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Temperature trajectory subphenotypes correlate with immune responses in patients with sepsis

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Abstract

Objective—We recently found that distinct body temperature trajectories of infected patients correlated with survival. Understanding the relationship between temperature trajectories and the host immune response to infection could allow us to immunophenotype patients at the bedside using temperature. The objective was to identify whether temperature trajectories have consistent associations with specific cytokine responses in two distinct cohorts of infected patients.

Design—Prospective observational study

Setting—Large academic medical center between 2013 and 2019

Subjects—Two cohorts of infected patients: 1) patients in the intensive care unit with septic shock and 2) hospitalized patients with *Staphylococcus aureus* (*S. aureus*) bacteremia.

Intervention(s)—Clinical data (including body temperature) and plasma cytokine concentrations were measured. Patients were classified into four temperature trajectory subphenotypes using their temperature measurements in the first 72 hours from onset of infection. Log-transformed cytokine levels were standardized to the mean and compared across the subphenotypes in both cohorts.

Measurements and Main Results—The cohorts consisted of 120 patients with septic shock (cohort 1) and 88 patients with *S. aureus* bacteremia (cohort 2). Patients from both cohorts were classified into one of four previously validated temperature subphenotypes: “hyperthermic, slow resolvers” (n=19 cohort 1; n= 13 cohort 2), “hyperthermic, fast resolvers” (n=18 C1; n= 24 C2),

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“normothermic” (n=54 C1; n= 31 C2), and “hypothermic” (n=29 C1; n= 20 C2). Both “hyperthermic, slow resolvers” and “hyperthermic, fast resolvers” had high levels of G-CSF, CCL2, and IL-10 compared to the “hypothermic” group when controlling for cohort and timing of cytokine measurement ($p<0.05$). In contrast to the “hyperthermic, slow resolvers,” the “hyperthermic, fast resolvers” showed significant decreases in levels of several cytokines over a 24-hour period, including IL-1RA, IL-6, IL-8, G-CSF and M-CSF ($p<0.001$).

Conclusion—Temperature trajectory subphenotypes are associated with consistent cytokine profiles in two distinct cohorts of infected patients. These subphenotypes could play a role in the bedside identification of cytokine profiles in patients with sepsis.

Keywords

sepsis; infection; cytokines; immunology

INTRODUCTION

Sepsis is defined as a dysregulated host response to infection that results in life-threatening organ dysfunction often leading to death.(1) For years, sepsis was thought to result from an unregulated pro-inflammatory response (often referred to as a “cytokine storm”), but multiple clinical trials of anti-inflammatory and anti-cytokine drugs failed to show uniform benefit.(2,3) Studies have since shown that patients with sepsis have variable pro- and anti-inflammatory responses, and many manifest features of immunosuppression, particularly later in their illness.(4–7) Despite the heterogeneity of immune responses and the potential benefit of immunomodulatory therapy, there is a lack of readily available clinical tools to characterize the immune state of patients with sepsis.(8–10)

We previously published a novel method of identifying sepsis subphenotypes using body temperature trajectories.(11) The routine and regular measurement of temperature makes this an appealing and universally available tool to characterize the immune state of patients with sepsis. The temperature trajectory subphenotypes had distinct demographics, physiological characteristics, and levels of commonly tested inflammatory markers (i.e., erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]). “Hyperthermic, slow resolvers” were the youngest patients, had the fewest comorbidities, least exposure to immunosuppressives, and highest ESR and CRP levels. Conversely, “hypothermic” patients were the oldest, had the most comorbidities, most exposure to immunosuppressives, and the lowest ESR and CRP levels. Both groups had relatively high mortality rates, suggesting that both had dysfunctional immune responses. We also identified a temperature trajectory subphenotype (“hyperthermic, fast resolvers”) with a consistently low mortality, suggestive a potentially favorable immune response. However, the original study was limited by the unavailability of immunological data on these subphenotypes to substantiate biological plausibility of these findings. The objective of this current study is to investigate the immunological correlates of these subphenotypes. First, we hypothesize that the “hyperthermic, slow resolvers” may have elevated levels of pro- and anti-inflammatory cytokines, while “hypothermic” patients may have suppressed levels. Second, there may be differential changes in cytokine levels over time between these temperature trajectory subphenotypes.

To investigate the cytokine signatures of our temperature trajectory subphenotypes, we used cytokine data from two distinct cohorts of infected patients: 1) prospectively enrolled patients with all-cause septic shock and 2) retrospective analysis of previously published data from hospitalized patients with *Staphylococcus aureus* (*S. aureus*) bacteremia.(12) These two cohorts differ in the type of pathogen, severity of illness, and the timing of cytokine measurements. The rationale for using two distinct cohorts was to investigate whether consistent associations of cytokines with temperature trajectories were present despite these clinical differences. Additionally, we investigate whether these cytokine profiles change over time.

METHODS

Patient cohorts

The study was conducted at the University of Chicago Medicine (Chicago, IL, USA), a 500-bed, urban academic tertiary medical center. The primary cohort consisted of prospectively enrolled adult patients with septic shock, as defined by the Sepsis-3 criteria, admitted to the intensive care unit between 2017 and 2019.(1) Patients were enrolled within 24 hours of developing shock requiring vasopressors. Blood samples were collected in sodium citrate tubes at the time of enrollment into the study, and a second sample was drawn 24 hours after the initial blood draw to evaluate for changes in immune markers over time. The second cohort was from a previously published study of adult inpatients (both wards and ICU) who had one or more positive blood cultures growing *S. aureus*, enrolled between July 1, 2013 and October 24, 2014. Blood samples were drawn into EDTA tubes two to four days after the first positive *S. aureus* blood culture. Informed consent was obtained in both studies, and both studies were approved by the University of Chicago Institutional Review (IRB# 13–1269 & 18–1163).

Clinical data for patients in both cohorts were collected from the electronic health record (EHR) (Epic, Verona, WI) and included demographic data, International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) billing codes, clinician orders (e.g., blood cultures), vital signs (e.g., axillary temperature), and laboratory values.

Collection and measurements of cytokines

A multiplex assay (EMD Millipore, Darmstadt, Germany) was used to determine plasma concentrations of circulating chemokines and cytokines. Immune marker levels were log transformed for normality. The multiplex assays were run in multiple batches, which resulted in “batch effects” (i.e., differences in levels of immune markers due to the calibration variability between different batches). On analysis of variance (ANOVA) rank testing, there were significant differences in levels of almost all cytokines between the batches. In order to remove the batch effect, immune markers were standardized to the mean of their batch before comparison.(13)

Temperature trajectory subphenotype determination

In our previous study, group-based trajectory modeling was used to identify four unique subphenotypes based on temperature trajectory.(11) Group-based trajectory modeling is a

type of finite mixture model that is used to identify patients following similar trajectories in a variable of interest (e.g., temperature).(14) In the original temperature trajectory study, all study patients had community-acquired infection, and thus time of onset of infection (the time at which measurement of temperature begins) was defined as the time of presentation to the hospital, and temperature measurements from the first 72 hours of admission were used in the analysis. In the current study, we had both community and hospital acquired infections (i.e., not all infections were present on admission). For patients with hospital acquired infections, we used four hours prior to the initial positive blood culture order as the time of onset of infection, to include abnormal temperature measurements that may have prompted the blood culture order. The frequency of temperature measurements reflect standard-of-care nursing practices; no additional temperature monitoring was required for the study.

The original temperature trajectory model was derived on a cohort of 12,413 patients with infection. The original algorithm was validated for use in all patients with infection; this included patients with *S. aureus* bacteremia and septic shock. Our goal in developing the original model on a diverse, generalizable cohort was to be able to then apply it to specific cohorts (*S. aureus*, septic shock, etc.). The four groups were: 1) “hyperthermic, slow resolvers” – patients with persistently elevated temperatures, 2) “hyperthermic, fast resolvers” – patients with elevated presenting temperature with defervescence over the ensuing 72 hours, 3) “normothermic” – patients with normal body temperatures, and 4) “hypothermic” – patients with low body temperatures. Each of these four temperature trajectories is a unique quadratic function describing temperature as a function of time (Temperature = $\beta_0 + \beta_1 * \text{Time} + \beta_2 * \text{Time}^2$). For group assignment, the temperature measurements from each patient were compared with the predicted measurement in each trajectory group using this model derived in the original study. The patient was classified to the group trajectory that resulted in the lowest squared residual error. Patients who died within the 72-hour temperature measurement period were excluded from analysis.

Statistical Analysis

Demographics, comorbidities, clinical characteristics, as well as inpatient mortality were compared between patients with septic shock and patients with *S. aureus* bacteremia. Within each cohort, these characteristics were compared between the four trajectory subphenotypes with ANOVA rank tests and chi-squared tests as appropriate. Log-transformed and batch-standardized cytokine levels were compared between the trajectory subphenotypes using ANOVA rank tests. To investigate cytokine changes over time, the first and second set of cytokines in the septic shock cohort were compared within each subphenotype using a paired t-test. Given the risk of multiple testing and false discovery, the Holm-Bonferroni correction method was applied to all cytokine analyses. This method controls for the maximum family-wise error rate, while having a lower increase in type II error risk compared to simple Bonferroni correction. P-values less than 0.05 that remained significant after Holm-Bonferroni correction were considered statistically significant.

To evaluate the consistency of association between cytokine levels and subphenotype in these two distinct cohorts, multivariable linear regression modeling was performed. Log-transformed cytokine levels were regressed on subphenotype, controlling for cohort and

timing of cytokine measurement. All analyses were performed using Stata version 14.1 (StataCorp, College Station, TX).

RESULTS

Clinical characteristics of the two study cohorts

A total of 120 patients with septic shock and 88 patients with *S. aureus* bacteremia were included in the study (eFigure 1). Patients with septic shock were older, had higher severity of illness, and a higher mortality rate (Table 1). The maximum temperature was higher in patients with *S. aureus* bacteremia compared to patients with septic shock (38.4 vs 38.0°C, $p=0.004$); variation in temperature over the 72-hour period (i.e., standard deviation) was also higher in patients with *S. aureus* bacteremia (0.8 vs 0.5°C, $p<0.001$) (eTable 1). The frequency of temperature measurements was similar in both cohorts, with an average frequency of temperature measurement once every three to four hours.

The time from onset of infection to cytokine measurement was different in the two cohorts. Cytokines were measured twice in the patients with septic shock: the first set was measured a median of 25 hours after onset of infection (IQR 14–61 hours), and the second set was measured approximately 24 hours after the initial set. Cytokines were measured much later in patients with *S. aureus* bacteremia since patients had to have positive blood cultures prior to enrollment. Cytokines were measured in this cohort a median of 61 hours (IQR 42–82 hours) after onset of infection.

Temperature trajectory subphenotypes in patients with septic shock

The 120 patients with septic shock were classified into the four trajectory subphenotypes: “hyperthermic, slow resolvers” ($n=19$, 16%), “hyperthermic, fast resolvers” ($n=18$, 15%), “normothermic” ($n=54$, 45%), and “hypothermic” ($n=29$, 24%) (Figure 1). Age was significantly different between the subphenotypes, with “hyperthermic, slow resolvers” having the youngest patients ($p=0.04$). Race was significantly different, with fewer African Americans in the hyperthermic subphenotypes ($p=0.007$). Bacteremia was significantly different, with 78% of “hyperthermic, fast resolvers” subphenotype having positive blood cultures ($p<0.001$). Although “hyperthermic, fast resolvers” had the fewest deaths and lowest median SOFA score, there were no significant differences in mortality rate between the four subphenotypes (Table 2).

At the first cytokine measurement (median of 25 hours after onset of infection), after correction for multiple testing, there were significant differences in the levels of IL-10, G-CSF, CCL2 and IL-27 ($p<0.01$) (eTable 2). In post-hoc comparisons between groups, the significance was driven by differences between the hyperthermic and non-hyperthermic groups. “Hypothermic” patients had the lowest levels of most pro- and anti-inflammatory cytokines, while “hyperthermic, fast resolvers” and “hyperthermic, slow resolvers” had high levels of most cytokines (Figure 2).

Change in cytokine levels over 24 hours in patients with septic shock

We evaluated the levels of cytokines at the second measurement (24 hours after the first measurement) in the septic shock cohort, and found differences in the levels of G-CSF, TNF- α , CCL2 and IL-27 (eTable 3). After correction for multiple testing, G-CSF and TNF- α remained statistically significant ($p < 0.01$). In post-hoc comparisons between groups, the significance was again driven by differences between the two hyperthermic groups compared to the non-hyperthermic groups (Figure 3).

From the first to second measurement (24 hours apart), the “hyperthermic, fast resolvers” had significant decreases in levels of most cytokines, with the decreases in IL-1RA, IL-6, IL-8, G-CSF and M-CSF remaining significant after correction for multiple testing ($p < 0.001$) (eTable 4 & eFigure 2).

Temperature trajectory subphenotypes in patients with *Staphylococcus aureus* bacteremia

The patients with *S. aureus* bacteremia were classified into the four trajectory subphenotypes: “hyperthermic, slow resolvers” ($n=13$, 15%), “hyperthermic, fast resolvers” ($n=24$, 27%), “normothermic” ($n=31$, 35%), and “hypothermic” ($n=20$, 23%) (Figure 1). There were no significant differences in age, comorbidities, SOFA score or mortality (eTable 5). There were differences across subphenotypes in the levels of CCL2, CXCL10, IL-6, IL-8 and IL-10. With correction for multiple testing, CCL2, CXCL10 and IL-10 remained statistically significant (eTable 6). Similar to the septic shock cohort, “hypothermic” patients had suppressed levels of most cytokines. In contrast to the septic shock cohort, the significance in cytokine levels were mainly driven by “hyperthermic, slow resolvers” rather than “hyperthermic, fast resolvers” (eFigure 3).

Cytokine levels regressed on temperature trajectory subphenotypes controlling for timing of measurement and cohort

Given the differences in timing of cytokine measurement, the patients in the *S. aureus* and septic shock cohorts were classified into three subgroups based on the timing of measurement in relation to the onset of infection (<48 hours from onset of infection, 48–72 hours, and >72 hours). In the septic shock cohort, 62% of the cytokine measurements were made <48 hours from onset of infection, 15% were 48–72 hours, and 23% were >72 hours. In the *S. aureus* cohort, 27% of the measurements were <48 hours from onset of infection, 33% were 48–72 hours, and 40% were >72 hours. Since G-CSF, IL-10, CCL2, and TNF- α were significantly different between the subphenotypes, log-transformed levels of these cytokines were regressed on subphenotype, controlling for timing of measurement and cohort. We found that membership in “hyperthermic, slow resolvers” and “hyperthermic, fast resolvers” subphenotype was associated with significantly higher levels of G-CSF, IL-10, and CCL2 compared to “hypothermics”, even when controlling for timing of measurement and cohort (eTable 7). The cytokine levels between subphenotypes across time are presented in eFigures 4–7.

DISCUSSION

We report significant associations between temperature trajectory subphenotypes and inflammatory cytokines in two distinct cohorts of infected patients. Although the two cohorts differed in the type of pathogen, severity of illness, and timing of cytokines, we found that “hypothermic” patients had consistently low levels of both pro- and anti-inflammatory cytokines. When controlling for the timing of cytokine measurement and cohort (septic shock vs. *S. aureus*), we found that both “hyperthermic, slow resolvers” and “hyperthermic, fast resolvers” had significantly higher cytokine levels compared to “hypothermic” patients. Finally, we found that “hyperthermic, fast resolvers” exhibited a significant decrease in levels of most cytokines from the first to second measurement in septic shock, in parallel with the clinically apparent defervescence of their elevated temperatures. These data suggest that an initially robust inflammatory response followed by a quiescence may contribute to the previously reported survival benefit in “hyperthermic, fast resolvers.”

Prior studies have found conflicting associations between static temperature measurements and cytokine profiles. One study found higher levels of IL-6 and TNF- α in hypothermic patients compared to febrile patients, while other studies found no association between these cytokines and admission temperature.(15–17) However, a single hypothermic or febrile measurement may not adequately capture the immunophenotype of a patient. For instance, we have previously reported that 80% of infected patients have at least one hypothermic measurement (temperature < 36°C).(11) Using the entire 72 hours of temperature measurements, we clearly demonstrated an association between low levels of key inflammatory cytokines and the “hypothermic” group. Therefore, longitudinal temperature measurements are likely needed in order to gain insight into the immunophenotype of infected patients.

With the increasing availability of immunostimulatory therapy, it is essential to identify patients with sepsis-induced immunosuppression.(8–10,18–20) For example, G-CSF, a commonly used immunostimulant for neutropenic fever, showed promise in treating sepsis in animal models but not in clinical human trials.(21–27) In our study, we demonstrate that “hypothermic” patients have low levels of G-CSF and other inflammatory cytokines. If larger studies confirm that “hypothermic” patients represent an immunosuppressed cohort, this subphenotype could also be targeted with other immunostimulatory therapies such as IL-7, IL-15 and GM-CSF.(9,28) Conversely, “hyperthermic, slow resolvers” had persistently elevated cytokine levels and may benefit from immunosuppressive therapies.

Just as temperature fluctuates over time, the immune response to sepsis is also dynamic and changing.(29–33) Prior studies have demonstrated that decreases in levels of IL-6, IL-8 and other immune markers are predictive of survival in sepsis.(34–37) In our study, we found that “hyperthermic, slow resolvers” had no significant changes in the levels of circulating cytokines over time. Conversely, “hyperthermic, fast resolvers” had significant decreases in levels of IL-6, IL-8, and G-CSF over 24 hours. This “defervescence” of the inflammatory milieu may be the mechanism of the previously reported survival benefit of “hyperthermic, fast resolvers.”(11) These findings suggest that precision immunotherapy approach in sepsis

requires targeting the correct patient, but also targeting the intervention at the correct time. (38–43)

To our knowledge, this is the first study to report on the immunological correlates of temperature trajectories. The strength of this study is the demonstration of consistent findings in two distinct cohorts of infected patients. Our study has several limitations. First, this was a single center study, which may limit the generalizability. Second, given the small cohort of patients with septic shock, we were unable to assess the role of pathogen type in immune profiles. Third, the cohorts were significantly different in terms of timing of cytokine measurements, with septic shock patients having much earlier measurements than the *S. aureus* patients. Therefore, further research is need with standardized timing of blood collection for conclusive comparisons between cohorts. Finally, although the “hyperthermic, fast resolvers” had the lowest SOFA score and mortality rate, these findings did not meet statistical significance. This is likely due to the small cohort size. However, the purpose of this current study was to investigate the immunological correlates of these subphenotypes, instead of the prognostic significance.

In conclusion, we found that “hypothermic” patients exhibited the lowest mean values of most cytokines in two distinct cohorts of patients, despite the differences in type of pathogens, severity of illness, and timing of cytokine measurement. Both “hyperthermic, slow resolvers” and “hyperthermic, fast resolvers” had elevated levels of pro- and anti-inflammatory cytokines. Unlike the “hyperthermic, slow resolvers”, the “hyperthermic, fast resolvers” exhibited a “defervescence” of their cytokine response, which may contribute to their survival. Use of the simple, dynamic, and well-documented clinical measurement of temperature could be used to define immunophenotypes at the bedside, allowing for personalized immunomodulatory treatment of sepsis. Future studies investigating earlier identification of these subphenotypes could lead to earlier immunophenotyping.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Temperature trajectory subphenotypes in patients with septic shock and patients with *Staphylococcus aureus* bacteremia.

Body temperature (°C) over time is presented for the four subphenotypes in the two cohorts of infected patients. Time zero represents the onset of infection – defined as the time of hospital presentation for community acquired infections, and as four hours prior to blood culture order for hospital acquired infections. Temperature measurements from the 72 hours after time zero were used to group patients into temperature trajectory subphenotypes using a previously published algorithm. The red lines indicate the median timing for cytokine measurement in both cohorts. The time from onset of infection to cytokine measurement was different between the two cohorts. Cytokines were measured twice in the patients with septic shock: the first set was collected a median of 25 hours after onset of infection (IQR 14–61 hours), and the second set was collected approximately 49 hours after the infection. Cytokines were measured much later in patients with *S. aureus* bacteremia, at a median of 61 hours (IQR 42–82 hours) after onset of infection.

Figure 2.

Cytokine levels in patients with septic shock at the first measurement.

Presented are log transformed levels of cytokines standardized to the mean to remove batch effect. Negative values of cytokines represent values below the mean log value of the cytokine, while positive values represent values above the mean. P-value represents the results of analysis of variance (ANOVA) comparisons of cytokine levels between the four subphenotypes. Differences in IL-10, G-CSF, CCL2 and IL-27 all remained significant after multiple testing correction. Post-hoc analyses were done comparing the levels of these cytokines between groups with t-tests. Pairwise comparisons between groups that resulted in statistically significant differences are marked by an asterisk, with the color indicating the group that was significantly different in levels of the cytokine. For instance, G-CSF levels were significantly different between the “hyperthermic, slow resolvers” and “hypothermic” patients. Similarly, these levels were significantly different between “hyperthermic, fast resolvers” and “normothermic”, as well as “hyperthermic, fast resolvers” and “hypothermic” patients. “Hypothermic” patients had the lowest mean levels of most cytokines.

Figure 3.

Cytokine levels in patients with septic shock at the second measurement.

Presented are log transformed levels of cytokines standardized to the mean to remove batch effect. Negative values of cytokines represent values that fall below the mean log value of the cytokine, while positive values represent values above the mean. P-value represents the results of analysis of variance (ANOVA) comparisons of cytokine levels between the four subphenotypes. Only G-CSF and TNF- α were significant after multiple testing correction. Post-hoc analyses were done comparing the levels of these cytokines between groups with t-tests. Pairwise comparisons between groups that resulted in statistically significant differences are marked by an asterisk, with the color indicating the group that was significantly different in levels of that cytokine. For instance, G-CSF levels were significantly different between the “hyperthermic, fast resolvers” and “normothermic”, as well as “hyperthermic, fast resolvers” and “hypothermic” patients.

Table 1.

Clinical characteristics compared between patients with septic shock and patients with *Staphylococcus aureus* bacteremia.

Characteristics	Septic Shock	<i>Staphylococcus aureus</i>	P-value
N	120	88	-
Age, y	65 (55–74)	61 (49.5–68)	0.02
Gender, female	45 (37.5)	34 (38.6)	0.9
Race			0.7
African American	63 (52.5)	51 (58)	-
Caucasian	46 (38.3)	30 (34.1)	-
Other	11 (9.2)	7 (8)	-
Comorbidity			
CHF	22 (18.3)	30 (34.1)	0.02
COPD	11 (9.2)	10 (11.4)	0.8
DM	32 (26.7)	28 (31.8)	0.5
HTN	57 (47.5)	45 (51.1)	0.7
Liver disease	4 (3.3)	6 (6.8)	0.4
Renal disease	21 (17.5)	33 (37.5)	0.002
Cancer	38 (31.7)	19 (21.6)	0.1
SOFA	11 (8–13)	4 (2–5)	<0.001
Mechanical ventilation	82 (68.3)	21 (23.9)	<0.001
Bacteremia	38 (31.7)	88 (100)	<0.001
Cytokine timing [†] , h	25 (14–61)	61 (42–82)	<0.001
LOS, d	11 (7–21)	10 (6–17)	0.4
Mortality	42 (35)	8 (9.1)	<0.001

Definition of abbreviations: y – years; CHF – congestive heart failure; COPD – chronic obstructive pulmonary disease; DM – diabetes mellitus; HTN – hypertension; SOFA – Sequential Organ Failure Assessment; h – hours; LOS – length of stay; d – days.

[†] Cytokine timing represents the hours from onset of infection (time zero in the temperature model) to the time of cytokine collection. Since patients in the *Staphylococcus aureus* cohort had to have positive cultures before enrollment, the time from onset of infection to cytokine collection was much longer than for patients in the septic shock cohort.

All values presented as median (IQR) or total count (%).

Table 2.

Clinical characteristics compared across temperature trajectory subphenotypes in patients with septic shock.

Characteristics	HSR	HFR	NT	HT	P-value
N	19	18	54	29	-
Age, y	58 (41–68)	63 (57–66)	68 (55–75)	65 (59–73)	0.04
Gender, female	5 (26.3)	5 (27.8)	24 (44.4)	11 (37.9)	0.4
Race					0.007
African American	8 (42.1)	3 (16.7)	31 (57.4)	21 (72.4)	-
Caucasian	8 (42.1)	11 (61.1)	19 (35.2)	8 (27.6)	-
Other	3 (15.8)	4 (22.2)	4 (7.4)	0 (0)	-
Comorbidities					
CHF	3 (15.8)	3 (16.7)	9 (16.7)	7 (24.1)	0.8
COPD	1 (5.3)	2 (11.1)	6 (11.1)	2 (6.9)	0.8
DM	3 (15.8)	6 (33.3)	16 (29.6)	7 (24.1)	0.6
HTN	6 (31.6)	9 (50)	31 (57.4)	11 (37.9)	0.2
Liver disease	1 (5.3)	0 (0)	2 (3.7)	1 (3.4)	0.8
Renal disease	1 (5.3)	4 (22.2)	8 (14.8)	8 (27.6)	0.2
Cancer	7 (36.8)	8 (44.4)	20 (37)	3 (10.3)	0.04
SOFA	11 (9–11)	6 (6–10)	11 (8–13)	12 (7–13)	0.2
Mechanical ventilation	10 (52.6)	15 (83.3)	38 (70.4)	19 (65.5)	0.2
Bacteremia	4 (21.1)	14 (77.8)	11 (20.4)	9 (31)	<0.001
LOS, d	18 (9–24)	12 (7–15)	11 (8–25)	9 (6–15)	0.03
Mortality	7 (36.8)	4 (22.2)	16 (29.6)	15 (51.7)	0.1

Definition of abbreviations: *HSR* – hyperthermic, slow resolvers; *HFR* – hyperthermic, fast resolvers; *NT* – normothermic; *HT* – hypothermic; *y* – years; *CHF* – congestive heart failure; *COPD* – chronic obstructive pulmonary disease; *DM* – diabetes mellitus; *HTN* – hypertension; *SOFA* – Sequential Organ Failure Assessment; *LOS* – length of stay; *d* – days.

All values presented as median (IQR) or total count (%).