the pharmacological control of fever. If none of these routes of administration could be used, ibuprofen was administered rectally in the form of a suppository. Cooling blanket or an environmental cooling method was used for physical cooling. Once the patient was

randomised to a study arm, the same antipyretic intervention algorithm was used for all other episodes of fever until the end of ICU stay.

In the *aggressive arm*, control of fever was initiated with ibuprofen (800 mg) as soon as body temperature rose above 38.3°C. Another dose of ibuprofen (400 mg) could be repeated after 6 hours. If ibuprofen was contraindicated (known hypersensitivity, history of ulcer) or if the antipyretic effect of ibuprofen was absent even after the second dose, then acetaminophen or metamizole was used. If the body temperature rose above 39.5°C, physical cooling was added to the pharmacological intervention. The goal of antipyretic interventions in this arm was to reduce the body temperature below 38.3°C as soon as possible. If the body temperature dropped below 38.3°C, then the antipyretic intervention was terminated.

In the *conservative arm*, the antipyretic interventions as described for the aggressive arm were initiated only when the body temperature rose above 39.5°C. If the body temperature dropped below 39.5°C, the antipyretic intervention was terminated.

Endpoints

The primary endpoint was the total Sequential Organ Failure Assessment (*SOFA*) score on day 7 from randomisation. The SOFA score was designed to sequentially assess the severity of organ dysfunction in patients who are critically ill from sepsis (25). The total SOFA score was calculated daily as the sum of the highest score recorded for each organ system. The secondary endpoints were the serum levels of procalcitonin (PCT), interleukin-6 (IL-6), lactate and central venous oxygen saturation (ScvO₂) on day 7 from randomisation. Blood samples were taken at randomisation and then every morning for the next 7 days.

The last aim (tertiary endpoint) of our study was to determine whether fever control in patients with low cardiorespiratory risk is associated with any change in the length of mechanical lung ventilation, the length of ICU and hospital stay, or changes in ICU mortality and in-hospital mortality.

Sample size calculation and statistical analysis

Based on Schulman's study (26), a power analysis was carried out to determine the number of patients needed to demonstrate the difference in morbidity between the arms assuming the same group size, statistical significance limit of 0.05, required test strength 0.8, and use of Pearson's chi-squared test. In the control arm, the expected incidence of the endpoint was 16% of patients, and in the compared arm 1, 2, 3, 4, and 6%. In the case of a difference of 2% vs. 16%, 57 patients are needed in each arm, for a total of 114 patients in the study. Power analysis was computed using PASS 13 Power Analysis and Sample Size Software (2014). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

All analyses were conducted on an intention-to-treat basis. Categorical variables are presented as absolute and relative frequencies. Continuous variables are presented as mean ± standard deviation (SD)

or median and interquartile range (IQR) according to the distribution. Categorical variables were compared by chi-square test. Continuous variables were compared by Mann-Whitney U test. $P < 0.05$ was considered as statistically significant. All analyses were performed with R 3.6.2. software (www.R-project.org).

Results

Patient characteristics

From September 2013 to February 2019, a total of 5998 patients were screened for fever of infectious etiology. 609 patients (10.2%) met inclusion criteria, of whom 455 (74.7%) were excluded (**Figure 1**). The most common reason for the exclusion was acute cerebral injury (168 patients, 36.9%). A risk of cardiorespiratory maladaptation to the increased metabolic demands caused by fever was identified in 100 patients (21.9%). A total of 154 patients were randomised: 79 patients in the aggressive arm and 75 patients in the conservative arm. During the study, 14 patients were lost due to protocol violations. In all cases, the violation was an incorrect antipyretic intervention. A total of 69 patients in the aggressive arm and 71 patients in the conservative arm completed the study.

At randomisation, patients in both arms had similar characteristics (**Table 1**), notably with no differences in mean age of patients (56.1 ± 15.9 years in the aggressive arm vs. 53.8 ± 16.3 years in the conservative arm). Most patients were admitted to ICU after surgery or trauma. The history of beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) were similar in both arms, only statins use was more common in the aggressive arm. The mean Acute Physiology and Chronic Health Evaluation (APACHE II) score and mortality prediction on admission to ICU were comparable in both arms (21 ± 9 in the aggressive arm vs. 20 ± 9 in the conservative arm; $43 \pm 26\%$ in the aggressive arm vs. $39 \pm 25\%$ in the conservative arm). More than one half of the patients in both arms were in septic shock at the time of randomisation, and most of them were on mechanical lung ventilation.

Description of the first septic episode and the effects of antipyretic interventions

Description of the first septic episode and the effects of antipyretic interventions are summarized in **Table 2**. Lung infection was the most common source of sepsis, followed by intra-abdominal infection. Infection was microbiologically confirmed, and the initial antibiotic treatment covered the causative microorganisms in most patients. No significant difference in the duration of antibiotic treatment was found. The number of febrile episodes was similar in both arms, but the total duration of the febrile episodes was significantly shorter and the mean body temperature significantly lower in the aggressive arm (median 12 hours [IQR 37] in the aggressive arm vs. median 34 hours [IQR 86.5] in the conservative arm, $p < 0.01$; 38.6 ± 0.2 °C in the aggressive arm vs. 38.8 ± 0.3 °C in the conservative arm, $p < 0.001$). The use of ibuprofen was significantly more frequent in the aggressive arm than in the conservative arm, but the use of other antipyretics and physical cooling was similar.

The cumulative fluid balance during the first 7 days from randomisation was significantly higher in the conservative arm than in the aggressive arm (**Table 2**). Differences in the duration of norepinephrine support and in the total amount of norepinephrine administered during the first 7 days from randomisation were not significant.

Endpoints

The endpoints of this study are summarized in **Table 3**. The total SOFA score on day 7 from randomisation was significantly lower in the conservative arm compared to the aggressive arm (median 6 [IQR 5] vs. median 8.5 [IQR 7.5], respectively; $P=0.03$). Similarly, the lactate level was significantly lower on day 7 in the conservative arm. The differences between the two arms in the other secondary endpoints on day 7 were not significant. We also did not find any significant differences in the length of mechanical lung ventilation and the length of ICU and hospital stay. ICU mortality and in-hospital mortality were similar in both arms (21.1% in the aggressive arm vs. 21.7% in the conservative arm; 23.9% in the aggressive arm vs. 24.6% in the conservative arm, respectively).

When analysing plots (**Figure 2**) of daily total SOFA score, lactate, PCT and IL-6 levels, we found that SOFA score and lactate level increased from day 5 after randomisation in the aggressive arm, and this increase was accompanied by the absence of a decrease in PCT level (**Figure 2**). Moreover, we found that the course of the total SOFA score had, in addition to the late peak in the aggressive arm (on day 7 after randomisation), also an early peak in the conservative arm (on day 2 after randomisation). Based on these findings, we decided to examine endpoints in two subgroups of patients: those with ICU stay < 4 days from randomisation and those with ICU stay ≥ 4 days from randomisation.

Data describing patient characteristics, the first septic episode, the effects of antipyretic interventions and study endpoints in these two subgroups are detailed in **Table 1, Table 2 and Table 3 in Additional file 1 and Additional file 2**. Briefly, in both subgroups of patients (i.e., with ICU stay < 4 days and with ICU stay ≥ 4 days) the total duration of febrile episodes was significantly shorter among the patients in the aggressive arm. Regarding the subgroup of patients with ICU stay < 4 days, the total dose of norepinephrine administered from randomisation to day 3 was significantly lower in the aggressive arm than in the conservative arm, with no difference in cumulative fluid balance (**Table 2 in Additional file 1**). In the subgroup of patients with ICU stay ≥ 4 days, no significant difference in the total dose of norepinephrine administered from randomisation to day 7 was found. However, the cumulative fluid balance was significantly higher in the conservative arm than the aggressive arm (**Table 2 in Additional file 2**).

In the subgroup of patients with ICU stay < 4 days, the total SOFA score on day 3 was significantly lower in the aggressive arm than in the conservative arm (**Table 3 in Additional file 1**). The PCT, IL-6 and lactate levels on day 3 were also lower in the aggressive arm, but these differences did not achieve statistical significance. ScvO₂ levels were similar in both arms. ICU mortality was 17.6% in the aggressive arm vs. 53.3% in the conservative arm ($P=0.06$).

In the subgroup of patients with ICU stay ≥ 4 days, the total SOFA score on day 7 and the lactate level on day 7 were significantly lower in the conservative arm compared to the aggressive arm (**Table 3 in Additional file 2**). The IL-6 and ScvO₂ levels were similar in both arms. However, a marked increase in PCT level was observed between day 3 and day 4 in the aggressive arm (day 3 = median 0.59 ug/L [IQR 2.1], day 4 = median 0.79 ug/L [IQR 1.4]) and, in the subsequent course, the PCT levels remained higher in the aggressive arm compared to the conservative arm (**Figure 1 in Additional file 2**). This finding could also be proved by day-to-day analysis of PCT levels in each arm: in the conservative arm the level of PCT on day 7 was significantly lower compared to day 3 (P=0.02), whereas the levels of PCT did not change between day 3 and day 7 in the aggressive arm. ICU mortality and in-hospital mortality were lower in the conservative arm; however, these differences were not statistically significant (12.5% vs. 23.1%; 16.1% vs. 26.9%).

The primary endpoints in our study could be skewed by the fact that some patients terminated their stay at the ICU before the 7th day after randomisation. For this reason, we also analysed data in the 88 patients staying in the ICU ≥ 6 days after randomisation. The results of this analysis are presented in detail in **Additional file 3**. In short, the mean body temperature was significantly higher in the conservative arm, the total SOFA score and lactate level on day 7 were significantly lower in the conservative arm. Except for PCT, whose level rose again between day 3 and 4 in the aggressive arm, no other differences in total SOFA score, lactate, IL-6 and ScvO₂ levels were found (**Figure 1 in Additional file 3**). In tertiary endpoints, ICU mortality and in-hospital mortality were significantly lower in the conservative arm (12.8% vs. 30.9%, P=0.04; **Figure 3**).

Discussion

The aim of this study was to evaluate the effect of antipyretic treatment on the outcome of critically ill patients with sepsis who were presumed to have sufficient cardiorespiratory reserve to cover the increased metabolic demands caused by fever.

The main result of this study is that the conservative approach to the treatment of fever (i.e., the initiation of antipyretic intervention only when the body temperature rose above 39.5°C) was associated with a significantly lower SOFA score and lactate level on day 7 after randomisation (**Table 3**). Similar results were observed in the additional analysis done on the subgroup of patients with ICU stay ≥ 4 days from randomisation (**Table 3 in Additional file 2**). Moreover, in the subgroup of patients with ICU stay ≥ 6 day, the conservative approach to the treatment of fever was associated with significantly lower in-hospital mortality (**Table 3 in Additional file 3**). On the contrary, the aggressive approach to the treatment of fever (i.e., initiation of antipyretic intervention immediately when the body temperature rises above 38.3°C) was associated with significantly lower SOFA score, norepinephrine requirement, and tendency for lower ICU mortality in the subgroup of patients with ICU stay of < 4 days from the day of randomisation (**Table 3 in Additional file 1**). To explain these contradictory results when comparing two different antipyretic interventions, we decided to look at the results in the context of evolving stages of sepsis.

Control of fever in the early stage of sepsis

Severe cardiovascular alteration (i.e., hypotension with decreased tissue perfusion requiring fluid resuscitation and vasopressor support) due to the dysregulated host's inflammatory response to infection is a key symptom in the early stage of sepsis and significantly affect the patient's prognosis (27, 28). Undoubtedly, subjecting such an affected patient to further stress in the form of fever will be associated with a high risk of progression of hemodynamic failure, regardless of the previous cardiorespiratory reserve (29). Thus, it seems logical to treat fever actively in the early stage of sepsis, thereby reducing the metabolic demands superimposed on the already overloaded cardiorespiratory system and improving the prognosis of the patients (30). A recent meta-analysis of RCTs focused on the control of fever in septic patients also supported the view that the more active approach to the treatment of fever (i.e., achieving normothermia as quickly as possible) in the early stage of sepsis appears to significantly reduce early mortality (31).

In the Sepsiscool trial (11), which was also included in the meta-analysis, 201 sedated patients with sepsis and vasopressor support were randomised to compare physical cooling for the first 48 hours after ICU admission to no physical cooling. The physical cooling significantly decreased body temperature (36.8 ± 0.7 vs. 38.4 ± 1.1 °C; $P < 0.01$), decreased vasopressor requirement ($P = 0.02$), and reduced 14-day mortality (19% vs. 34%; $P = 0.01$). In agreement with the Sepsiscool trial, the aggressive approach to the treatment of fever in our study was likewise associated with a shorter duration of febrile episode, lower norepinephrine requirements, and a tendency for reduced ICU mortality in the subgroup of patients staying in the ICU < 4 days from randomisation (**Table 2 and 3 in Additional file 1**). Furthermore, the similarity of our results to the Sepsiscool trial suggests that even a commonly used antipyretic strategy in a febrile patient (i.e., initiation of treatment with an antipyretic drug and physical cooling only as a rescue procedure at very high body temperatures) is as effective as physical cooling alone in terms of short-term patient prognosis. However, if the therapeutic goal is only to lower the temperature, then physical cooling is more effective than pharmacological methods (32). It should be noted that physical cooling may cause an undesirable increase in catecholamine levels, oxygen consumption and energy expenditure, especially if the patient is not deeply sedated (33).

The superimposed metabolic stress might not be so far the only explanation of worse outcome in the subgroup of patients staying in the ICU < 4 days and receiving the conservative approach to the treatment of fever. If we look at the data in more detail, then we cannot overlook that the cumulative fluid balance was almost the same in both arms of this subgroup (**Table 2 in Additional file 1**), though it would be expected to be significantly more positive in patients with longer duration of fever. Therefore, it is uncertain whether the patients in the conservative arm could not be under-filled due to uncovered extra insensible fluid losses caused by fever. Similar uncertainty has also been discussed in the reaction to the Sepsiscool trial (34, 35). Surely this uncertainty may affect the correct interpretation of the study results.

Control of fever in the stage of sepsis remission

In both arms of our study, IL-6 levels significantly decreased during the study period, which can be viewed as a receding dysregulation of the host's inflammatory response to infection (36). This is usually the result of well-managed causal and supportive treatment of sepsis, with systemic anti-inflammatory mechanisms also playing an important role (37). In opposite to the early stage of sepsis, fever most likely does not represent any superimposed stress to the organism during the regression of the inflammatory response. Moreover, if sufficient cardiorespiratory adaptation is present, fever may confer even benefit to the septic patients (38). These circumstances were apparently met in the conservative arm during the late stage of sepsis, where we found significantly lower SOFA score on day 7 after randomisation (**Table 3**). In addition, we did not observe any differences in ScvO₂ between the arms. Since ScvO₂ level reflects the imbalance between oxygen supply and demand in sepsis (39), we can assume that cardiorespiratory adaptation to the increased metabolic demands caused by fever was sufficient among patients receiving the conservative approach to the treatment of fever.

Fever may favourably affect the development of organ dysfunction in the stage of sepsis remission for example by accelerating the microbial clearance or by fine-tuning immune surveillance, which strengthens the resistance to superinfection (40). The increase in lactate level and the SOFA score preceded by the marked increase in PCT level in the aggressive arm of our study suggests that the aggressive approach to the treatment of fever in the stage of sepsis remission may be associated with a risk of acquiring superinfection, resulting in another septic episode. Schulman et al. also observed that the amount of antimicrobial drugs was significantly higher in patients with the aggressive treatment of fever by acetaminophen (26). Similarly, the authors of the Sepsiscool trial stated that the frequency of late nosocomial infections was higher in patients with the treatment of fever by physical cooling (11).

Treat fever, or not to treat fever, or do both?

The results of our study suggest that both approaches to the treatment of fever might be associated with benefits. The aggressive approach to the treatment of fever is beneficial in the early stage of sepsis because it blunts the danger associated with fever (i.e., superimposed metabolic stress on the already overloaded cardiorespiratory system). In contrast, the conservative approach to the treatment of fever is beneficial in the stage of sepsis remission because it maintains fever-induced fine-tuning of immune surveillance with increased resistance to further infection. This hypothesis must of course be verified by further studies. However, the findings suggest that the question *"when to treat and when not to treat fever"* is rather more important than the question *"whether or not to treat fever"* in patients with sepsis. Otherwise, it cannot be ruled out that the studies comparing these interventions against each other will continue to have insignificant results when assessing patient survival.

Study limitation

The first limitation was the slow recruitment of patients, which is related to the relatively low incidence of fever of infectious origin in our department. The low incidence of fever is probably related to most patients in our department being surgical patients with a short stay in the ICU. In a group of 2419

critically ill surgical patients, Barie et al. noted fever (core temperature $\geq 38.2^{\circ}\text{C}$) in a total of 626 patients (26%) (41). Of these patients, 46% had fever of infectious origin, which roughly corresponds to the incidence of fever of infectious origin in our department. The rate of patient recruitment was also significantly affected by the strict exclusion criteria. Up to 75% of patients eligible for randomisation were excluded due to the presence of at least one exclusion criterion. The second limitation was the use of ibuprofen to treat fever, making the results of this study less comparable to most published studies in which acetaminophen was used as an antipyretic. We chose ibuprofen because it has a potent antipyretic effect and the benefits of its anti-inflammatory effect has not been demonstrated in patients with sepsis (42). In addition, ibuprofen is considered to be safe for use in critically ill patients (43). The use of the enteral route for the administration of ibuprofen may also be a limitation, as the bioavailability of drugs administered via the gastrointestinal route could be altered in critically ill patients (44). Despite this limitation, the antipyretic effect of ibuprofen after enteral administration was significant, as reflected by the low incidence of requiring another antipyretic due to a failure of ibuprofen to reduce fever. The last potential limitation is the so-called Hawthorne effect (45). In our department, we routinely suppress fever in all patients with sepsis and it is not customary to see any patient with a purposefully untreated fever. For this reason, it is uncertain whether patients randomised to the conservative arm were not given extra attention and, thus, extra care.

Conclusions

The aim of this study was to evaluate the effect of antipyretic treatment on the outcome of critically ill patients with sepsis who were presumed to have sufficient cardiorespiratory reserve to cover the increased metabolic demands caused by fever. The conservative approach to the treatment of fever was associated with significantly higher mean body temperature, longer febrile episode duration, and lower total SOFA score on day 7 after randomisation compared to the aggressive approach. However, when analysing a subgroup of patients with ICU stay < 4 days, significantly lower SOFA score on day 3 and a tendency for lower in-hospital mortality was observed if the aggressive approach was applied. In contrast, among patients with ICU stay ≥ 6 days, significantly lower SOFA score on day 7 and in-hospital mortality was found if the conservative approach was applied. Thus, both approaches may positively influence outcome of septic patients: the aggressive approach seems to be beneficial in the early stage of sepsis, and the conservative approach in the stage of sepsis remission.

List Of Abbreviations

APACHE II score - Acute Physiology and Chronic Health Evaluation score

ARDS – The acute respiratory distress syndrome

CABG – Coronary artery bypass grafting

ICU – Intensive care unit

IQR – Interquartile range

IL-6 – Interleukine-6

PCT – Procalcitonin

RND – Randomisation

ScvO₂ – Central venous oxygen saturation

SOFA score – The Sequential Organ Failure Assessment *score*

Declarations

Ethics approval and consent to participate

The study protocol and informed consent procedures were approved by Local Medical Ethics Committee (Ref.no. 523/2011). Informed consent was obtained from all patients who were able to consent. In the case of an altered state of consciousness, informed consent was obtained prior to randomisation from two study-independent physicians.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RK designed the study. RK, MK, JV, JN, J Janišová, KR and KT acquired the data. JK and J Jarkovský performed the data analysis. RK and RKjr interpreted the data. RK drafted the manuscript. RKjr substantively revised the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1.

Characteristics of the patients at the baseline

	Aggressive arm (n=69)	Conservative arm (n=71)
Age – yr	56.1 ± 15.9	53.8 ± 16.3
Male sex – no (%)	54 (78.3)	62 (87.3)
Body mass index	27.5 ± 5.1	27.4 ± 6.3
Admitted after trauma – no (%)	24 (34.8)	29 (40.8)
Admitted after surgery – no (%)	35 (50.7)	39 (54.9)
Admitted with medical diagnosis – no (%)	10 (14.5)	3 (4.3)
Transferred from another ICU – no (%)	29 (42.0)	26 (36.6)
Medication history		
- beta blockers – no (%)	19 (27.5)	13 (18.3)
- ACE inhibitors – no (%)	11 (15.9)	11 (15.5)
- statins – no (%)	12 (17.4)	4 (5.6) ⊗
APACHE II – score at admission to ICU	21.3 ± 9.2	20.1 ± 8.9
APACHE II – mortality prediction (%)	42.6 ± 25.7	38.6 ± 24.8
Sepsis status at the day of randomisation		
- sepsis – no (%)	16 (23.2)	17 (23.9)
- severe sepsis – no (%)	12 (17.4)	14 (19.7)
- septic shock – no (%)	41 (59.4)	40 (56.4)
- norepinephrine support – no (%)	49 (71)	46 (64.8)
- mechanical ventilation – no (%)	56 (81.2)	57 (80.3)

Plus–minus values are means ± SD. APACHE II score = The Acute Physiology and Chronic Health Evaluation score. Sepsis was defined as suspected or confirmed infection, with signs of a systemic inflammatory response. Severe sepsis was defined as sepsis with evidence of organ dysfunction. Septic shock was defined as sepsis induced hypotension despite adequate fluid resuscitation.

⊗ $P < 0.05$.

Table 2.

Description of the first septic episode

	Aggressive arm (n=69)	Conservative arm (n=71)
Source of infection		
- lung – no (%)	35 (44.9)	39 (45.9)
- abdomen – no (%)	16 (20.5)	23 (27.1)
- urinary tract – no (%)	13 (16.7)	5 (5.9)
- bloodstream – no (%)	3 (3.8)	3 (3.5)
- soft tissue – no (%)	9 (11.5)	15 (17.6)
- unknown – no (%)	2 (2.6)	0 (0)
Microbiologically confirmed infection – no (%)	60 (87)	58 (81.7)
Antibiotic therapy was adequate – no (%)	54 (78.3)	58 (81.7)
Duration of antibiotic therapy in days		
– median (IQR)	8 (8.3)	9 (8.5)
Number of febrile episodes		
– median (IQR)	3 (4)	3 (4)
Total duration of febrile episodes in hours		
– median (IQR)	12 (37)	34 (86.5) ⊗⊗
Temperature during febrile episodes - °C	38.6 ± 0.2	38.8 ± 0.3 ⊗⊗
Antipyretic strategy		
- ibuprofen only – no (%)	56 (81.2)	41 (57.7) ⊗
- another antipyretics – no (%)	13 (18.8)	10 (14.1)
- physical cooling – no (%)	25 (36.2)	32 (45.1)
Duration of norepinephrine support in hours		
– median (IQR)	24 (81)	34 (84)
Total dose of norepinephrine in mg/kg		
– median (IQR)	0.1 (0.69)	0.21 (0.64)
Cumulative fluid balance in millilitres		
– median (IQR)	3600 (2720)	4980 (4600) ⊗

Plus–minus values are means \pm SD. IQR are expressed as difference between the 75th and the 25th percentile of data. Initial antibiotic treatment was considered adequate when the microbe was susceptible to at least one of the antibiotics administered. As febrile episode was considered temperature of 38.3 °C lasting at least 60 minutes. Other antipyretics were administered in a case of failure of antipyretic effect of ibuprofen or if ibuprofen was contraindicated. Total dose of norepinephrine in mg/kg is expressed as median (IQR) of total dose administered from randomisation to day 7 or, if shorter, to death or discharge. Cumulative fluid balance in millilitres is expressed as median (IQR) of cumulative fluid balance from the day of randomisation day 7 or, if shorter, to death or discharge.

⊗ P < 0.01, ⊗⊗ P < 0.001

Table 3.

Study endpoints

Endpoints	Aggressive arm (n=69)	Conservative arm (n=71)	P value
Primary endpoint:			
SOFA _{sum} score on the day of RND	9 (6)	10 (8)	0.35
SOFA _{sum} score on day 3	8 (9.5)	9 (6)	0.27
SOFA _{sum} score on day 7	8.5 (7.5)	6 (5) (*)	0.03
Secondary endpoints:			
PCT level on the day of RND	1.21 (4.78)	0.89 (5.6)	0.85
PCT level on day 3	0.82 (2.04)	0.81 (2.03)	0.80
PCT level on day 7	0.61 (0.79) (*)	0.32 (0.67) (*)	0.27
IL-6 level on the day of RND	176 (412,5)	183 (509.6)	0.93
IL-6 level on day 3	51.5 (86.5) (*)	59 (92.1) (*)	0.83
IL-6 level on day 7	51.2 (56.1) (*)	33.5 (73.7) (*)	0.97
Lactate level on the day of RND	1.4 (1)	1.5 (1.2)	0.48
Lactate level on day 3	1.1 (0.9) (*)	1.1 (0.6) (*)	0.80
Lactate level on day 7	1.5 (0.9)	1.1 (0.4) (*)	0.01
ScvO ₂ level on the day of RND	73 (17.3)	74 (13.1)	0.44
ScvO ₂ level on day 3	73.2 (13.5)	72.5 (10.3)	0.62
ScvO ₂ level on day 7	71.1 (9.4)	70.6 (9.2)	0.68
Tertiary endpoints:			
Length of mechanical ventilation in hours	207.8 (290.5)	237.3 (328.1)	0.55
Length of ICU stay in days	12 (16)	14 (17)	0.44
Length of hospital stay in days	26 (31)	23 (17)	0.52
ICU mortality – no (%)	15 (21.7)	15 (21.1)	0.99
In-hospital mortality – no (%)	17 (24.6)	17 (23.9)	0.99

The primary endpoint was the total SOFA score on day 7 from randomisation. The secondary endpoints were serum levels of PCT, IL-6, lactate and ScvO₂ on day 7 from randomisation. Tertiary endpoints were the length of mechanical lung ventilation, the length of ICU and hospital stay, ICU mortality and in-hospital mortality.

All data are expressed as median (IQR). IQR are expressed as difference between the 75th and the 25th percentile of data. SOFA_{sum} score = The Sequential Organ Failure Assessment score expressed as the sum of all items, PCT = serum procalcitonin level in ug/L, IL-6 = serum interleukine-6 level in ng/L, Lactate = serum lactate level in mmol/L, ScvO₂ = central venous oxygen saturation in %, RND = randomisation.

(*) – the value is significantly lower than the value on the day of RND.

Figures

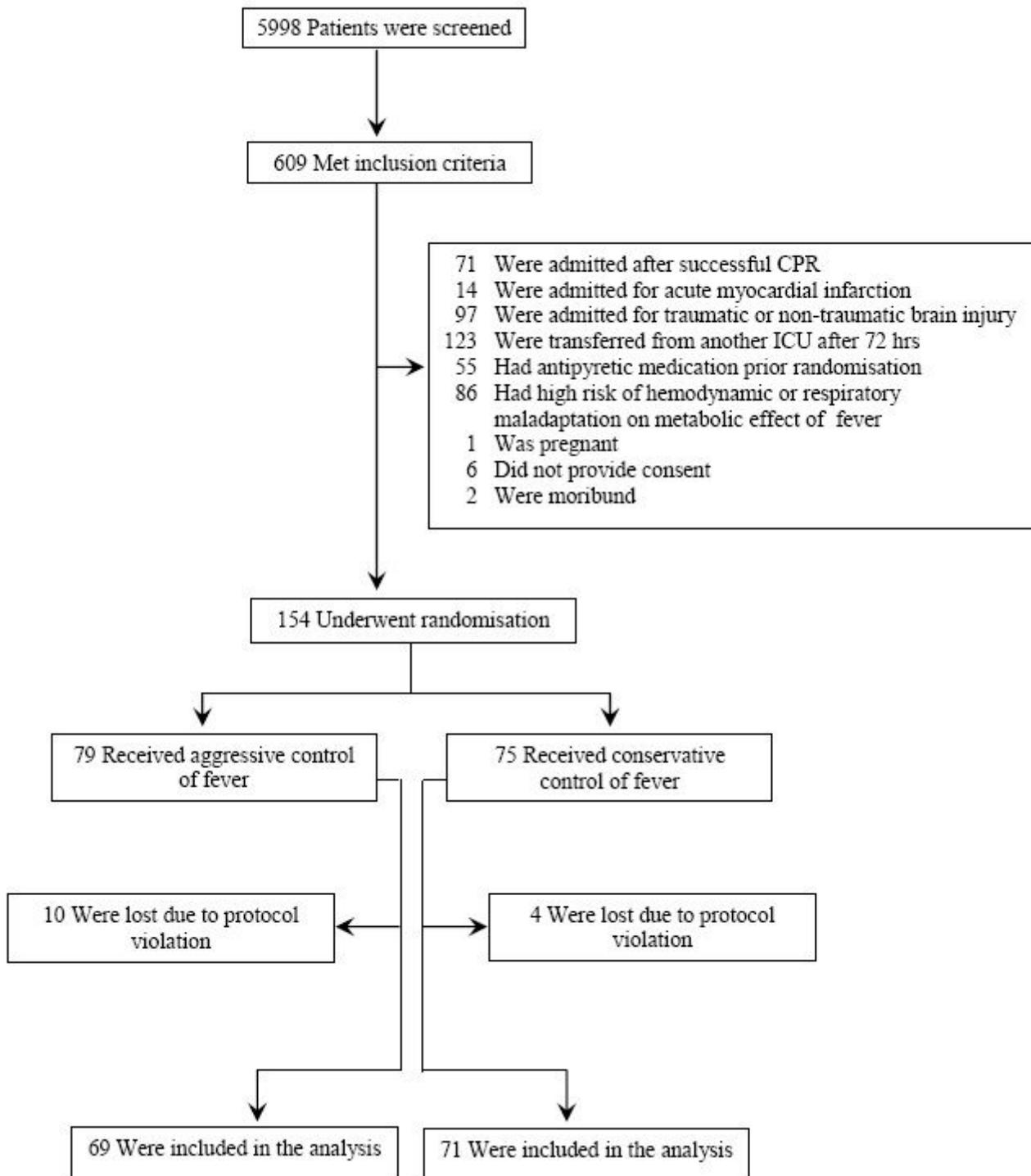


Figure 1

Screening, randomisation and follow-up. Legend: The patients met inclusion criteria if they developed a fever (body temperature > 38.3 °C lasting at least 60 minutes) and the infectious origin of the fever was suspected or confirmed.

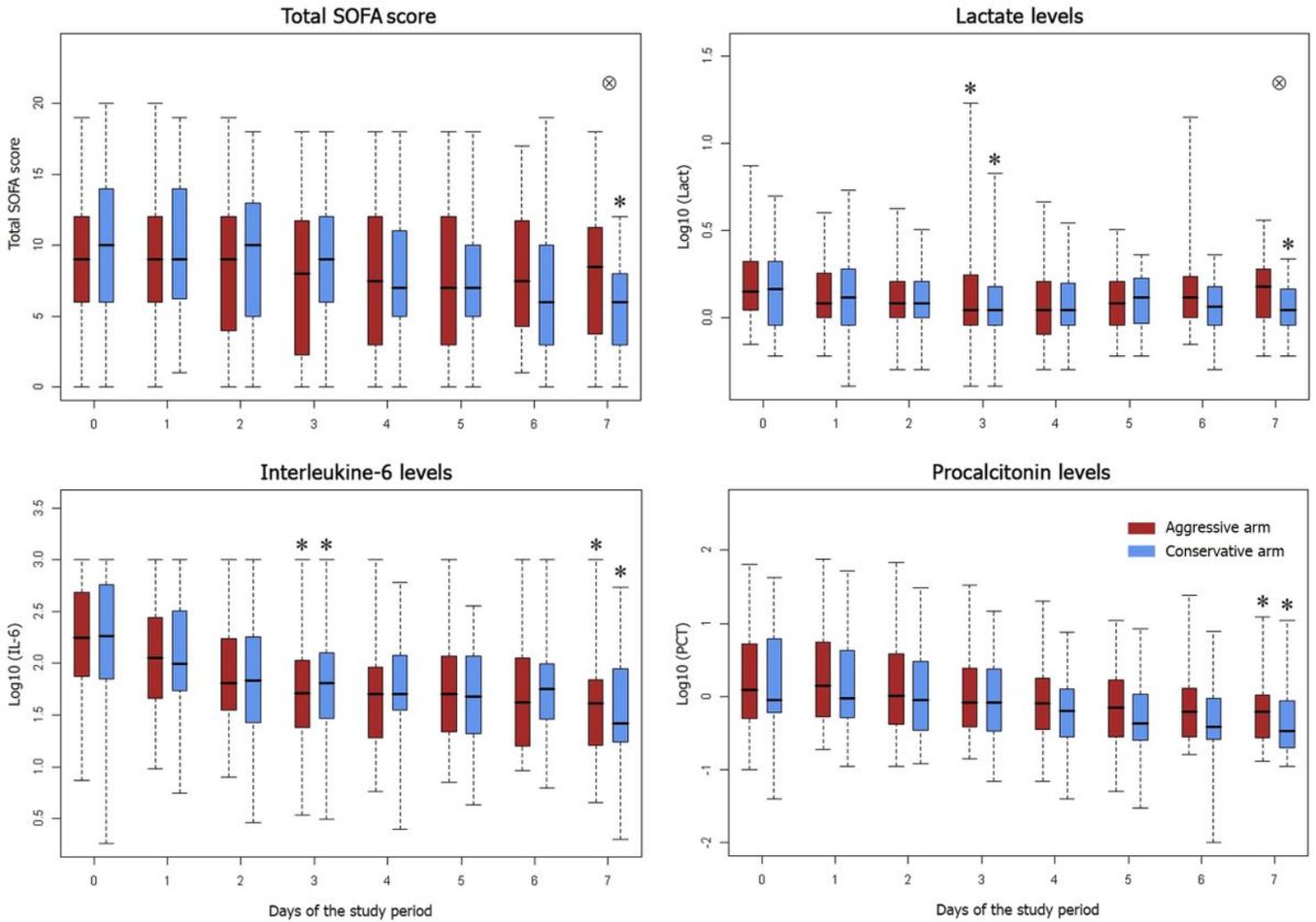


Figure 2

The total SOFA score, lactate, PCT and IL-6 levels during the study period. Legend: All data are expressed as median (IQR). Median is marked by a horizontal line inside the box. The ends of the box represent the interquartile range (IQR) and the vertical lines outside the box extend to the highest and lowest observations. Procalcitonin (PCT), lactate and interleukin-6 (IL-6) levels are displayed on a logarithmic scale. The total SOFA score was calculated daily as the sum of the highest score recorded for each organ system. Blood samples for the examination of PCT, lactate and IL-6 were taken at randomisation and then every morning for the next 7 days. Day 0 is the day of randomisation. * = the value is significantly lower than the value on the day of randomisation. ⊗ = the difference between the values in study arms is statistically significant.

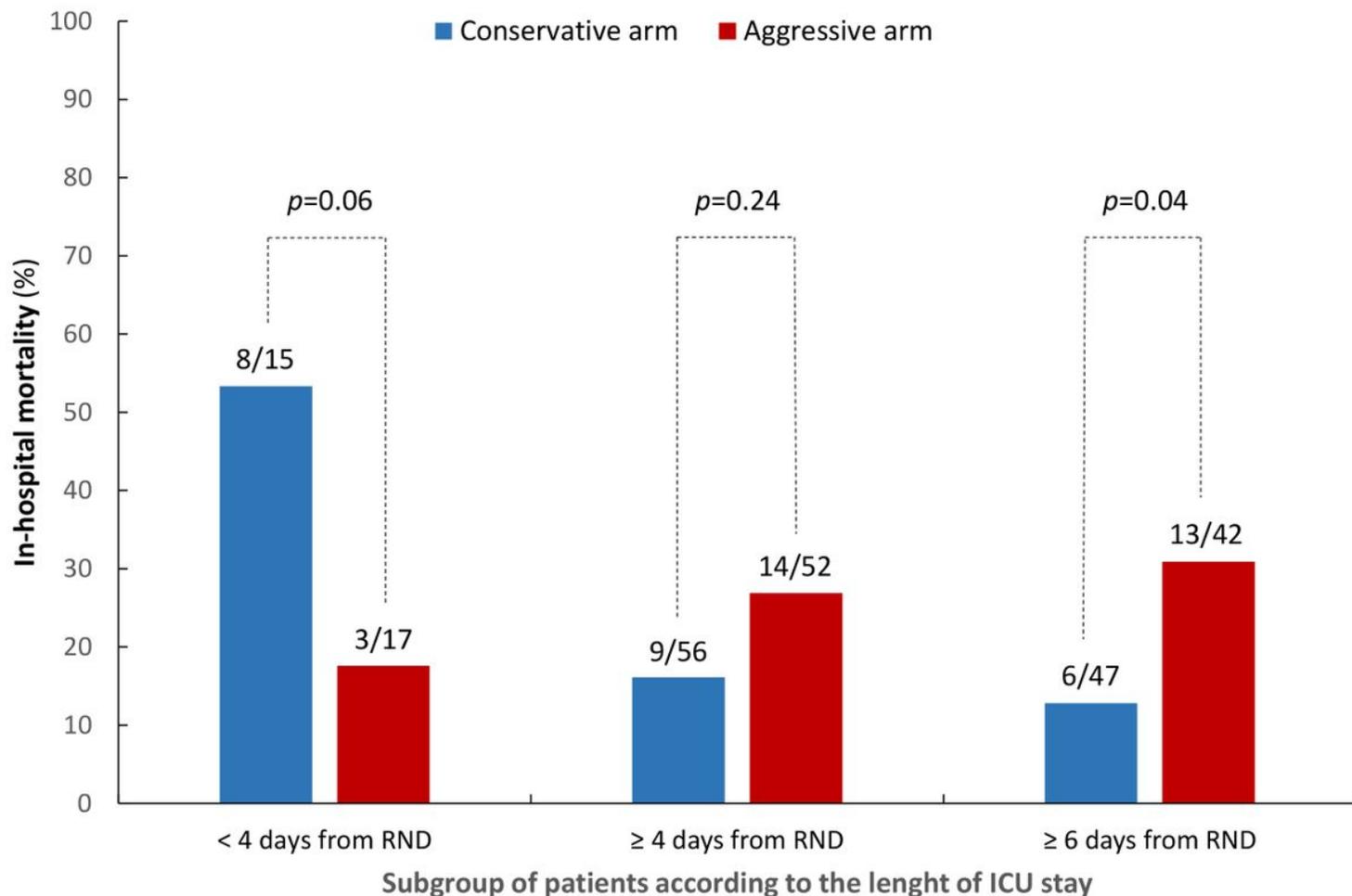


Figure 3

In-hospital mortality in three subgroups of patients according to their length of ICU stay from the day of randomisation. Legend: The numerical fraction above each bar graph represents the number of deaths / number of patients in the arm of the patient subgroup.

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