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Association of hypothermia with increased mortality rate in SARS-CoV-2 infection

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ABSTRACT

Objective: Patients were observed to have variable temperatures. The objective of this study was to identify whether hypothermia in a patient infected with SARS-CoV-2 was associated with a higher than expected mortality.

Methods: In total, 331 charts from patients hospitalized with SARS-CoV-2 between March 9 and April 20, 2020 were reviewed.

Results: The probability of death was 2.06 times higher for those with hypothermia than for those without (95% CI 1.25–3.38)]. In ventilated patients, there were 32 deaths. Of these, 75% had been hypothermic. In a prior review of 10 000 non-SARS-CoV-2 patients with sepsis, the mortality rate in patients with hypothermia was 47%. A review of previous studies demonstrated a range of expected mortality rates in patients with ventilator-dependent respiratory failure and sepsis. In comparison, our study showed that within a group of critically ill patients with SARS-CoV-2 and hypothermia, the mortality rate exceeded those rates.

Conclusion: Our review showed a significant association between hypothermia and death ($p = 0.0033$). Predictors of mortality in SARS-CoV-2 disease can expedite earlier aggressive care. Additionally, in areas with limited resources or overburdened healthcare systems, where there may be a need for resource allocation management, information about mortality risk may be helpful.

Introduction

In the current SARS-CoV-2 pandemic, it has been important to identify features of clinical presentation that would serve as indicators of disease progression. There were 21 813 451 diagnosed cases of SARS-CoV-2 throughout the world as of August 16, 2020, with 5 564 376 of those cases in the United States (COVID-19 Coronavirus Pandemic, 2020). As of April 26, 2021 there were 148,442,514 cases worldwide, with the numbers continuing to rise. There have been times throughout the pandemic when we have been faced with limited resources with regard to remdisivir and convalescent plasma — treatment options that have shown potential to be beneficial (Grein et al., 2020; Joyner et al., 2020). Studies are ongoing to verify the efficacy of these interventions. As providers we have worried about the possibility of having to scale patients in order to determine who should receive these treatments. This eventuality did not manifest as a reality in our center, but it came close. However, we surmise that in resource-poor areas, or in the event of a large surge of patients, this could become a necessity.

Fever has been identified as one of the hallmark presenting symptoms used as a marker for whom to screen for SARS-CoV-2 infection. However, in patients with this infection, temperature readings vary. During the course of our clinical care of patients with SARS-CoV-2, patients were identified with hypothermia, normothermia, and hyperthermia. The number of patients with hypothermia appeared to exceed the number typically seen during the course of our clinical care of patients with infection and sepsis. Our study sought to investigate this observation further.

Hypothermia is sometimes utilized as a therapeutic approach to sustaining the life of a person who presents with cardiac arrest. Likewise, hypothermia can be induced in trauma patients in an effort to minimize tissue damage (Hildebrand et al., 2004). The decline in temperature is associated with a decrease in metabolic rate, which can be protective against ischemia (Sailhamer et al., 2007). Accidental hypothermia is an unintentional decrease in

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temperature in a person who does not have obvious intrinsic thermoregulatory dysfunction. This form of hypothermia may be a result of excessive cold exposure (Hildebrand et al., 2014). Hypothermia as it relates to this review is that which can be seen in sepsis, and is thought to be a consequence of impaired thermoregulation. The etiology of this has been described as a failure of the hypothalamus to regulate the core body temperature (Faulds and Meekings, 2013). This may the result of an alteration in the baseline temperature setpoint by the hypothalamus as a result of sepsis or severe infection. Alternatively, it may be a nonspecific response to widespread systemic inflammation (Leon, 2004).

Sepsis is the body's harmful systemic reaction to microbial infection. Hypothermia has been clearly associated with sepsis. ICU and hospital mortality have been identified as being higher in septic patients with hypothermia (Wiewal et al., 2016). Fever or hypothermia are symptoms that can be identified in any degree of sepsis. In 2017, a meta-analysis of studies was carried out to look at temperature and mortality rates in patients with sepsis. Approximately 10 000 cases of sepsis were reviewed. The reviewers found that septic patients with fever had an estimated mortality rate of 22%. The estimated mortality rate in patients with normal temperature was 31% and the highest estimated mortality rate of 47% was found in hypothermic patients (Rumbus et al., 2017).

Admission to the ICU for SARS-CoV-2 patients has been associated with a high mortality rate, ranging from 16% to 78%, with an Italian review of 3988 patients showing a mortality rate of close to 50% (Grasselli et al., 2020). While understanding that ICU patients, as a baseline, have a high mortality, this study aimed to discover what impact hypothermia had on the SARS-CoV-2 patients.

A higher mortality rate was expected in SARS-CoV-2 patients with hypothermia. Our study examined the significance of this association and whether there were any significant correlations with age, weight, oxygen requirement, or inflammatory markers.

Literature review

In 1868, Carl Reinhold Wunderlich measured body temperature in about 25 000 people and established a normal temperature as 98.6 °F and an elevated body temperature as 100.4 °F (Mackowiak, 1998).

Hypothermia is defined as a core temperature < 35 °F (95 °F) and is further classified as follows: mild, 35–32 °C; moderate, 32–28 °C; severe, 28–20 °C; and profound, < 20 °C (Fagenholz and Bittner, 2013). Body temperature is closely regulated through a balance between heat production and heat dissipation. The preoptic nucleus of the anterior hypothalamus is the thermal control center. In response to a decrease in core body temperature, the hypothalamus initiates mechanisms to conserve heat, including shivering and non-shivering thermogenesis (increased activity of thyroxine and catecholamines). However, as the core temperature decreases below 35 °C (95 °F), the coordinated systems responsible for thermoregulation begin to fail (Kobeissi and Zimmerman, 2015). Proinflammatory cytokines, including interleukin-6, interleukin-1, and TNF-alpha, play a crucial role in the genesis of fever. However, there appears to be no correlation between decreased circulation of these cytokines and hypothermia (Marik and Zaloga, 2000; Wiewal et al., 2016). The mechanism of hypothermia in sepsis is unclear; however, many studies agree that hypothermic patients with septic shock have a significantly higher mortality rate and higher incidence of organ dysfunction compared with patients who mount a febrile response (Kushimoto et al., 2013).

Early case reports pointed out fever as a common presenting symptom for SARS-CoV-2 infection, as commonly seen with other viral infections. In a meta-analysis of 3062 patients with SARS-CoV-2, fever was noted in 80.4% of the patients (Zhu et al., 2020). Acute hypothermia has been described in a SARS-CoV-2 case report (Allard et al., 2020).

Methods

The medical records of 331 patients who had been hospitalized at Broward Health Medical System hospitals were retrospectively reviewed, and the clinical outcomes of these adult patients with laboratory-confirmed SARS-CoV-2 infection were examined. The patients were hospitalized and treated for SARS-CoV-2 infection between March 31, 2020 and April 20, 2020. Our Institutional Review Board granted full waiver for this retrospective chart review research project. The reviewed data points were temperature, age, oxygen requirements, inflammatory markers, weight, underlying medical conditions, and outcomes. Five physicians reviewed the medical records. Age, body mass index (BMI), oxygen requirement, measures of C reactive protein, D dimer, and ferritin, and outcomes (discharge, discharge with oxygen, death) were documented (Table 1). Statistical analysis was used to establish significant associations.

Statistical analysis and results

Analysis 1: hypothermic status — outcomes

The data included only hypothermic patients, and therefore a regression to determine the effect of hypothermia on the odds of death, relative to other patient-specific variables, could not be performed. However, a frequency analysis was performed using the categories of hypothermia (versus not) and death (versus not) (Table 2). In all cases, a significance level of 0.05 was used.

A Fisher's exact test was performed on the data in Table 2, indicating that there was a significant association between hypothermia and death ($p = 0.0033$). In particular, the probability

Table 2
Hypothermic status and outcomes.

	Dead	Alive	*% dead*
Hypothermic patients	39	96	*28.9%*
Non-hypothermic patients	43	218	*16.5%*
% hypothermic	*47.6%*	*30.6%*	

Table 1
Parameters reviewed from charts of SARS-CoV-2 patients.

Temperature Oxygen requirements	Hypothermia ≤ 96.5 °F Room air	Hyperthermia ≥ 100.4 °F Oxygen supplementation	Ventilator
D-dimer	< 0.5 μg/ml	0.5–3.0	> 3.0
Ferritin	< 275 ng/ml	≥ 275	
C-reactive protein	> 1.0 mg/dl		
Weight	BMI 18–29	BMI ≥ 30	
Outcomes	Discharge	Discharge with O_2	Death

of death was 2.06 times higher for those with hypothermia than for those without (95% CI 1.25–3.38).

Analysis 2: hypothermic status of deceased patients — steroid administration

Although regression is preferable when dealing with multiple, possibly related, independent variables, the count statistics associated with individual categorical variables can be useful. In all cases, *p*-values represent the outcome of either a chi-squared or Fisher's exact test, as appropriate.

Analysis was carried out to check for variable interactions within the regression and contingency tables, analyzing differences between deceased patients who were hypothermic versus not, and assessing the relationship between deceased patients having hypothermia and use of steroids.

There was no statistically significant association between hypothermia status and steroid administration (Table 3).

Analysis 3: hypothermic status of deceased patients — multinomial logistic regression

An exhaustive search of all linear and interactive models yielded no statistically significant predictors of hypothermia in deceased patients, among all the variables considered above.

There were no statistically significant relationships found between elevated C-reactive protein (CRP) at a level of > 1.0 μg/dl, elevated ferritin at a level of > 275 ng/ml, or elevated body mass index (BMI) ≥ 30 with respect to category and discharge status for the hypothermic patients in this study.

Discussion/conclusions

The proposed pathophysiological mechanism of sepsis in SARS-CoV-2-associated infections is complex and typically involves patients with severe disease. A cytokine response syndrome has been identified as the precursor to shock in cases of severe disease; however, the virological mechanism remains unidentified for the time being. Inference of the exact process has been drawn from similarities in severe disease seen with influenza, which involves the release of cytokines in lung epithelial cells. Elevated temperatures can augment aspects of humoral and cellular immunity (Launey et al., 2011). However, a percentage of septic patients present with hypothermia rather than hyperthermia. As with hyperthermia, studies have shown that hypothermia is associated with an increased risk of mortality in sepsis (Young et al., 2012). Our review used a cutoff of 35.8 °C (96.5 °F) to define hypothermia. Allard et al. (2020) described acute hypothermia in a patient with SARS-Cov2 infection, which was present in 34% of the cases we reviewed.

The Recovery Trial (2020) showed a reduction in 28-day mortality among those who received the glucocorticoid class drug dexamethasone. The study was published later than the dates for most of the patients whose charts we reviewed. However, our study still found that patients had received hydrocortisone or solumedrol more often later in the course of their hospitalization. It is known that the use of glucocorticoids affects body temperature and can result in hypothermia (Kainuma et al., 2009). In our review, the effect of steroid use in patients who had expired was therefore taken into consideration. Of the 39 hypothermic patients who died, 21 (53.8%) had received steroids and 18 (46.1%) had not. Of the 24 non-hypothermic patients who died, 9 (37.5%) had received steroids and 15 (62.5%) had not. Statistical analysis did not reveal any statistically significant association between hypothermia and steroid administration.

Table 3
Steroid administration.

	Yes	No
Hypothermic patients	21 (70.0%)	18 (54.5%)
Non-hypothermic patients	9	15

A review of 624 patients diagnosed with severe sepsis showed that patients with hypothermia, as defined by a temperature of less than 36.5 °C on presentation, had worse sequential organ failure assessment scores compared with those with a temperature above 36.5 °C. 28-day and in-hospital mortality was found to be higher in the group with hypothermia (Kushimoto et al., 2013). In reviewing our results, there were 32 deaths in the category of ventilated patients (Table 1). Of those deaths, 75% of the patients had been hypothermic. In a prior review of 10 000 non-SARS-CoV-2 patients with sepsis, the mortality rate in patients with hypothermia was 47%. The reviewed studies demonstrated a range of expected mortality rates in patients with ventilator-dependent respiratory failure and sepsis (Rumbus et al., 2017). In comparison, our study showed that within the group of critically ill patients with SARS-CoV-2 and hypothermia, the mortality rate exceeded those rates. A comparison of critically ill patients with SARS-CoV-2 and sepsis patients from historical data can be made because the SARS-CoV-2 patients met some or all of the criteria for diagnosis of sepsis, particularly when in the intensive care unit.

While it is understood that the mere presence of hypothermia indicates that a patient is severely ill, the finding that there is a statistically significant association between hypothermia and death in the SARS-CoV-2 population can be used as an indicator of poor outcome. Throughout the pandemic, we have been faced with limited resources, such as the antiviral remdisivir, or convalescent plasma. By having a better understanding of potential patient outcomes, this information can be used to assist in resource management.

Our review identified a significant association between hypothermia and death ($p = 0.0033$). In particular, the probability of death was 2.06 times higher for those with hypothermia than for those without (95% CI 1.25–3.38). Older, heavier patients, or those with one or more underlying medical conditions (data not shown) were no more prevalent among the hypothermic patients who died. Our review showed that, among the hypothermic patients, the percentage of patient deaths increased as the D-dimer level increased. Although these associations were statistically significant, causality cannot be inferred. Previous reports have noted this, and autopsy correlation has been documented. A comprehensive literature review performed by Sakka et al. (2020) identified elevated D-dimer levels as being significantly associated with the risk of mortality. Thromboses of small and mid-sized arteries were found in a pathology case series during autopsies on 11 patients who had died from SARS-CoV-2 infection (Lax et al., 2020). Our study supported what had been detailed by Yao et al. (2020) — that D-dimer does serve as a biomarker for disease severity.

The National Institute of Health treatment guidelines include a report indicating possible side-effects of hypothermia in association with convalescent plasma transfusion (NIH, 2021). We therefore reviewed our data to see if there was any correlation in the patients between receipt of convalescent plasma and hypothermia — no causal relationship was found.

We would recommend that patients with hypothermia be recognized as being at higher risk for poor outcome, particularly if intubated. Our report describes our single institution's experience and therefore might not be generalized to other institutions or locations. Additional studies are warranted to verify these results and identify a larger comparator group.

Conflict of interest

The authors declared that they have no conflict of interest.

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Ethical approval

The Institutional Review Board of Broward Health Medical Center reviewed and approved this study.

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