CRITICAL ROUNDS

MICRO LABS LIMITED

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A study on effects of therapeutic-dose heparin vs intermediate dose heparins for treating thromboprophylaxis in high risk hospitalized COVID-19 patients

Introduction:

Thrombosis, including venous thromboembolism (VTE), pulmonary embolism, and arterial thromboembolism (ATE), is common among hospitalized adults with COVID-19. The incidence of VTE seems to be increased in COVID-19 population. Microvascular thrombosis and intravascular coagulopathy have been suggested in progression to acute respiratory distress syndrome. Autopsy studies have identified in situ pulmonary arterial thrombosis in more than 60% of patients with COVID-19. Patient comorbidities and immobility, as well as cytokine storm and virus-induced endothelial changes, are some of the risk factors for COVID-19 thrombosis. Elevated plasma D-dimer levels, more than upper limit of normal, predict a more than 2-fold increased risk of VTE or mortality. Based on low quality data, universal thromboprophylaxis with standard prophylactic-dose unfractionated heparin (UFH) or low-molecular weight heparin (LMWH) is recommended, but severely ill inpatients with COVID-19 may experience thrombosis despite standard thromboprophylaxis. Although the multiplatform trials have shown a reduction in organ-support– free days with therapeutic anticoagulation in noncritically ill patients, it is unknown whether high-risk inpatients with COVID-19 may benefit from empirical therapeutic-dose heparin as a thromboprophylactic strategy.

Aim: To compare the safety and efficacy of therapeutic dose heparin (LMWH) and standard or intermediate dose heparins in treating hospitalized COVID-19 patients with thromboprophylaxis

Methods:

Multicenter and randomized controlled clinical trial, around 257 subjects diagnosed with COVID-19 were randomized into two groups. 130 patients were randomized to therapeutic dose heparin (therapeutic dose group) and 127 patients to the intermediate dose (standard dose group). Patients in the therapeutic group received 1 mg/kg enoxaparin subcutaneously twice daily and patients in the standard dose group received dose unfractionated heparin (UFH) up to 22500 IU subcutaneously; 30 mg or 40 mg of enoxaparin once or twice daily subcutaneously.

Primary outcome:

To evaluate the venous thromboembolism (VTE) or arterial thromboembolism (ATE) or death from any cause within 30 days after randomization.

Safety outcome:

Bleeding based on the criteria of International Society on Thrombosis and Hemostasis within 30 days after randomization.

Results:

The primary efficacy outcome was met in 52 of 124 patients (41.9%) (28.2% VTE, 3.2% ATE, 25.0% death) with standard-dose heparins vs 37 of 129 patients (28.7%) (11.7% VTE, 3.2% ATE, 19.4% death) with therapeutic-dose LMWH (relative risk [RR], 0.68; 95% CI, 0.49-0.96; P = .03), including a reduction in thromboembolism (29.0% vs 10.9%; RR, 0.37; 95% CI, 0.21-0.66; P < .001). The incidence of major bleeding was 1.6% with standard-dose vs 4.7% with therapeutic-dose heparins (RR, 2.88; 95% CI, 0.59-14.02; P = .17). The primary efficacy outcome was reduced in non-ICU patients (36.1% vs 16.7%; RR, 0.46; 95% CI, 0.27-0.81; P = .004) but not ICU patients (55.3% vs 51.1%; RR, 0.92; 95% CI, 0.62-1.39; P = .71)

Table 1: Clinical Outcomes During the 30-Day Postrandomization Phase

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
Primary efficacy outcome				
VTE, ATE, or death	37/129 (28.7)	52/124 (41.9)	0.68 (0.49-0.96)	.03
Non-ICU stratum	14/84 (16.7)	31/86 (36.1)	0.46 (0.27-0.81)	.004
ICU stratum	23/45 (51.1)	21/38 (55.3)	0.92 (0.62-1.39)	.71
VTE + ATE	14/129 (10.9)	36/124 (29.0)	0.37 (0.21-0.66)	<.001
Death	25/129 (19.4)	31/124 (25.0)	0.78 (0.49-1.23)	.28
Secondary efficacy outcomes				
Primary efficacy outcome at day 14	30/129 (23.3)	45/124 (36.3)	0.64 (0.43-0.95)	.02
Progression to ARDS	11/127 (8.7)	6/121 (5.0)	1.75 (0.67-4.58)	.25
Rehospitalization	1/129 (0.8)	3/124 (2.4)	0.32 (0.03-3.04)	.36
Intubation	17/122 (13.9)	21/121 (17.4)	0.80 (0.45-1.45)	.46
ECMO	1/129 (0.8)	1/124 (0.8)	0.96 (0.06-15.20)	>.99
Nonfatal cardiac arrest	0	2/124 (1.6)	0.19 (0.01-3.97)	.24
Acute kidney injury[b]	17/129 (13.2)	12/124 (9.7)	1.36 (0.68-2.73)	.38
New-onset atrial fibrillation	4/129 (3.1)	5/124 (4.0)	0.77 (0.21-2.80)	.75
Principal safety outcome				
Major bleeding	6/129 (4.7)	2/124 (1.6)	2.88 (0.59-14.02)	.28
Non-ICU stratum	2/84 (2.4)	2/86 (2.3)	1.02 (0.15-7.10)	>.99
ICU stratum	4/45 (8.9)	0	7.62 (0.42-137.03)	.12

Table 2: Clinical Outcome Components During the 30-Day Postrandomization Phase in the Modified Intention-to-Treat Population

Outcome	No./total No. (%)		RR (95% CI)	*P* value[a]
	Therapeutic dose (n = 129)	Standard dose (n = 124)		
VTE				
Symptomatic DVT	7/129 (5.4)	19/124 (15.3)	0.35 (0.15-0.81)	.01
Asymptomatic proximal DVT	2/129 (1.6)	3/124 (2.4)	0.64 (0.11-3.77)	.68
Symptomatic pulmonary embolism	4/129 (3.1)	10/124 (8.1)	0.38 (0.12-1.19)	.08
Other VTE[a]	2/129 (1.6)	3/124 (2.4)	0.64 (0.11-3.77)	.68
ATE				
Myocardial infarction	0	3/124 (2.4)	0.14 (0.01-2.63)	.12
Stroke	1/129 (0.8)	1/124 (0.8)	0.96 (0.06-15.20)	>.99
Major adverse limb event	2/129 (1.6)	0	4.81 (0.23-99.13)	.50
Other ATE[b]	1/129 (0.8)	0	2.88 (0.12-70.13)	>.99
Death, No./total No. (%)				
Cardiovascular	10/129 (7.8)	15/124 (12.1)	0.64 (0.30-1.37)	.25
Infectious/sepsis	12/129 (9.3)	8/124 (6.5)	1.44 (0.61-3.41)	.40
Other	3/129 (2.3)	8/124 (6.5)	0.36 (0.10-1.33)	.11
Bleeding, No./total No. (%)				
Decrease in hemoglobin ≥2 g/dL within 24 h	4/129 (3.1)	1/124 (0.8)	3.85 (0.44-33.93)	.37
Transfusion of ≥2 U of packed red blood cells	0	1/124 (0.8)	0.32 (0.01-7.79)	.49
Critical site bleeding	2/129 (1.6)	0	4.81 (0.23-99.13)	.50
Fatal bleeding	0	0	NA	NA

Conclusion:

In this study, therapeutic-dose LMWH prevented major thromboembolism and death among inpatients with COVID-19 and very high D-dimer values when compared to the standard heparin thromboprophylaxis.

Reference:

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Spyropoulos AC, et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. JAMA Intern Med. 2021 Oct 7:e216203.

A nationwide observational study on polymyxin B hemoperfusion, an adjunctive therapy for treating

Introduction:

Sepsis is the most common cause of death in the ICU. Sepsis-related deaths were 11 million per year, representing 19.7% of global deaths. When the disease progresses to septic shock with circulatory failure, the mortality rate is high. The standard treatment for sepsis includes early administration of antimicrobial agents, removal of the infected foci, and early infusion of fluids and vasopressors in case of shock. One of the adjunctive therapies for septic shock is polymyxin B hemoperfusion (PMX). This therapy uses a polymyxin B-immobilized fiber column to remove endotoxin from the bloodstream. Many studies determined the efficacy of PMX in improving blood pressure and respiratory function. Randomized controlled trials (RCTs) of PMX using survival rate as an endpoint have shown mixed results. Some show mortality reduction, and others show no effect. RCTs are the means of clinical research that provide the highest level of evidence regarding the efficacy of treatments.

Aim:

To evaluate the efficacy of polymyxin B hemoperfusion (PMX) using two years of DPC and to assess the association between SOFA score in patients with sepsis.

Methods:

A retrospective observational study with 44,177 patients included whose primary diagnosis was sepsis. Analysis of efficacy of PMX on adult sepsis patients using the propensity score matching method and the Japanese Diagnosis Procedure Combination (DPC) national inpatient database. Patient were stratified into five categories based on their baseline Sequential Organ Failure Assessment (SOFA) score and compared the mortality between PMX-treated and non-treated groups in each category and also continuous hemodiafltration (CHDF)-, ventilator- and noradrenaline-free days between the groups

Table 3: Baseline patient characteristics before and after propensity score matching

Variable	Unmatched groups			Matched groups		
	PMX ($n=2191$)	Control ($n=41,986$)	ASD (%)	PMX ($n=2033$)	Control ($n=2033$)	ASD (%)
Age						
≦50	167 (7.6)	2477 (5.9)	5.7	159 (7.8)	144 (7.1)	2.3
51–70	640 (29.2)	9,048 (21.6)	14.7	593 (29.2)	674 (33.2)	7.0
>70	1384 (63.1)	30,461 (16.8)	16.8	1281 (63.0)	1215 (59.8)	5.4
Sex (male)	1282 (58.5)	22,234 (9.1)	9.1	1183 (58.2)	1231 (60.6)	3.9
Emergency admission	1963 (89.6)	40,447 (23.5)	23.5	1835 (90.3)	1839 (90.5)	0.5
CCI						
0	529 (24.1)	9,798 (23.3)	1.6	492 (24.2)	488 (24.0)	0.4
1	457 (20.9)	10,388 (24.7)	7.5	420 (20.7)	421 (20.7)	0.1
2	498 (22.7)	9,383 (22.3)	0.7	460 (22.6)	441 (21.7)	1.8
≧3	707 (32.3)	12,417 (29.6)	4.8	661 (32.5)	683 (33.6)	1.9
University hospital	490 (22.4)	4383 (10.4)	28.1	449 (22.1)	496 (24.4)	4.4
Max noradrenaline						
<5	483 (22.0)	30,812 (73.4)	96.8	476 (23.4)	416 (20.5)	5.9
5–9.9	402 (18.3)	4292 (10.2)	19.9	372 (18.3)	384 (18.9)	1.2
10–15.9	577 (26.3)	3691 (8.8)	41.7	528 (26.0)	560 (27.5)	2.9
≧16	729 (33.3)	3191 (7.6)	60.3	657 (32.3)	673 (33.1)	1.4
CHDF	1440 (65.7)	2715 (6.5)	142.4	1284 (63.2)	1297 (63.8)	1.1
HD	94 (4.3)	1119 (2.7)	7.5	90 (4.4)	118 (5.8)	5.0
Mechanical ventilation	1471 (67.1)	5430 (12.9)	114.8	1326 (65.2)	1352 (66.5)	2.2
Surgery	1200 (54.8)	3912 (9.3)	99.6	1048 (51.5)	1024 (50.4)	1.9
ER/ICU admission	1596 (72.8)	12,260 (29.2)	78.9	1469 (72.3)	1573 (77.4)	9.7
γ-Globulin	718 (32.8)	2417 (5.8)	66.6	620 (30.5)	593 (29.2)	2.4
rTM	1091 (49.8)	2353 (5.6)	104.8	946 (46.5)	901 (44.3)	3.6
AT III	538 (24.6)	1078 (2.6)	64.1	455 (22.4)	433 (21.3)	2.1
Steroid	1023 (46.7)	6847 (16.3)	59.5	941 (46.3)	996 (49.0)	4.4
RBC transfusion	881 (40.2)	3301 (7.9)	73.7	785 (38.6)	774 (38.1)	0.9
Platelet transfusion	424 (19.4)	1336 (3.2)	49.0	380 (18.7)	387 (19.0)	0.7

Results:

Of 44,177 patients included in the study, 2191 received PMX. PMX significantly improved the survival of the patients in the SOFA score categories of 7–9 and 10–12. No significant difference in the survival rate in SOFA score categories of 0–6, 13–15, and 16–24. In analyzing organ support-free days, PMX was also beneficial in the 7–9 and 10–12 SOFA categories compared to other categories.

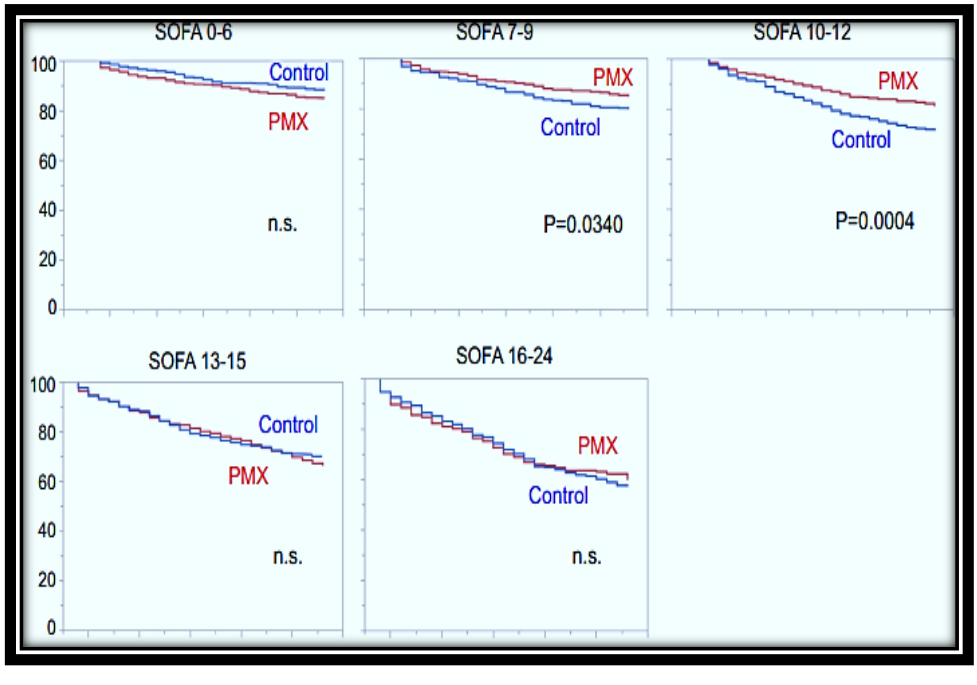

Figure 1: patients treated with or without PMX in propensity score-matched cohorts. Patients were stratified into five categories: SOFA score, 0–6, 7–9, 10–12, 13–15, and 16–24. Then, we compared the survival curves in each category

SOFA score	Unmatched groups				Matched groups		
	PMX (n=2191)	Control (n=41,986)	ASD (%)		PMX (n= 2033)	Control (n 2033)	ASD (%)
0-6	483 (22.0)	27,006 (64.3)	75.3		456 (22.4)	407 (20.0)	4.8
7-9	580 (26.5)	7729 (18.4)	16.2		553 (27.2)	463 (22.8)	8.4
10-12	551 (25.1)	4499 (10.7)	33.1		510 (25.1)	529 (26.0)	1.7
13-15	399 (18.2)	1991 (4.7)	38.9		356 (17.5)	404 (19.9)	4.9
16-24	178 (8.1)	761 (1.8)	26.9		158 (7.8)	230 (11.3)	9.6

Table 4: The number of patients in each SOFA score category before and after propensity score matching

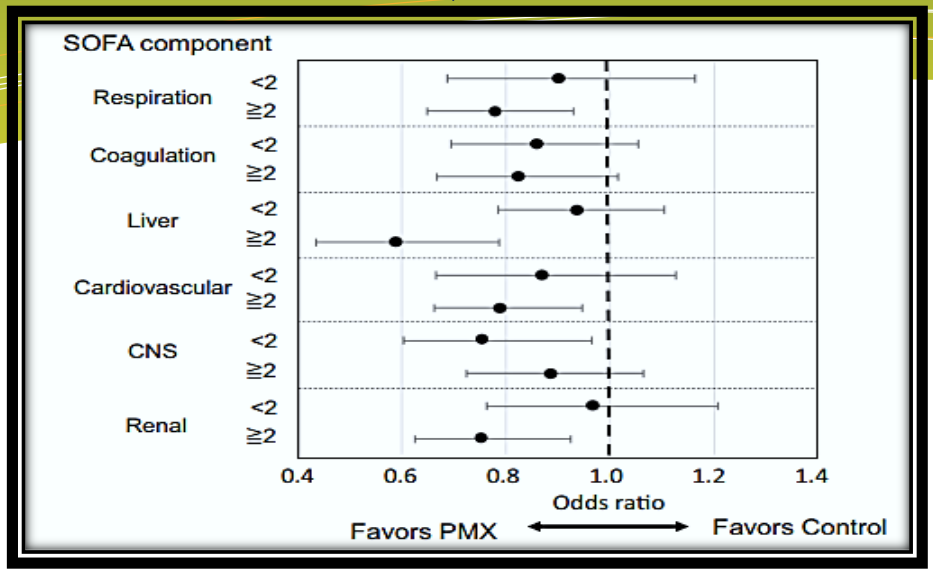

Figure 2: Odds ratio of 28-day mortality across subsets defined according to individual SOFA score components of each organ

Conclusion:

A substantial relationship between PMX efficacy and baseline SOFA score was discovered in a large-scale inpatient database. This data revealed that patients with a medium SOFA score of 7–12 had a better effectiveness. The findings suggest a viable theory for choosing PMX-eligible patients, which should be tested in future RCTs.

Reference:

Fujimori K, Tarasawa K, Fushimi K. Effectiveness of polymyxin B hemoperfusion for sepsis depends on the baseline SOFA score: a nationwide observational study. Ann Intensive Care. 2021 Sep 26;11(1):141.

Fever and hypothermia represent two populations of sepsis patients and are associated with outside temperature

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Introduction:

Fever is caused by release of pyrogens such as acute phase proteins and is frequently the first symptom of infection. It has long been recognized that there are variable thermoregulatory responses in sepsis. The sepsis-1 definition of the Systemic Inflammatory Response Syndrome, therefore, had included both fever and hypothermia. In a meta-analysis of clinical data, hypothermic sepsis patients showed a higher mortality than those with fever. However, most included studies were small and there was a high heterogeneity. The immunological theory of resistance versus tolerance as two distinct, well-regulated response patterns to infection gained acceptance over the last decade. Recent animal studies added a pathophysiological and metabolic perspective whereby hypothermia is aimed at tolerance and energy conservation and fever is aimed at pathogen clearance. Physiological fitness, feeding, environmental temperature and the degree of the immune challenge seem to be important factors promoting fever or hypothermia in animal experiments. To evaluate whether similar processes might play a role in humans, we assessed the thermoregulatory response of septic patients and its association with predisposing factors including environmental temperature, disease severity and outcome in a secondary analysis of a large dataset.

Methods: A secondary analysis of a large clinical dataset from a quality improvement trial. A binary logistic regression model was calculated to assess the association of the thermal response with outcome and a multinomial regression model to assess factors associated with fever or hypothermia.

Results: Around 6542 analyzable cases we observed a bimodal temperature response characterized by fever or hypo- thermia, normothermia was rare. Hypothermia and high fever were both associated with higher lactate values.

Frequency distribution of body temperature (°C) in 6542 patients with new onset of severe sepsis

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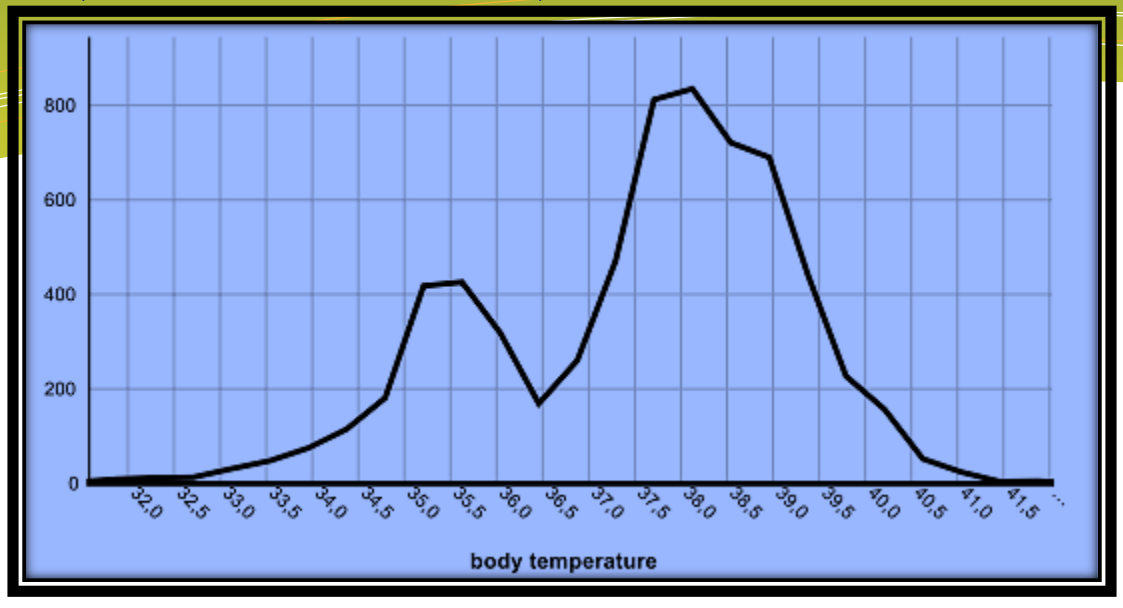
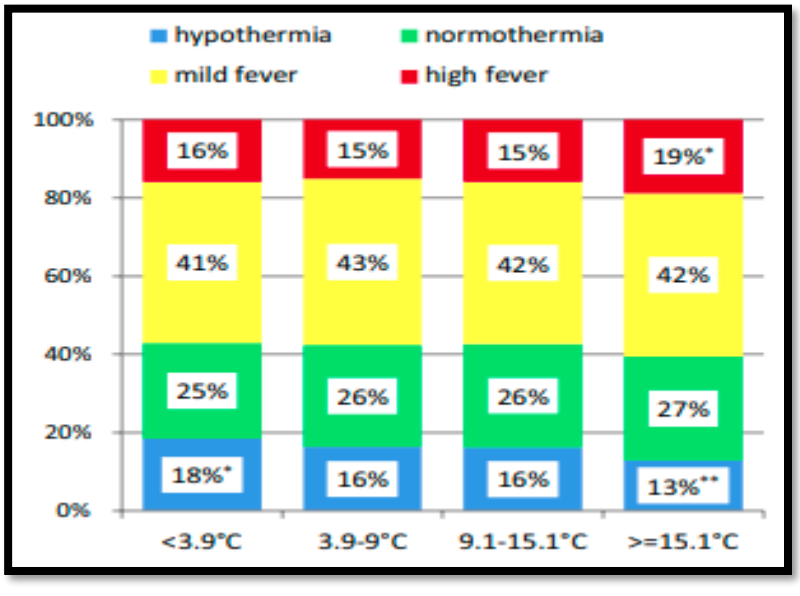


Frequency of body temperature groups depending on mean outside temperature quartiles up to two days before sepsis onset



Odds ratios for 28-day mortality from a logistic regression model without and with adjustment for other predictors of mortality

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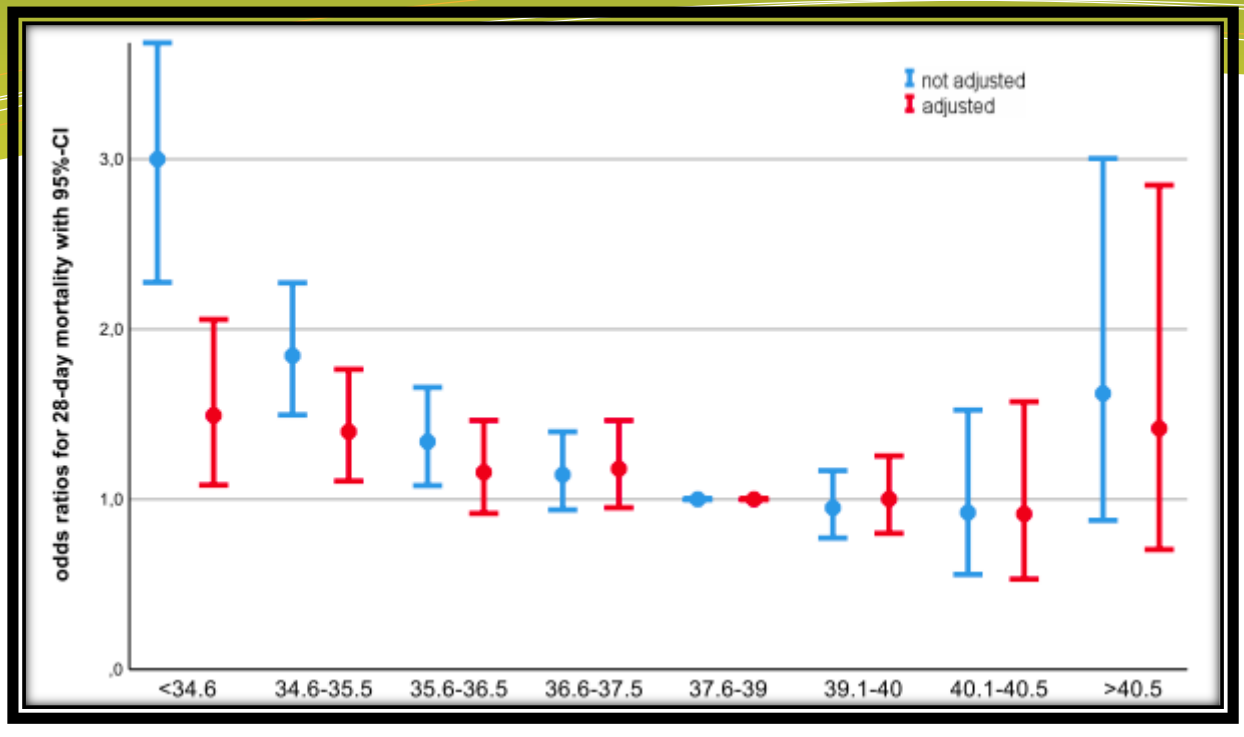

Hypo- thermia was associated with higher mortality, but this association was reduced after adjustment for other risk factors. Age, community-acquired sepsis, lower BMI and lower outside temperatures were associated with hypothermia while bacteremia and higher procalcitonin values were associated with high fever.

Conclusions: Septic patients show either a hypothermic or a fever response. Whether hypothermia is a maladaptive response, as indicated by the higher mortality in hypothermic patients, or an adaptive response in patients with limited metabolic reserves under colder environmental conditions, remains an open question.

Source: Thomas-Rüddel et al. Fever and hypothermia represent two populations of sepsis patients and are associated with outside temperature. Crit Care (2021) 25:368