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ORIGINAL ARTICLE

Fever management in critically ill COVID-19 patients: a retrospective analysis

Lorenzo PELUSO [1] *, Federica MONTANARO [1, 2], Antonio IZZI [1], Alessandra GARUFI [1], Narcisse NDIEUGNOU DJANGANG [1], Amandine POLAIN [1], Andrea MININI [1], Elisa GOUVEA BOGOSSIAN [1], Filippo ANNONI [1], Savino SPADARO [2], Jacques CRETEUR [1], Fabio S. TACCONE [1]

[1]Department of Intensive Care Medicine, Erasme University Hospital, Brussels, Belgium; [2]Intensive Care Unit, Department of Morphology, Surgery and Experimental Medicine, Sant'Anna University Hospital, Ferrara, Italy

*Corresponding author: Lorenzo Peluso, Department of Intensive Care, Erasme University Hospital, Route de Lennik 808, 1070 Brussels, Belgium. E-mail: lorenzopeluso80@gmail.com

ABSTRACT

BACKGROUND: Fever has been reported as a common symptom in COVID-19 patients. The aim of the study was to describe the characteristics of COVID-19 critically ill patients with fever and to assess if fever management had an impact on some physiologic variables.

METHODS: This is a retrospective monocentric cohort analysis of critically ill COVID-19 patients admitted to the Department of Intensive Care Unit (ICU) of Erasme Hospital, Brussels, Belgium, between March 2020 and May 2020. Fever was defined as body temperature ≥38 °C during the ICU stay. We assessed the independent predictors of fever during ICU stay. We reported the clinical and physiological variables before and after the first treated episode of fever during the ICU stay.

RESULTS: A total of 72 critically ill COVID-19 patients were admitted to the ICU over the study period and were all eligible for the final analysis; 53 (74%) of them developed fever, after a median of 4 [0-13] hours since ICU admission. In the multivariable analysis, male gender (OR 5.41 [C.I. 95% 1.34-21.92]; P=0.02) and low PaO_2/FiO_2 ratio (OR 0.99 [C.I. 95% 0.99-1.00]; P=0.04) were independently associated with fever. After the treatment of the first febrile episode, heart rate and respiratory rate significantly decreased together with an increase in PaO_2 and SaO_2.

CONCLUSIONS: In our study, male gender and severe impairment of oxygenation were independently associated with fever in critically ill COVID-19 patients. Fever treatment reduced heart rate and respiratory rate and improved systemic oxygenation.

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KEY WORDS: Sars-CoV-2; Cell respiration; Intensive care units; Lung injury.

In the last year, the spread of SARS-CoV-2, a type of coronavirus that can lead to a severe disease identified as COVID-19, has emerged as a global pandemic.[1] The most common symptoms reported in COVID-19 patients are fever, cough, dyspnea and fatigue.[2] In particular, fever has been reported in 45-89% of the adults and more than 40% of the children affected by mild to moderate forms of the disease[3] and remains one of the typical clinical sign associated with the release of immunological mediators, which are responsible for the body temperature (BT) elevation, through the impairment of thermoregulatory centers of the hypothalamus.[4] The physiological purpose of fever is to enhance the immune function, increasing motility and activity of white blood cells and stimulating T-cells function, thus promoting viral clearance.[5]

Nevertheless, the impact of fever in most severe cases and its management, including the use of antipyretic drugs,[6] remain controversial. In experimental models of sepsis, fever was associated with increased lung injury and reduced endothelial barrier function and was associated with delayed ventilator weaning and worse outcome,[7] although these effects are more difficult to be evaluated in the clinical setting. In COVID-19 patients, some studies have reported an association of body temperature with patients' outcome, in particular suggesting a prognostic role for low BT (<36 °C) on admission and for high BT (>38 °C) during the hospital stay.[8] However, it remains unclear whether temperature control in critically ill COVID-19 patients would impact some important physiological variables and how different interventions are effective in this setting.

The aim of this study was therefore to describe the characteristics of critically ill COVID-19 patients who developed fever and fever management according to a local protocol. Also, the effects of temperature control on some hemodynamic and respiratory variables were analyzed.

Materials and methods

Study design

We performed a monocentric retrospective cohort study in the Intensive Care Unit of the Erasme Hospital in Brussels, Belgium. The study protocol was approved by the local ethics committee (P2020/252), which waived the need for informed written consent because of its retrospective design and since all interventions were part of the standard patients' care. The study was performed in accordance with the ethical standards of the Declaration of Helsinki.

Study population

We enrolled all adult (>18 years) patients admitted to our hospital from March 10th, 2020 (*i.e.* first admitted patient) to May 10th, 2020 with the following inclusion criteria: 1) positive real-time polymerase chain reaction (RT-PCR) assay on the nasopharyngeal swab and/or bronchoalveolar lavage (BAL) specimens for SARS-CoV-2; 2) available data on the admission to the hospital. Exclusion criteria were patients in which Sars-CoV-2 was not the reason for admission to ICU, patients transferred from other hospitals and pregnant women.

Data collection

We collected demographics, comorbidities and patients' characteristics on admission. Results of the blood sample tests on admission, including complete blood count (CBC), coagulation and inflammatory markers (*i.e.* D-dimers; C-reactive protein, CRP; troponin; lactic dehydrogenase, LDH; PaO_2/FiO_2 ratio) were also collected. The use of life support therapies, such as non-invasive ventilation, mechanical ventilation, prone positioning, extracorporeal membrane oxygenation (ECMO), vasopressors and/or inotropic agents and renal replacement therapy was also recorded. The use of hydroxychloroquine (HCQ), remdesivir, lopinavir/ritonavir and oseltamivir, which were used during the first wave of the pandemics in Belgium, was collected.

Fever assessment

Fever was defined as a body temperature ≥38 °C during the ICU stay. Temperature monitoring was performed continuously using either a bladder (in general for conscious patients), esophageal and blood (in general for patients on mechanical ventilation) probes and recorded into the patient data monitoring system. The time from ICU admission to the first episode of fever was recorded, as the time to resolution (*i.e.* temperature ≤37 °C) after treatment of this first episode and the highest daily temperature, for a maximum of 14 days, since ICU admission.

Fever management included either drugs (*i.e.* paracetamol - 1g for a maximal daily regimen q6h and/or non-steroidal anti-inflammatory drugs, NSAIDs, in particular diclofenac 75 mg q12h) or specific devices, including either a surface cooling system (*i.e.* Arctic Sun 5000, BD, Franklin Lakes, NJ, USA) or an intravascular catheter-based device (*i.e.* Icy catheter, ZOLL Medical Corporation, Chelmsford, MA, USA), which was dedicated for conscious patients on mechanical ventilation in case of uncontrolled shivering.

Outcome assessment

The primary endpoint of this study was to assess the characteristics of critically ill COVID-19 patients with fever and identify predictors of fever. Secondary outcomes included: 1) the changes in physiologic variables associated with fever management; 2) the changes in such variables according to the use of mechanical ventilation; 3) the changes in such variables according to the type of therapy (*i.e.* drugs vs. devices).

Statistical analysis

Descriptive statistics were computed for all study variables. A Kolmogorov-Smirnov test was used, and histograms and normal-quantile plots were examined to verify the normality of distribution of continuous variables. Discrete variables were expressed as count (percentage) and continuous variables as mean±SD or median (25^{th}-75^{th} percentiles), as appropriate. Demographics and clinical differences between groups (patients with fever *vs.* patients without fever) were assessed using a Chi-square test or Fisher's Exact test for categorical variable, and Student's *t*-test or Mann-Whitney U-test for continuous variable, as appropriate. Multivariable logistic regression analysis with development of fever during ICU stay as the dependent variable was performed; collinearity between variables (*i.e.* a linear correlation coefficient higher than 0.3) was excluded prior to modelling; only variables associated with fever development in the univariate analysis ($P<0.05$) were included in the multivariate model. Odds ratios (OR) with 95% confidence intervals (CI) were computed. To assess the differences between pre- and post-treatment, we used paired samples *t*-test or Wilcoxon matched-pair signed rank test for continuous variables, as appropriate and McNemar's test for categorical variables. All tests were two-tailed and a $P<0.05$ was considered as statistically significant. Statistical analyses were performed using SPSS 25.0 for Macintosh (IBM, USA).

Results

Study population

A total of 72 critically ill COVID-19 patients were admitted to the ICU over the study period and were all eligible for final analysis. The characteristics of the study cohort are shown in Table I; median age was 62 (53-70) years and 48 patients (67%) were male. Most patients had hypertension (60%), some presented chronic obstructive pulmonary disease (29%) and were obese (29%). Forty-eight patients (67%) were mechanically ventilated, with 33 patients being in prone position and 11 patients (15%) treated with ECMO. Twenty-one patients (29%) died during the ICU stay.

Occurrence of fever

Body temperature on ICU admission was 37.5 (36.8-38.2) °C and the highest temperature during the ICU stay was 38.9 (37.6-39.4) °C; 53 (74%) patients developed fever, after a median of 4 (0-13) hours since ICU admission. Patients with fever were more frequently male and obese, presented higher body temperature at admission, CRP and hemoglobin values and lower PaO_2/FiO_2 ratio on admission than others. Also, febrile patients received more frequently mechanical ventilation, prone positioning, vasopressors, ECMO and hydroxychloroquine than others (Table I). As such, ICU length of stay was longer and ICU mortality higher in febrile when compared to non-febrile patients. In the multivariable analysis, we found that male gender (OR 5.41 [C.I. 95% 1.34-21.92]; P=0.02) and PaO_2/FiO_2 ratio (OR 0.99 [C.I. 95% 0.99-1.00]; P=0.04) were independently associated with the development of fever (Table II).

Fever management and effects on physiological variables

Most of febrile patients (51/53, 96%) received at least one dose of paracetamol. Only three (6%) patients received NSAIDs; 30 (57%) patients were treated with surface cooling devices and 12 of those received also the intravascular device, before weaning from mechanical ventilation.

The effects of the first treatment to control fever on hemodynamic and respiratory variables is reported in Table III; 39 patients were treated with drugs (38 with paracetamol and 1 with NSAIDs) and 14 patients were directly treated with surface cooling system. The median

TABLE I.—*Characteristics of study population, according to development of fever during ICU stay.*

	Overall (N.=72)	Patients with fever (N.=53)	Patients without fever (N.=19)	P values
Age, years	62 [53-70]	61 [53-68]	66 [54-75]	0.25
Gender male, N. (%)	48 (67)	41 (77)	7 (37)	<0.01
Comorbidities				
Hypertension, N. (%)	43 (60)	31 (59)	12 (63)	0.79
Coronary artery disease, N. (%)	15 (21)	10 (19)	5 (26)	0.52
COPD, N. (%)	21 (29)	13 (25)	8 (42)	0.24
Diabetes, N. (%)	13 (18)	9 (17)	4 (21)	0.73
Chronic renal failure, N. (%)	6 (8)	3 (6)	3 (16)	0.18
Liver cirrhosis, N. (%)	3 (4)	3 (6)	-	0.56
Immunosuppression, N. (%)	8 (11)	6 (11)	2 (11)	0.99
Cancer, N. (%)	8 (11)	6 (11)	2 (11)	0.99
Cerebrovascular disease, N. (%)	7 (10)	3 (6)	4 (21)	0.07
Smoking, N. (%)	10 (14)	7 (13)	3 (16)	0.72
Obesity, N. (%)	21 (29)	19 (36)	2 (11)	0.04
Previous DVT, N. (%)	3 (4)	-	3 (16)	0.02
Laboratory findings at admission				
White blood cells	9725 [6560-12655]	9660 [7450-12530]	9870 [5865-12265]	0.75
Lymphocytes	845 [580-1225]	870 [600-1220]	800 [480-1300]	0.84
Hemoglobin	12.6 [10.7-14.0]	12.8 [11.2-14]	11.4 [9.7-12.9]	0.04
Platelets	238 [186-291]	238 [188-291]	238 [174-277]	0.80
D-Dimer	1864 [1173-3878]	1902 [1180-4120]	1589 [997-3176]	0.25
C-Reactive protein	135 [74-230]	170 [97-240]	59 [22-120]	<0.01
Lactate dehydrogenase	455 [343-651]	476 [358-697]	383 [223-561]	0.11
Troponin	29 [16-64]	27 [16-47]	45 [15-131]	0.14
PaO_2/FiO_2	151 [117-243]	134 [97-168]	270 [177-332]	<0.01
Therapies				
Non-invasive ventilation, N. (%)	36 (50)	23 (43)	13 (68)	0.11
Mechanical ventilation, N. (%)	48 (67)	45 (85)	3 (16)	<0.01
Prone position, N. (%)	33 (46)	33 (62)	-	<0.01
ECMO/$ECCO_2R$, N. (%)	11 (15)	11 (21)	-	0.03
Vasopressors, N. (%)	40 (56)	39 (74)	1 (5)	<0.01
Renal replacement therapy, N. (%)	19 (26)	17 (32)	2 (11)	0.08
Hydroxychloroquine, N. (%)	54 (75)	44 (83)	10 (53)	0.01
Remdesivir, N. (%)	3 (4)	3 (6)	-	0.56
Lopinavir/ritonavir, N. (%)	23 (32)	23 (43)	-	<0.01
Oseltamivir, N. (%)	6 (8)	6 (11)	-	0.33
Temperature data				
Temperature on admission, °C	37.5 [36.8-38.2]	37.7 [37.2-38.6]	36.6 [36.4-37.0]	<0.01
Highest Temperature, °C	38.9 [37.6-39.4]	39.0 [38.8-39.7]	37.6 [37.3-37.6]	<0.01
Outcome				
ICU mortality, N. (%)	21 (29)	20 (38)	1 (5)	<0.01
ICU length of stay, days	9 [2-27]	19 [8-29]	2 [2-3]	<0.01
Mechanical ventilation, days	8 [0-22]	15 [5-25]	0 [0-0]	<0.01

Data are expressed as counts (percentage) or median [interquartile range].
COPD: chronic obstructive pulmonary disease; DVT: deep vein thrombosis; ECMO: extracorporeal membrane oxygenation; $ECCO_2R$: extracorporeal carbon dioxide removal; ICU: intensive care unit.

TABLE II.—*Univariate and multivariate logistic regression to predict fever during ICU stay.*

	Univariate		Multivariate	
	OR [C.I. 95%]	c	OR [C.I. 95%]	n (%)
Gender male	5.86 [1.89-18.18]	<0.01	5.41 [1.34-21.92]	0.02
Obesity	4.75 [0.98-22.81]	0.05	3.02 [0.47-19.50]	0.25
PaO_2/FiO_2	0.99 [0.98-0.99]	<0.01	0.99 [0.99-1.00]	0.04
Hemoglobin	1.29 [1.02-1.64]	0.03	1.09 [0.80-1.50]	0.58
C-Reactive protein	1.01 [1.00-1.01]	0.06	1.00 [0.99-1.01]	0.18

Hosmer and Lemeshow goodness-of-fit: P=0.26.

TABLE III.—*Physiologic variables and continuous infusion drugs pre- and post-temperature treatment in fever group (N.=53). Time to temperature normalization: 4 [3-5] hours.*

	Pre-temperature treatment	Post-temperature treatment	P values
Temperature, °C	38.4 [38.1-38.8]	37.1 [36.8-37.4]	<0.01
Heart Rate, bpm	97 [84-109]	88 [75-102]	< 0.01
Mean arterial pressure, mmHg	81 [72-95]	78 [74-88]	0.14
Lactate, mmol/L	1.3 [1.0-1.7]	1.2 [1.0-1.5]	0.10
Vasopressors, N. (%)	23 (43)	29 (55)	0.03
Norepinephrine dose, mcg/min	12 [9-15]	7 [5-11]	<0.01
Inotropes, N. (%)	-	-	-
Respiratory rate,	28 [23-32]	25 [22-29]	0.03
Tidal volume, mL	400 [355-445]	410 [355-450]	0.80
FiO_2	50 [40-60]	50 [40-60]	0.25
PEEP, cmH_2O	10 [8-12]	10 [8-12]	0.75
pH	7.41 [7.34-7.47]	7.41 [7.33-7.47]	0.62
PaO_2	71 [64-82]	84 [75-102]	<0.01
$PaCO_2$	42 [37-52]	42 [38-50]	0.50
PaO_2/FiO_2	147 [119-200]	188 [146-245]	<0.01
SaO_2	95 [93-97]	97 [96-98]	<0.01
Propofol, N. (%)	23 (43)	21 (40)	0.50
Propofol dose, mg/kg/h	2.5 [2.0-3.0]	2.5 [1.7-3]	0.22
Midazolam, N. (%)	15 (28)	15 (28)	0.99
Midazolam dose, mg/h	5 [3-7]	5 [2-6]	0.50
Dexmedetomidine, N. (%)	2 (4)	2 (4)	0.99
Clonidine, N. (%)	4 (8)	3 (6)	0.99
Sufentanyl, N. (%)	15 (28)	15 (28)	0.99
Sufentanyl dose	0.1 [0.05-0.1]	0.05 [0.01-0.10]	0.32
Morphine, N. (%)	5 (9)	5 (9)	0.99

Data are expressed as counts (percentage) or median [interquartile range]. Legend: FiO_2=Fraction of inspired oxygen; PEEP=Positive end-expiratory pressure.

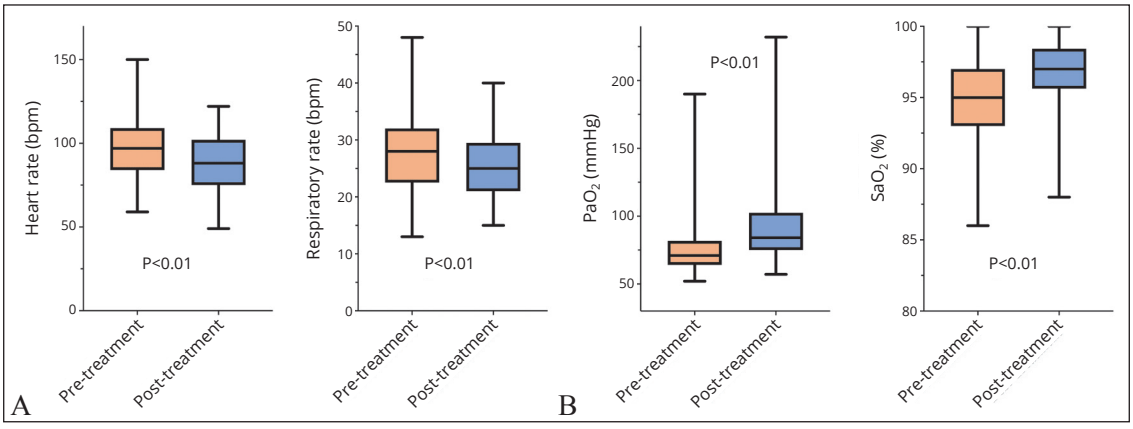

Figure 1.—A) Heart rate (beats per minute – left panel) and respiratory rate (breath per minute – right panel) of the patients with fever pre- and post-treatment; B) Arterial partial pressure of oxygen (mmHg – left panel) and arterial saturation of oxygen (% – right panel) of the patients with fever pre- and post-treatment.

time to temperature normalization was 4 [3-5] hours. After treatment we observed a significant reduction in heart rate (from 97 [84-109] bpm to 88 [75-102] bpm; P<0.01) and respiratory rate (from 28 [23-32] bpm to 25 [22-29] bpm; P=0.03, Figure 1) together with an increase in PaO_2 (from 71 [64-82] mmHg to 84 [75-102] mmHg; P<0.01) and SaO_2 (from 95 [93-97] % to 97 [96-98] %; P<0.01, Figure 1). More patients required the use of vasopressors after therapy, though the median dose of vasopressors was lower than baseline.

Fever management and effects on physiological variables in subgroups

In patients treated with non-invasive ventilation (N.=8), a significant reduction in heart rate and respiratory rate was observed (Table IV), while in patients treated with mechanical ventilation (N.=45) heart rate and norepinephrine doses decreased while PaO_2, PaO_2/FiO_2 and SaO_2 significantly increased after fever treatment.

A significant reduction in heart rate and norepinephrine dose was observed in patients receiving antipyretic drugs (N.=39) or surface cooling device (N.=14, Table V); however, reduction in respiratory rate and improvement in oxygenation was observed only in those receiving drugs.

Discussion

In this small cohort study, we found that 74% of critically ill COVID-19 patients developed fever during the ICU stay; male gender and high respiratory impairment, as suggested by low PaO_2/FiO_2 ratio, were independently associated with fever in this setting. Fever treatment, either with drugs or surface cooling devices, could decrease heart and respiratory rate and provide an improvement in blood oxygenation.

Although reported in a high proportion of critically ill COVID-19 patients, the effects of fever on patients' outcome remain unknown. A reduction in body temperature, as reported in other clinical studies,[9, 10] was associated with a reduction in oxygen consumption (VO_2) and carbon dioxide production (VCO_2), which might significantly affect gas exchanges in the most severe patients. As such, a significant increase in PaO_2 and SaO_2 was observed in our study, as well as a significant reduction in the respiratory rate of non-mechanically ventilated patients. Whether these physiological effects could have

TABLE IV.—*Physiologic variables and continuous infusion drugs pre- and post-temperature treatment in fever group, according to the use of mechanical ventilation.*

	Mechanical ventilation (N.=45)		Non-Invasive ventilation (N.=8)	
	Pre-temperature treatment	Post-temperature treatment	Pre-temperature treatment	Post-temperature treatment
Temperature, °C	38.3 [38.1-38.8]	37.1 [36.9-37.4] *	38.7 [38.2-38.9]	36.9 [36.7-37.1]*
Heart Rate, bpm	97 [84-109]	88 [77-100] *	103 [78-109]	87 [71-104]*
Mean arterial pressure, mmHg	81 [73-91]	78 [75-87]	91 [70-102]	83 [72-97]
Lactate, mmol/L	1.4 [1.1-1.7]	1.2 [1.1-1.5]	1.0 [0.9-1.3]	0.9 [0.8-1.1]
Vasopressors, N. (%)	22 (49)	27 (60)	1 (13)	2 (25)
Norepinephrine dose, mcg/min	12 [9-17]	7 [5-11] *	9 [8-10]	10 [8-12]
Inotropes, N. (%)	-	-	-	-
Respiratory rate,	28 [22-32]	26 [22-30]	28 [26-33]	20 [18-23]*
Tidal volume, mL	400 [355-445]	410 [355-450]	-	-
FiO_2	50 [40-70]	50 [40-60]	40 [33-50]	40 [33-50]
PEEP, cmH_2O	10 [8-12]	10 [8-12]	8 [8-8]	8 [5-8]
pH	7.39 [7.33-7.45]	7.40 [7.32-7.44]	7.46 [7.41-7.49]	7.48 [7.44-7.49]
PaO_2	72 [63-83]	85 [75-105] *	70 [67-79]	83 [76-93]
PaO_2/FiO_2	144 [110-191]	177 [144-245] *	165 [154-204]	195 [176-281]
$PaCO_2$	43 [37-55]	43 [39-52]	38 [35-41]	37 [32-42]
SaO_2	95 [93-97]	97 [96-99] *	96 [95-97]	97 [95-98]
Propofol, N. (%)	23 (51)	21 (47)	-	-
Propofol dose, mg/kg/h	2.5 [2.0-3.0]	2.5 [1.7-3]	-	-
Midazolam, N. (%)	15 (33)	15 (33)	-	-
Midazolam dose, mg/h	5 [3-7]	4.5 [2-6]	-	-
Dexmedetomidine, N. (%)	2 (4)	2 (4)	-	-
Clonidine, N. (%)	4 (9)	3 (7)	-	-
Sufentanyl, N. (%)	15 (33)	15 (33)	-	-
Sufentanyl dose	0.10 [0.05-0.10]	0.05 [0.01-0.10]	-	-
Morphine, N. (%)	5 (11)	5 (11)	-	-

Data are expressed as counts (percentage) or median [interquartile range].
*P<0.05.
FiO_2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure.

TABLE V.—*Physiologic variables and continuous infusion drugs pre- and post-temperature treatment in fever group, according to treatment with drugs or devices.*

	Drugs (N.=39)		Devices (N.=14)	
	Pre-temperature treatment	Post-temperature treatment	Pre-temperature treatment	Post-temperature treatment
Time to normalization, hours	4 [3-5]		3 [2-4]	
Temperature, °C	38.4 [38.1-38.8]	37.1 [36.9-37.4]*	38.4 [38.2-38.8]	37.2 [36.7-37.4]*
Heart Rate, bpm	97 [85-109]	89 [76-102]*	99 [84-109]	88 [75-93]*
Mean arterial pressure, mmHg	81 [73-96]	80 [74-92]	79 [72-91]	76 [75-80]
Lactate, mmol/L	1.2 [1.0-1.56]	1.1 [0.95-1.35]	1.5 [1.2-1.8]	1.5 [1.1-2.0]
Vasopressors, N. (%)	15 (39)	19 (49)	8 (60)	10 (71)
Norepinephrine dose, mcg/min	11 [10-14]	9 [5-12]*	13 [9-21]	6 [5-7]*
Inotropes, N. (%)	-	-	-	-
Mechanical Ventilation, N. (%)	31 (80)	31 (80)	14 (100)	14 (100)
Respiratory rate,	26 [23-31]	23 [21-29]*	28 [24-32]	27 [24-33]
Tidal volume, mL	400 [360-440]	410 [360-445]	413 [345-455]	400 [345-455]
FiO_2	50 [40-60]	50 [38-60]	50 [40-70]	45 [40-70]
PEEP, cmH_2O	10 [8-12]	10 [8-13]	10 [8-12]	10 [8-12]
pH	7.42 [7.34-7.47]	7.41 [7.33-7.46]	7.40 [7.33-7.42]	7.40 [7.33-7.47]
PaO_2	71 [62-81]	84 [75-98]*	75 [68-82]	85 [75-109]
PaO_2/FiO_2	144 [117-178]	191 [140-237]*	173 [128-214]	173 [148-253]
$PaCO_2$	42 [37-48]	42 [38-50]	43 [35-58]	42 [35-50]
SaO_2	95 [93-97]	96 [96-98]*	96 [94-97]	98 [95-99]
Propofol, N. (%)	15 (39)	15 (39)	8 (60)	6 (43)
Propofol dose, mg/kg/h	2.5 [2.0-3.0]	2.0 [2.0-3.0]	2.0 [1.5-3.4]	2.9 [1.5-4.0]
Midazolam, N. (%)	8 (21)	8 (21)	7 (50)	7 (50)
Midazolam dose, mg/h	5 [1-7]	5 [1-6]	5 [5-7]	4 [4-6]
Dexmedetomidine, N. (%)	1 (3)	1 (3)	1 (7)	1 (7)
Clonidine, N. (%)	2 (5)	1 (3)	2 (14)	2 (14)
Sufentanyl, N. (%)	10 (26)	10 (26)	5 (36)	5 (36)
Sufentanyl dose	0.08 [0.05-0.10]	0.05 [0-0.1]	0.01 [0.00-0.01]	0.01 [0.01-0.01]
Morphine, N. (%)	5 (13)	5 (13)	-	-

Data are expressed as counts (percentage) or median [interquartile range].
*P<0.05.
FiO_2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure.

an impact on COVID-19 patients' outcome remains debatable, as the reduction of the respiratory rate and of the mechanical power, which is one of the determinant of ventilator associated lung injury (VILI), have beneficial effects in mechanically ventilated patients. To the best of our knowledge, there are not prospective studies with a large sample size that provide information on the effects of fever control on respiratory parameters or other indicators of VILI, such as driving pressure or MP, in COVID-19 patients. In studies conducted in ARDS patients, Netzer *et al.* showed a significant decrease in ventilator free-days in hypothermic patients, while fever was not associated with in-hospital mortality.[7] In another study, Schell-Chaple *et al.* showed that early fever in ARDS was associated with improved survival rate.[11] These conflicting results are probably due to the heterogeneity in study cohorts and different duration of ARDS and fever control strategies. However, Villar *et al.* showed that in severe ARDS patients, mild hypothermia (*i.e.* 32-35 °C), initiated as salvage therapy because of severe hypoxemia, was associated with improvement in gas exchange, reduction in heart rate and improved outcome.[12]

Previous reports in COVID-19 patients, showed that use of mild hypothermia may lead to a significant improvement in oxygenation and a reduction of CO_2 production[13] and treatment with TTM was associated with a rapid increase of PaO_2/FiO_2;[14] these results are partially consistent with our results, although we did not observed significant changes in $PaCO_2$ values, which could be related to persistent dead space, due to the microvascular thrombosis occurring in COVID-19 patients,[15] or to a reduction in respiratory rate in patients not on mechanical ventilation.

Our results are not in favor of the use of hypothermia in COVID-19 patients, as this intervention was not evaluated in our cohort; however, in febrile patients with severe hypoxemia, fever control (*i.e.* targeting normothermia) might help in the management of adequate gas exchanges, without escalation to more aggressive therapies. Interestingly, 57% of the patients in our cohort received a specific device to maintain normal body temperature, as drugs were ineffective to control fever. Whether this strategy is more effective and cost-effective when compared to antipyretic drugs alone should be further evaluated. In a large, randomized trial evaluating the effects of one NSAID, ibuprofen, on the outcome of critically ill septic patients, body temperature was significantly reduced among febrile patients receiving the drug, as well as heart rate and lactate levels, but no significant effects on mortality was observed.[16] In another study, the use of acetaminophen and ibuprofen was an independent predictor of increased mortality in large cohort of septic patients.[17] Considering the elevated risk of renal failure in critically ill COVID-19 patients[18] and the unpredictable effects of antipyretic drugs to reduce body temperature,[19] specific temperature control devices might offer a more adequate and targeted control of fever and avoid significant fluctuations in gas exchanges and heart rate, which might be secondary to fever occurrence. This strategy needs to be further described and compared to other potential protocols for fever control, as associated costs accurately quantified.

Limitations of this study

This study presents some limitations. First, as it is retrospective study, several biases related to unmeasured confounders are present. Second, external validity and the generalizability are influenced by the specific protocol of temperature control which was applied in our ICU. Third, due to the small sample size, it was not possible to adjust the possible confounders to evaluate the role of fever on patients' outcome using a multivariable model. Fourth, this study reflect data of the first wave of COVID-19; after the publication of the RECOVERY trial,[20] the widespread use of corticosteroids may have contributed, through their anti-inflammatory effects, to further control the fever burden and the requirements for additional antipyretic therapies. Fifth, we have selected 38 °C as the threshold to define fever, such value is not unanimously accepted for this definition,[21] however it is largely used in clinical practice and it is used in our center to initiate specific treatments.

Conclusions

In this study, male gender and severe impairment of oxygenation were independently associated with fever in critically ill COVID-19 patients. Fever treatment reduced heart rate and respiratory rate and improved systemic oxygenation. Further prospective studies are necessary to better define the role of fever control in the management of critically ill COVID-19 patients.

What is known

- Fever is one of the most common symptoms in COVID-19 critically ill patients.
- The impact of fever on physiologic variables and on mortality in such patients remains poorly described.

What is new

- Male gender and severe oxygenation impairment at baseline are independently associated with fever during ICU stay in COVID-19 critically ill patients.
- In spontaneous breathing patients, treating fever would lead to a reduction in the heart and respiratory rate as well as to an improvement of systemic oxygenation.
- In patients mechanically ventilated, fever treatment could improve systemic oxygenation.

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