

The Effect of Body Temperature Changes on the Course of Treatment in Patients with Pneumonia and Sepsis: Results of an Observational Study

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Table of Contents

Original Manuscript..... 4

Supplementary Files..... 15

 Figures 16

 Figure 0..... 17

 Figure 0..... 18

 Figure 0..... 19

 Figure 0..... 20

The Effect of Body Temperature Changes on the Course of Treatment in Patients with Pneumonia and Sepsis: Results of an Observational Study

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Abstract

Background: Traditionally, critically ill patients with infection and fever have been cooled in order to decrease metabolic demands.

Objective: To determine the effect of body temperature on the course of intensive care unit (ICU) treatment of mechanically ventilated patients with pneumonia with positive tracheal aspirates on admission and sepsis.

Methods: We performed a single-center retrospective study comparing patients with negative tracheal aspirates one week after ICU admission (P-N group), to patients with a different pathogen in tracheal aspirates one week after ICU admission (P-HAP group), and to patients with a persisting pathogen in tracheal aspirates one week after ICU admission (P-P group).

Results: We observed a significantly higher average temperature in the first 48 hours after ICU admission in patients who survived to hospital discharge (37.2°C (36.6°C, 37.6°C) vs. 36.9°C (35.8°C, 37.4°C), $p=0.038$). We observed a significantly greater use of paracetamol in the P-N group (1.0±1.1 g vs. 0.4±0.7 g vs. 0.4±0.8 g, $p=0.009$), a trend towards greater use of active cooling in the first 24 hours after ICU admission in the P-N group (44% vs. 33.3% vs. 32%, $p=0.57$), and no other significant differences in parameters of ICU treatment between patient groups.

Conclusions: Our data supports the strategy of temperature tolerance in intubated patients with pneumonia and sepsis. Clinical Trial: /

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Original Manuscript

Original Paper

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The Effect of Body Temperature Changes on the Course of Treatment in Patients with Pneumonia and Sepsis: Results of an Observational Study

Abstract

Background: Traditionally, critically ill patients with infection and fever have been treated with antipyretics or even physically cooled. Presumed benefits of the reduction of body temperature are mostly based on decreased metabolic demands. However, it has been shown that decreasing body temperature in critically ill patients is not associated with improvement in treatment outcomes. Additionally, there is some data to support the use of temperature modulation (therapeutic hyperthermia) as adjuvant treatment strategy in patients with infection.

Objective: To determine the effect of body temperature on the course of intensive care unit (ICU) treatment of mechanically ventilated patients with pneumonia, sepsis, and positive tracheal aspirates on admission.

Methods: We performed a single-center retrospective study. Core body temperature was measured in all patients. We analyzed associations between average temperatures in the first 48 hours after admission to ICU and ICU treatment parameters. Additionally, patients were divided into three groups; patients with negative tracheal aspirates one week after ICU admission (P-N group), patients with a different pathogen in tracheal aspirates one week after ICU admission (P-HAP group), and patients with a persisting pathogen in tracheal aspirates one week after ICU admission (P-P group), and differences in body temperature and interventions aimed at temperature modulation were determined.

Results: We observed a significantly higher average temperature in the first 48 hours after admission to ICU in patients who survived to hospital discharge compared to nonsurvivors (37.2°C [1°C] vs. 36.9°C [1.6°C], $P=.038$). We observed no associations between average temperatures in the first 48 hours after ICU admission and days of mechanical ventilation in the first 7 days of treatment ($\rho=-0.090$, $P=.300$), the average maximum daily requirement for noradrenaline in the first 7 days of treatment ($\rho=-0.029$, $P=.800$), average maximum FiO_2 in the first 7 days of ICU treatment ($\rho=0.040$, $P=.700$) and requirement for renal replacement therapy in the first 7 days of ICU treatment (37.3°C [1.4°C] vs. 37.0°C [1.3°C], $P=.232$). In additional analysis we observed a significantly greater use of paracetamol in the P-N group (1.0 ± 1.1 g vs. 0.4 ± 0.7 g vs. 0.4 ± 0.8 g,

$P=.009$), a trend towards greater use of active cooling in the first 24 hours after ICU admission in the P-N group (44% vs. 33.3% vs. 32%, $P=.57$), and no other significant differences in parameters of ICU treatment between patient groups.

Conclusions: We observed better survival in patients who developed higher body temperatures in the first 48 hours after admission to ICU, however, we observed no changes in other treatment parameters. Similarly, we observed greater use of paracetamol in patients with negative tracheal aspirates one week after ICU admission. Our results support the strategy of temperature tolerance in intubated patients with pneumonia and sepsis.

Trial Registration /

Keywords: fever; targeted temperature management; pneumonia; sepsis; intensive care unit

Introduction

Increased body temperature has been recognized as a sign of illness for more than 2000 years and antipyretics have been used for at least 100 years with the aim of lowering body temperature in febrile patients [1]. However, a body of evidence exists ranging from studies in the pre-antibiotic era to a recently published pilot trial, where increased body temperature is investigated as a treatment option in patients with infection [2-4]. Fever-range increase of body temperature is a highly preserved response which is probably beneficial in patients who develop fever as a part of a normal immune response to infection [5]. Recently, we have observed that patients with lower body temperature are at a higher risk of acquiring the presence of multi-drug resistant pathogens [6]. The aim of the present study was to investigate the association between body temperature and the course of ICU treatment in patients with pneumonia and sepsis and to evaluate the effect of temperature on the persistence of positive control tracheal aspirates.

Methods

Study Design and Settings

We performed a retrospective observational data collection from 1. 1. 2018 to 31. 12. 2021. The study was performed in a medical ICU (intensive care unit) in a tertiary centre and supported by institutional research grant (grant IRP-2022/01-01).

Ethical Considerations

The study was approved by the institutional ethics committee and informed consent was waived because of the observational and retrospective nature of the study (No. UKC-MB-KME-35/22). Patients data has been anonymized and de-identified. No compensation was provided to the participants.

Study Population

We included adult (>18 years) patients with pneumonia, septic shock, positive tracheal aspirates within 24 hours after admission ("admission" tracheal aspirates) and tracheal aspirates withdrawn 8-14 days after admission to ICU ("week 2" tracheal aspirates). We excluded patients who were treated with targeted temperature management for accidental hypo- or hyperthermia, patients after cardiac arrest and neurocritical patients (e.g. patients with meningitis, encephalitis, ischaemic or haemorrhagic stroke, subarachnoid haemorrhage or similar). Temperature management in our patient cohort was as per the treating physician.

Measurements

We collected basic demographic data and data related to ICU treatment, namely outcome of ICU treatment, ICU length of stay, core body temperature during ICU stay, use of renal replacement therapy, use of acetaminophen, maximum concentration of noradrenaline, maximum fraction of inspired oxygen, maximum level of positive end-expiratory pressure and maximum minute ventilation, and microbiological results of tracheal aspirates. Source data was paper-based for temperature and therapeutic charts and electronic for other data. Core body temperature was used for study data. As per department policy, temperature was measured via thermal probe urinary catheters (Rüsch Sensor urinary catheters, Teleflex Medical, Athlone, Ireland), and temperature measurements were continuously displayed on ICU monitors (Philips IntelliVue MX800 patient monitoring system, Koninklijke Philips N.V., Amsterdam, Netherlands). If insertion of a urinary catheter is not possible, then esophageal temperature probe is inserted, however, temperature measurement in all of the included patients was performed via urinary catheter. Temperature results from 2-hourly notations were used for statistical analysis. We compared the association between body temperature and course of treatment parameters between three groups of patients: patients with sterile week 2 tracheal aspirates (P-N group), patients with a different pathogen in week 2 tracheal aspirates (P-HAP group), and patients with a persistent pathogen presence in week 2 tracheal aspirates (P-P group).

Data Analysis

Statistical analyses were carried out using R (R Core Team 2021, Vienna, Austria). Nominal variables are presented with frequencies (percentages) and numerical variables with mean $\pm$ standard deviation or median [IQR] when the normality assumption was violated. For the comparison of nominal dichotomous variables, Fisher's exact test was used. Continuous variables were first assessed for normality using D'Agostino's omnibus test. A comparison of continuous variables across groups was carried out using Kruskal Wallis test. Dunn's post-hoc test with Bonferroni correction was used to adjust for multiple comparisons. The association between average temperature in the first 48 hours and the duration of mechanical ventilation, the average maximum daily requirement for noradrenaline and the average maximum FiO₂ in the first 7 days was evaluated using Spearman correlation. Generalized linear models were used in order to additionally estimate the ICU and hospital survival in association with abovementioned risk factors. A statistically significant observation was considered at $P < .05$.

Results

Baseline characteristics

In all, 117 patients were included to study analysis, 84 (71.8%) were males, and mean age was 63.7 ± 13.5 years. All patients were invasively mechanically ventilated on ICU day 1. Mean APACHE II and SOFA scores on admission were 21.7 ± 6.6 , and 10.1 ± 2.6 , respectively. Seventy-seven patients (65.8%) were discharged alive from the ICU, and 46 patients (39.3%) were discharged alive from the hospital. P-N, P-HAP and P-P groups consisted of 25, 42 and 50 patients each, respectively. We observed no significant differences between the P-N, P-HAP and P-P groups in all treatment parameters, apart from the use of paracetamol on day 1, which was significantly greater in the P-N group (1.0 ± 1.1 g vs. 0.4 ± 0.7 g vs. 0.4 ± 0.8 g, $P = .009$). General demographic data and parameters describing the course of the treatment in the ICU are described in Table 1. The study patient population and inclusion flowchart are presented in Figure 1.

Main Results

Body temperature changes in the first 28 days of treatment are presented in Figure 2. We observed a significantly higher average temperature in the first 48 hours after admission to ICU in patients who

survived to hospital discharge compared to nonsurvivors (37.2°C [1°C] vs. 36.9°C [1.6°C], $P=.038$), and nonsignificant differences in average temperatures in the first 48 hours after admission to ICU between survivors and non-survivors to ICU discharge (37.0°C [1.3°C] vs. 37.0°C [1.2°C], $P=.597$). We observed no associations between average temperatures in the first 48 hours after ICU admission and days of mechanical ventilation in the first 7 days of treatment ($\rho=-0.090$, $P=.300$), the average maximum daily requirement for noradrenaline in the first 7 days of treatment ($\rho=-0.029$, $P=.800$), average maximum FiO_2 in the first 7 days of ICU treatment ($\rho=0.040$, $P=.700$) and requirement for renal replacement therapy in the first 7 days of ICU treatment (37.3°C [1.4°C] vs. 37.0°C [1.3°C], $P=.232$).

P-N, P-HAP and P-P groups consisted of 25, 42 and 50 patients each, respectively. No significant differences in average body temperature in the first 48 hours were observed between the P-P, P-HAP and P-N groups. Temperature variations increased after day 16 (Figure 2), however, and approximately 2/3 of patients have been discharged from ICU or have died until day 16. Both hospital and ICU survival were higher in the P-N group compared to P-HAP and P-P groups, however, the differences were not statistically significant (Figure 3). We observed a statistically significant greater use of paracetamol in the first 24 hours after ICU admission in the P-N group compared to P-HAP and P-P groups (1.0 ± 1.1 g vs. 0.4 ± 0.7 g vs. 0.4 ± 0.8 g; $P=.009$). Active cooling was used more frequently on day 1 in the P-N group, but no significant differences were observed (Figure 4).

Microbiological Data

In all, 148 different causal pathogens were isolated. In admission tracheal aspirates the majority (66%) of pathogens were Gram-negative bacteria, followed by Gram-positive bacteria (29.8%) and fungal pathogens (4.2%). In week 2 tracheal aspirates the great majority (86.5%) of pathogens were Gram-negative bacteria, followed by Gram-positive bacteria (9.5%) and fungal pathogens (4.1%). We observed no differences between the P-N, P-HAP and P-P groups in causative pathogens in admission tracheal aspirates (Table 2). There were no differences between the P-N, P-HAP and P-P groups in the rate of change of antimicrobial therapy within the first week after ICU admission, and we observed no changes in the duration of initial (combined empiric and antibiogram-guided antimicrobial therapy) and cumulative ICU-stay antibiotic therapy (7.6 ± 2.7 days vs. 8.4 ± 3.1 days vs. 8.2 ± 2.9 days, $P=.55$, and 15.2 ± 5.6 days vs. 14.8 ± 6.8 days vs. 15.9 ± 6.2 days, $P=.70$, respectively).

Discussion

We observed higher initial body temperatures in patients who survived to hospital discharge and a trend towards higher initial temperatures in patients who survived to ICU discharge. We did not observe any differences in body temperature between the P-N, P-HAP and P-P groups of patients, but we did observe a significantly greater use of paracetamol in the P-N group of patients, and a trend towards greater use of active cooling in the P-N group of patients. Also, we observed a trend toward better survival to ICU- and hospital discharge in the P-N group of patients.

Traditionally, antipyretic therapy (mostly paracetamol), and in some cases active cooling, have been used to lower body temperature in febrile patients with infection. The presumed patient benefit comes from decreased metabolic demands associated with lower body temperature [7, 8].

The survival of our patients is comparable to studies performed by Gursel et al., Depuydt et al. and Qiao et al. who reported survival to ICU discharge of critically ill patients with pneumonia in the range between 46% and 75%, compared to 65.8% survival to ICU discharge in our patients. They included patients with similar severity of illness, with SOFA scores in the range between 4 and 6 points, and APACHE II scores around 20 points, compared to SOFA score 10.1 ± 2.6 , and APACHE II score 21.7 ± 6.6 in our study [9-11].

Our findings are in line with a number of other studies where better survival was observed in patients with infection and physiological-grade fever (i.e., body temperature between around 37 and 39°C). Both Kushimoto et al. in a prospective observational study, and Shimazui et al. in retrospective observational study, observed higher mortality in patients with sepsis and lower body temperature on admission [12, 13]. Lee et al. also observed lower mortality in patients with physiological-grade fever in their prospective study [14]. Rumbus et al. performed a meta-analysis of 42 studies reporting body temperature and mortality in patients with sepsis [15]. They discovered a correlation between higher body temperature and lower mortality; higher body temperature predicted better survival, and hypothermia predicted lower survival. Similar to our findings the number of patients with body temperature over 39.5°C was very low. Thomas-Rüddel et al performed a secondary analysis of a large dataset of sepsis patients and discovered that initial body temperatures were distributed in two peaks: a smaller peak at around 35.5°C and an approximately twice larger peak at around 38°C [16]. Again, the highest survival rate was observed in patients with hyperthermia and the lowest in patients with hypothermia. They also observed that ambient temperatures were significantly associated with body temperatures; lower ambient temperatures were associated with hypothermia, and higher outside temperatures were associated with hyperthermia. The potential benefits of active warming of patients with infection were further highlighted by Drewry et al [4], who performed a pilot randomized controlled study evaluating the use of therapeutic hyperthermia in patients with sepsis and observed a significantly better survival in the hyperthermia group, however, there were no differences in the primary results.

We can speculate that higher doses of paracetamol and greater use of active cooling probably decreased body temperatures in the P-N group of patients, however, this was not associated with any improvement during the course of ICU treatment – we observed no differences in the use of noradrenalin, parameters of mechanical ventilation, requirement for renal replacement therapy or organ dysfunction scores, and we observed a trend towards greater ICU and hospital survival in the P-N group. Our results suggest that there is probably no clinical benefit associated with the treatment of physiological-grade fever. Similarly, Zhang et al and Ye et al performed retrospective studies on patients with fever and sepsis, and they observed no beneficial effects of antipyretic therapy, and possible harm associated with the use of external cooling [17, 18]. In a prospective randomized controlled trial, Young et al [19] observed approximately 0.5°C lower body temperature in patients who received paracetamol (4 g daily) compared to patients who received placebo. They also observed that patients who received more paracetamol experienced longer ICU stay if they were non-survivors, and shorter ICU stay if they were survivors, which was explained by the probable effect of lower body temperature on clinicians' perception of the patients' prognosis. Lower body temperature in the paracetamol group was not associated with any improvement in the ICU course of treatment parameters [19, 20].

To our knowledge, there is no other data to compare our results regarding the clearance or persistence of pathogens in tracheal aspirates. In 42.7% of our patients (i.e., the P-P group of patients) the same pathogen persisted in tracheal aspirates one week after initial samples were obtained. There were no differences in causative pathogens between the P-N, P-HAP and P-P groups of patients, and we observed no significant changes in baseline data between the groups, including the rate of change of empiric antibiotic therapy. There was a trend towards higher temperature in the first 48 h in the P-N group, compared to P-HAP and P-P groups, possibly indicating that tolerance of hyperthermia could be beneficial for intubated patients with pneumonia and sepsis. There were no significant differences in the course of ICU treatment parameters despite greater use of paracetamol and active cooling, indicating that pharmacological and/or active cooling has no benefit in patients where fever is part of an appropriate response to infection.

There are a number of limitations to our study. We performed a single-centre, retrospective, observational study with all inherent biases associated with this study design. The sample size - of the initial 488 patients with pneumonia, 249 were not included because there were no tracheal

aspirates one week after ICU admission (because of extubation, death or no clinical need for obtaining samples if the patients were still intubated). Additionally, target temperatures were defined by the treating physicians. However, there are no guidelines regarding target temperatures for this patient population and we observed no differences in baseline data between different groups.

Conclusions

We observed better survival in patients who developed higher body temperatures in the first 48 hours after admission to ICU, however, we observed no changes in other treatment parameters. Additionally, we observed greater use interventions aimed at cooling the patients (use of paracetamol and a trend towards greater use of active cooling) in patients with negative tracheal aspirates one week after ICU admission. Also, in this group of patients we observed a trend towards better survival. Our results speak against the use of interventions aimed at reduction of body temperature and support the strategy of temperature tolerance in mechanically ventilated patients with pneumonia and sepsis.

Author contributions

Conceptualization, A.M., J.F. and Ž.K.; methodology, A.M., P.P.B.; software, P.P.B.; validation, A.M., P.P.B.; formal analysis, P.P.B.; investigation, D.G, A.G and N.G; resources, D.G, A.G and N.G.; data curation, A.M.; writing—original draft preparation, D.G, A.G and N.G.; writing—review and editing, A.M, P.P.B., J.F., Ž.K., D.G, A.G and N.G. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

None declared.

Abbreviations

APACHE: acute physiology and chronic health evaluation

ICU: intensive care unit

IQR: interquartile range

SOFA: sequential organ failure assessment

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Tables

Table 1. Demographic data and parameters describing the course of treatment in the ICU.

Label	Variable	Group			Total	P-value
		P-N	P-P	P-HAP		
Number of patients		25 (21.4 %)	50 (42.7 %)	42 (35.9%)	117 (100 %)	
Gender	Female	5 (15.2 %)	18 (54.5 %)	10 (30.3 %)	33 (28.2 %)	.2551
	Male	20 (23.8 %)	32 (38.1 %)	32 (38.1 %)	84 (71.8 %)	
Age (years)	Median [IQR]	62.0 [52.0; 74.0]	64.0 [57.2; 71.8]	67.0 [62.0; 76.0]	65.0 [57.0; 74.0]	.2147
	Min/Max	23.0/84.0	26.0/84.0	39.0/86.0	23.0/86.0	
BMI (kg/m ²)	Mean (std)	28.7 (7.0)	27.6 (4.3)	29.7 (6.4)	28.6 (5.8)	.1940
	Min/Max	17.2/47.7	18.8/39.2	16.3/44.8	16.3/47.7	
Length of hospitalization (days)	Median [IQR]	22.0 [17.0; 29.0]	19.5 [15.0; 26.8]	17.5 [13.0; 26.8]	20.0 [14.0; 26.9]	.3540
	Min/Max	8.0/53.0	10.0/43.0	8.0/69.0	8.0/69.0	
ICU survival	Died	6 (15.0 %)	16 (40.0 %)	18 (45.0 %)	40 (34.2 %)	.2641
	Survived	19 (26.1 %)	34 (44.2 %)	24 (31.2 %)	77 (65.8 %)	
Hospital survival	Died	13 (18.3 %)	31 (43.7 %)	27 (38.0 %)	71 (60.7 %)	.5901

	Survived	12 (26.1 %)	19 (41.3 %)	15 (32.6 %)	46 (39.3 %)	
SOFA at the time of admission	Median [IQR]	9.5 [7.0; 12.0]	10.0 [9.0; 12.0]	10.0 [9.0; 12.0]	10.0 [9.0; 12.0]	.7640
	Min/Max	5.0/16.0	5.0/15.0	4.0/15.0	4.0/16.0	
APACHE II at the time of admission	Mean (std)	20.4 (6.3)	22.0 (6.4)	22.1 (7.2)	21.7 (6.6)	.5319
	Min/Max	6.0/32.0	7.0/36.0	5.0/40.0	5.0/40.0	
Change of antibiotic in 7 days after admission	No	7 (18.4 %)	17 (44.7 %)	14 (36.8 %)	38 (32.5 %)	.8627

Table 2. Isolated pathogens from first and second sample divided by groups.

First sample							Second sample				
Genus		Group			Total:		Genus		Group		Total:
		P-P	P-HAP	P-N					P-P	P-HAP	
+ terria	1	<i>Staphylococcus</i>	8 (4.3 %)	15 (8.0 %)	6 (3.2 %)	29 (15.4 %)	1	<i>Staphylococcus</i>	5 (3.4 %)	2 (1.4 %)	7 (4.7 %)
	2	<i>Streptococcus</i>	5 (2.7 %)	11 (5.9 %)	5 (2.7 %)	21 (11.2 %)	2	<i>Corynebacterium</i>	1 (0.7 %)	3 (2.0 %)	4 (2.7 %)
	3	<i>Corynebacterium</i>	3 (1.6 %)	2 (1.1 %)	1 (0.5 %)	6 (3.2 %)	3	<i>Streptococcus</i>	1 (0.7 %)	1 (0.7 %)	2 (1.4 %)
	Total:		16 (8.5 %)	28 (14.9 %)	12 (6.4 %)	56 (29.8 %)	4	<i>Enterococcus</i>	0 (0.0 %)	1 (0.7 %)	1 (0.7 %)
	Total:						Total:		7 (4.7 %)	7 (4.7 %)	14 (9.5 %)
- terria	1	<i>Klebsiella</i>	17 (9.0 %)	6 (3.2 %)	8 (4.3 %)	31 (16.5 %)	1	<i>Klebsiella</i>	16 (10.8 %)	12 (8.1 %)	28 (18.9 %)
	2	<i>Haemophilus</i>	4 (2.1 %)	7 (3.7 %)	6 (3.2 %)	17 (9.0 %)	2	<i>Pseudomonas</i>	16 (10.8 %)	8 (5.4 %)	24 (16.2 %)
	3	<i>Escherichia</i>	9 (4.8 %)	4 (2.1 %)	1 (0.5 %)	14 (7.4 %)	3	<i>Escherichia</i>	11 (7.4 %)	4 (2.7 %)	15 (10.1 %)
	4	<i>Enterobacter</i>	9 (4.8 %)	3 (1.6 %)	2 (1.1 %)	14 (7.4 %)	4	<i>Enterobacter</i>	8 (5.4 %)	6 (4.1 %)	14 (9.5 %)
	5	<i>Pseudomonas</i>	10 (5.3 %)	0 (0.0 %)	1 (0.5 %)	11 (5.9 %)	5	<i>Acinetobacter</i>	10 (6.8 %)	3 (2.0 %)	13 (8.8 %)
	6	Other	23 (12.2 %)	7 (3.7 %)	7 (3.7 %)	37 (19.7 %)	6	Other	18 (12.2 %)	16 (10.8 %)	34 (23.0 %)

	Total:		72 (38.3 %)	27 (14.4 %)	25 (13.3 %)	124 (66.0 %)	Total:		79 (53.4 %)	49 (33.1 %)	128 (86.5 %)
gi	1	<i>Candida</i>	1 (0.5 %)	6 (3.2 %)	1 (0.5 %)	8 (4.3 %)	1	<i>Candida</i>	5 (3.4 %)	1 (0.7 %)	6 (4.1 %)
al:			89 (47.3 %)	61 (32.4 %)	38 (20.2 %)	188 (100.0 %)	Total:		91 (61,5 %)	57 (38.5 %)	148 (100.0 %)

Figures

Figure 1. The study patient population and inclusion flowchart.

Figure 2. Average body temperature by groups in the first 28 days of treatment in the ICU.

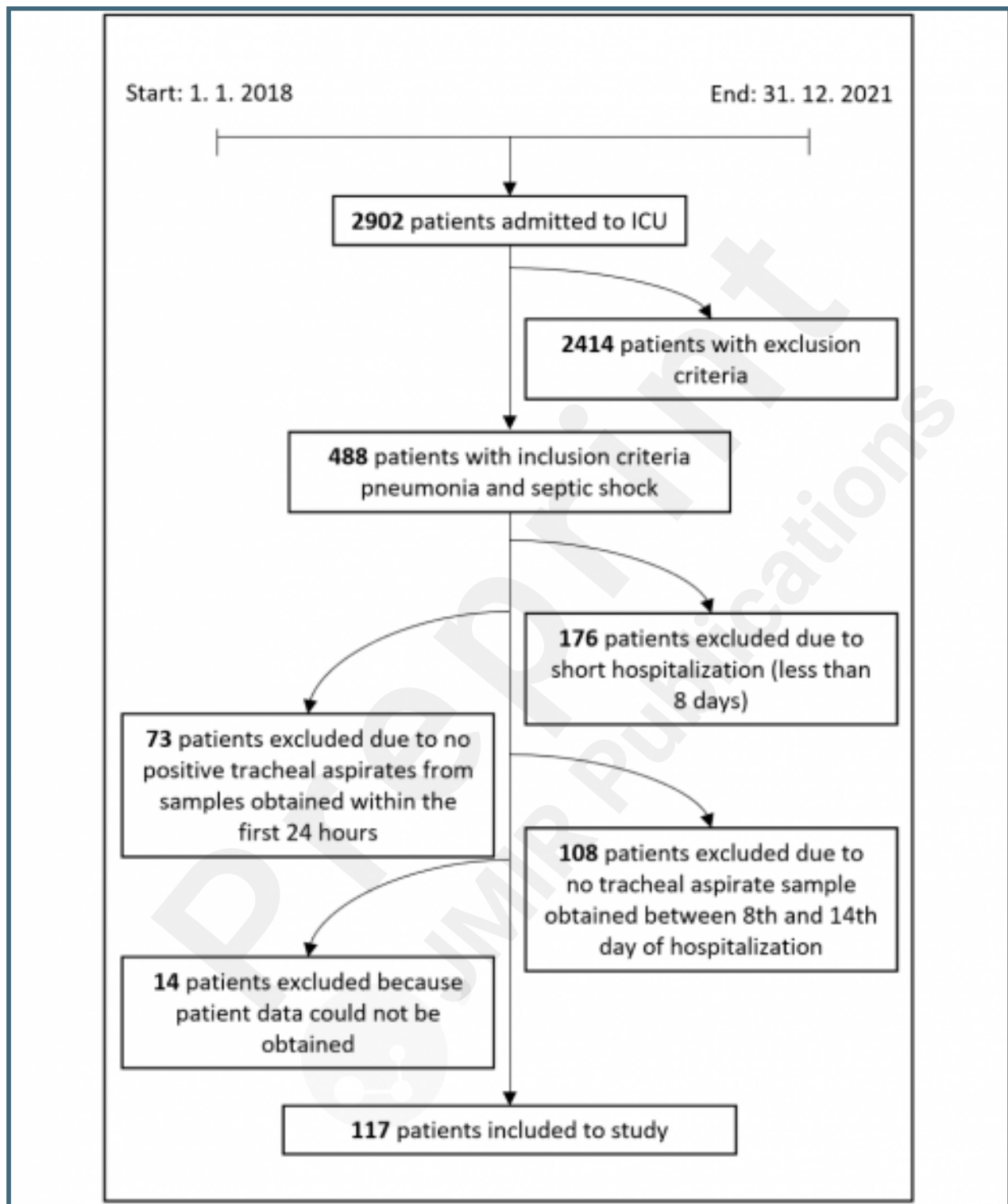
Figure 3. ICU and hospital survival by groups.

Figure 4. Active cooling on day one of hospitalization in the ICU divided by groups.

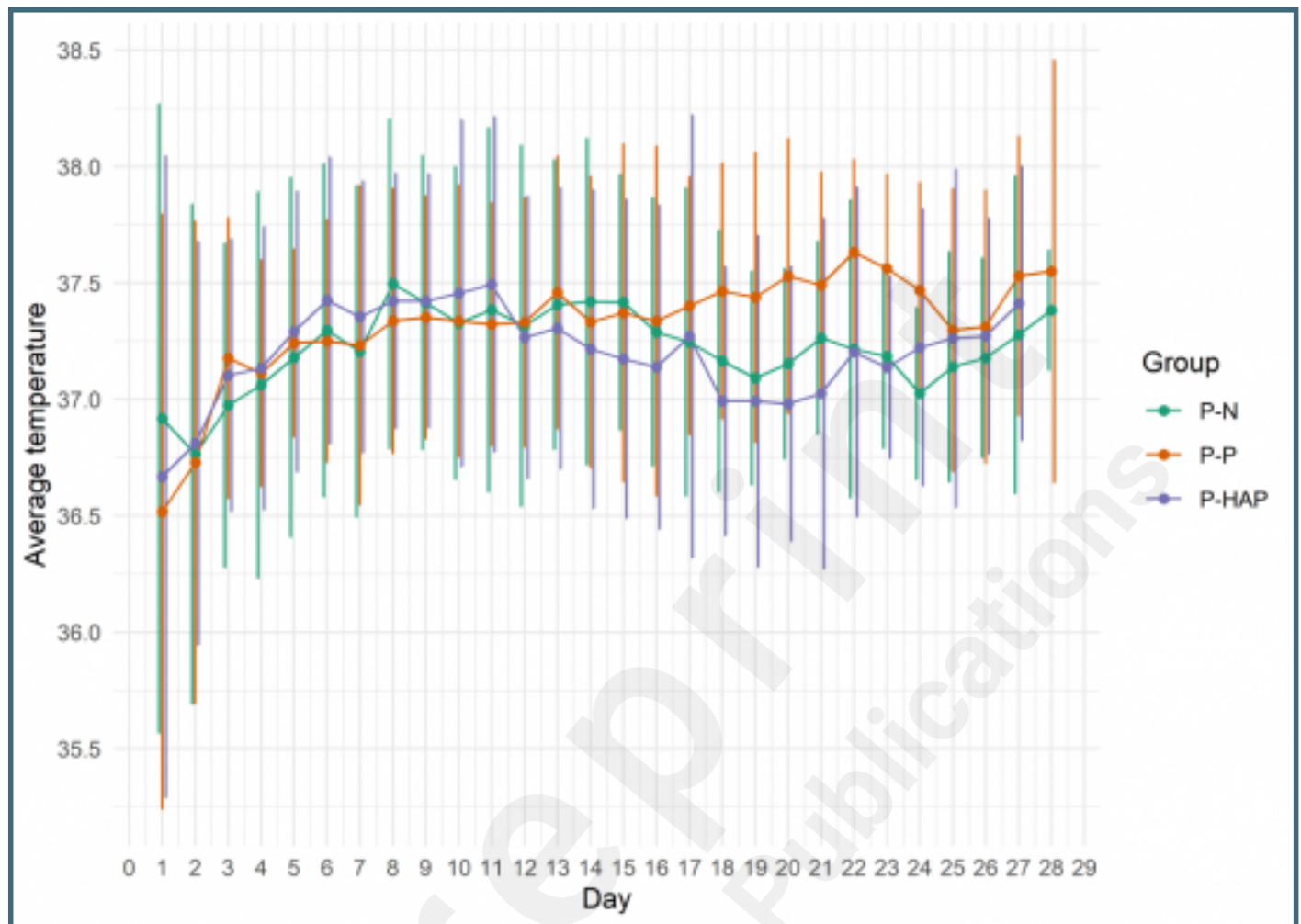
Supplementary Files

Figures

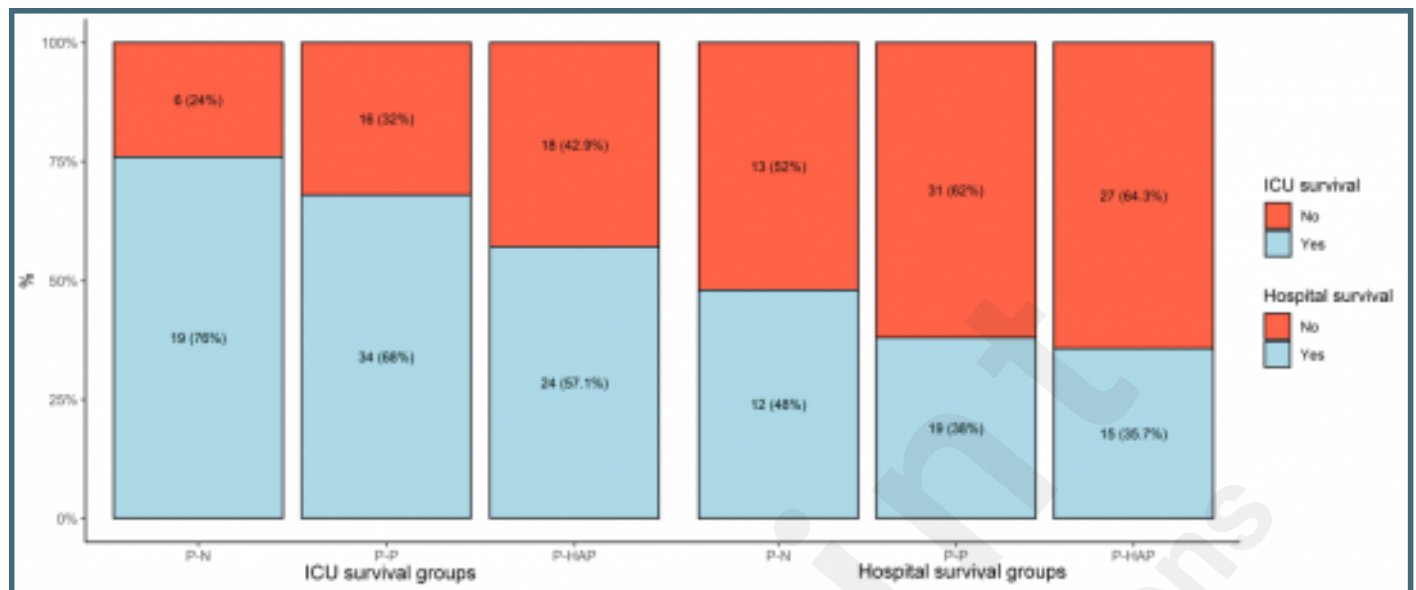
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