Coronavirus Disease 2019 Temperature Trajectories Correlate With Hyperinflammatory and Hypercoagulable Subphenotypes

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OBJECTIVES: Body temperature trajectories of infected patients are associated with specific immune profiles and survival. We determined the association between temperature trajectories and distinct manifestations of coronavirus disease 2019.

DESIGN: Retrospective observational study.

SETTING: Four hospitals within an academic healthcare system from March 2020 to February 2021.

PATIENTS: All adult patients hospitalized with coronavirus disease 2019.

INTERVENTIONS: Using a validated group-based trajectory model, we classified patients into four previously defined temperature trajectory subphenotypes using oral temperature measurements from the first 72 hours of hospitalization. Clinical characteristics, biomarkers, and outcomes were compared between subphenotypes.

MEASUREMENTS AND MAIN RESULTS: The 5,903 hospitalized coronavirus disease 2019 patients were classified into four subphenotypes: hyperthermic slow resolvers ($n = 1,452$, 25%), hyperthermic fast resolvers (1,469, 25%), normothermics (2,126, 36%), and hypothermics (856, 15%). Hypothermics had abnormal coagulation markers, with the highest D-dimer and fibrin monomers ($p < 0.001$) and the highest prevalence of cerebrovascular accidents (10%, $p = 0.001$). The prevalence of venous thromboembolism was significantly different between subphenotypes ($p = 0.005$), with the highest rate in hypothermics (8.5%) and lowest in hyperthermic slow resolvers (5.1%). Hyperthermic slow resolvers had abnormal inflammatory markers, with the highest C-reactive protein, ferritin, and interleukin-6 ($p < 0.001$). Hyperthermic slow resolvers had increased odds of mechanical ventilation, vasopressors, and 30-day inpatient mortality (odds ratio, 1.58; 95% CI, 1.13–2.19) compared with hyperthermic fast resolvers. Over the course of the pandemic, we observed a drastic decrease in the prevalence of hyperthermic slow resolvers, from representing 53% of admissions in March 2020 to less than 15% by 2021. We found that dexamethasone use was associated with significant reduction in probability of hyperthermic slow resolvers membership (27% reduction; 95% CI, 23–31%; $p < 0.001$).

CONCLUSIONS: Hypothermics had abnormal coagulation markers, suggesting a hypercoagulable subphenotype. Hyperthermic slow resolvers had elevated inflammatory markers and the highest odds of mortality, suggesting a hyperinflammatory subphenotype. Future work should investigate whether temperature subphenotypes benefit from targeted antithrombotic and anti-inflammatory strategies.

KEY WORDS: coronavirus disease 2019; group-based trajectory modeling; inflammation; temperature; venous thromboembolic event

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resulting illness, coronavirus disease 2019 (COVID-19), has resulted in millions of deaths worldwide (1). COVID-19 presents heterogeneous challenges with high rates of hypoxemic respiratory failure,

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dysregulated immune responses, coagulation abnormalities, and cardiac and renal dysfunction (2–6). Identification of COVID-19 subphenotypes could lead to targeted treatment of these heterogeneous manifestations.

To date, studies have used static measurements of labs and vitals to identify subphenotypes (7–12). However, the host response to SARS-CoV-2 and other infections is a dynamic process with physiologic responses that evolve over hours (13–15). We have previously shown that longitudinal body temperature trajectories can identify sepsis subphenotypes with distinct clinical characteristics and outcomes (16). Importantly, these subphenotypes correlate with dynamic immune responses to infection over the course of hospitalization (17). Temperature abnormalities are common in viral syndromes such as COVID-19 (18–20), and the thermoregulatory response to infection operates at the intersection of the immunological, neurologic, cardiovascular, and other body systems (21). Therefore, the universally available bedside measurement of temperature could provide key insights into the host response in COVID-19.

In a single-center pilot study, we found that temperature trajectories in COVID-19 were associated with different mortality rates (22). The objectives of this current study are 1) to determine the best-fit temperature trajectory model for a multicenter cohort of hospitalized COVID-19 patients, 2) to evaluate the inflammation and coagulation biomarker profiles of the resulting subphenotypes, 3) to evaluate the association of these subphenotypes with hypercoagulable manifestations such as venous thromboembolic events (VTEs) and cerebrovascular accidents (CVAs), as well as the association with outcomes such as shock, respiratory failure, and 30-day inpatient mortality, and 4) to investigate whether the prevalence of the hyperthermic slow resolvers subphenotype (in our prior work, found to have elevated inflammatory markers) has decreased over the course of the pandemic with the widespread use of the anti-inflammatory dexamethasone.

MATERIALS AND METHODS

Study Cohort

We included all adult patients admitted to four academic hospitals in the Emory Healthcare system. Patients who were admitted between March 1, 2020, and February 28, 2021, were included if they had laboratory-confirmed COVID-19 and/or had a primary or secondary *International Classification of Diseases*, 10th Version (ICD-10) diagnosis of COVID-19 (U07.1). We excluded patients who were discharged or died within 24 hours of hospitalization, as we have shown in prior work that trajectory fit drops in patients who are discharged/die early (22). We excluded patients who were transferred to a different hospital given incomplete encounter data. We included temperature measurements taken in the first 72 hours of hospitalization in the algorithm. Given that temperature measurements vary by site of measurement (e.g., oral, tympanic, etc.), only oral measurements were used for the analysis. The temperature measurements for study patients were standardized to the mean and SD of values for the subjects in the study. Patients with VTEs were identified using the following ICD-10 codes: I26, I80.1, I80.2, and I80.3 (23). Patients with CVAs were identified using the following ICD-10 codes: I61, I62, I63, I69, and I67 (24). Based on general impracticability and minimal harm, the Emory University Institutional Review Boards granted a waiver of consent for this study (STUDY00001627).

Temperature Trajectory Subphenotype Classification

Our previously validated temperature trajectory model was derived on a cohort of 12,413 hospitalized patients with all-cause infection (e.g., viral, bacterial, fungal) and identified four distinct temperature patterns: 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 (16). Each of the four temperature trajectories is a unique quadratic function describing temperature as a function of time from presentation to the hospital (i.e., Temperature = $\beta_0 + \beta_1 \times \text{Time} + \beta_2 \times \text{Time}^2$). As done in prior work, the study patients were classified to the trajectory that results in the lowest mean squared error (16, 17). In addition to the validated model, we tested de novo models with varying number of classes (2-, 3-, 4-, 5-, and 6-class models) and selected the optimal de novo model using Bayesian information criterion, Akaike information criterion, and group membership. The selected de

novo model's goodness-of-fit was compared with the validated model. The goodness-of-fit was calculated using the average mean squared error for the patients in each subphenotype. Between the de novo model and validated model, the model with the lower error was used for the remainder of analyses. After patients were classified into subphenotypes, the differences in demographics, comorbidities, and clinical characteristics between the subphenotypes were compared using analysis of variance (ANOVA) or chi-square tests, as appropriate.

Association of Subphenotypes With Laboratory Biomarkers

Laboratory biomarkers were selected a priori for comparison between subphenotypes and were categorized as inflammatory, coagulopathic, or markers of organ dysfunction:

1) Inflammatory—C-reactive protein (CRP), erythrocyte sedimentation rate, WBCs, absolute lymphocytes, procalcitonin, ferritin, and interleukin-6 (IL-6).
2) Coagulopathic—D-dimer, fibrinogen, platelets, prothrombin fragment 1.2, thrombin-antithrombin complex, and fibrin monomers.
3) Organ dysfunction—Creatinine, total bilirubin, troponin, brain natriuretic peptide (BNP), and lactic acid.

If a patient had multiple measurements of a biomarker, the maximum value of that biomarker from the first 72 hours of hospitalization was used. No imputation process was used for patients with missing biomarkers. Non-normally distributed biomarkers were log-transformed. Biomarker levels were compared between subphenotypes using ANOVA. Given the prespecified set of 18 biomarkers, all tests of significance were corrected for multiple testing using Bonferroni correction.

Association of Subphenotypes With Outcomes

The subphenotypes were evaluated for association with hypercoagulable outcomes: VTEs and CVAs. The subphenotypes were also evaluated for association with renal replacement therapy, vasopressors, mechanical ventilation, and 30-day inpatient mortality. Logistic regression was performed to evaluate these outcomes controlling for age, sex, race, comorbidities (congestive heart failure, chronic pulmonary disease, diabetes mellitus, hypertension, chronic renal disease, liver disease, and metastatic cancer), and maximum Sequential Organ Failure Assessment (SOFA) score in the first 72 hours of hospitalization. The hyperthermic fast resolvers were selected as the reference group based on our prior work, as this subphenotype has consistently demonstrated the lowest mortality rates (16, 17, 22).

Changes in Subphenotype Prevalence Over the Course of the Pandemic

Given the widespread use of the anti-inflammatory dexamethasone after publication of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial in July 2020 (25), we hypothesized that we would see a contemporaneous decrease in the prevalence of the hyperthermic slow resolvers (in our prior work in sepsis, this subphenotype had elevated inflammatory markers).

To evaluate whether dexamethasone was associated with decreased odds of membership in the hyperthermic slow resolvers subphenotype, we employed propensity scores with inverse probability weighting. The outcome was membership in the hyperthermic slow resolvers subphenotype. The publication of the RECOVERY trial served as a natural experiment, with the control group consisting of patients admitted pre-RECOVERY trial (March 2020 to June 2020) who did not receive dexamethasone. The treatment group was patients admitted post-RECOVERY trial (August 2020 to February 2021) who received dexamethasone during the first 72 hours of hospitalization. Patients who received other corticosteroids were excluded. Patients who received dexamethasone may have confounders that are significantly different from patients who did not receive dexamethasone. To account for these measurable confounders, we created a propensity score for treatment with dexamethasone based on pretreatment characteristics that would be associated with subphenotype membership: age, sex, race, ethnicity, comorbidities, and admission SOFA score. We evaluated for distributional overlap of propensity scores to ensure common support between treatment and control. Inverse probability weighting was applied to the propensity scores to weigh patients such that the measured confounding variables were balanced between the treatment (dexamethasone) and control groups. We checked covariate balance to ensure that after adjustment, all absolute standardized differences between confounding variables were below the threshold of 0.1. Finally, we evaluated the probability weights to ensure there were no abnormally weighted patients (weight > 10) (26–28).

To estimate the effect of dexamethasone treatment on subphenotype membership, a logistic regression model of treatment on hyperthermic slow resolvers subphenotype membership was fitted with application of the probability weights.

Early Identification of Subphenotypes

We tested whether the temperature trajectory subphenotypes could be identified using temperature data from the first 24 hours of hospitalization. Temperature measurements from each study patient in the first 24 hours were compared with the predicted measurement of each trajectory function, and patients were classified to the subphenotype resulting in the lowest mean squared error. The accuracy was evaluated using agreement in classification between the 24-hour and 72-hour models. Propensity score analyses were performed using Stata Version 16 (StataCorp, College Station, TX). All other analyses were performed using R Version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

The study cohort consisted of 5,903 hospitalized patients with COVID-19 (**Appendix Fig. 1**, http://links.lww.com/CCM/G926). The median age was 61 years (49–73 yr), with 7.1% prevalence of VTEs and 7.7% prevalence of CVAs during hospitalization. Furthermore, 12% required mechanical ventilation, 12% required vasopressors, and the 30-day inpatient mortality rate was 7.4% (**Table 1**). Our previously validated temperature trajectory model was compared with a de novo model and was found to have better fit (**Appendix Table 1** and **Appendix Fig. 2**, http://links.lww.com/CCM/G926). All trajectory analyses in the article are based on the previously validated model.

The distribution of subphenotype membership was: hyperthermic slow resolvers (n = 1,452, 25%), hyperthermic fast resolvers (1,469, 25%), normothermics (2,126, 36%), and hypothermics (856, 15%) (**Fig. 1**). Individual patient trajectories are also presented in Figure 1. Age was significantly different between subphenotypes ($p < 0.001$): hyperthermic slow resolvers were the youngest (median age, 58 yr; interquartile range [IQR], 46–69 yr), while hypothermics were the oldest (69 yr; IQR, 56–80 yr). Comorbidities were significantly different, with hypothermics having the highest burden of several comorbidities: 22% having congestive heart failure ($p < 0.001$), 18% chronic pulmonary disease ($p = 0.02$), 64% hypertension ($p = 0.02$), and 26% chronic kidney disease ($p < 0.001$).

The hyperthermic slow resolvers had the highest rates of mechanical ventilation (17%), renal replacement therapy (9.7%), and vasopressors (17%). Hyperthermic slow resolvers had the lowest prevalence of VTEs (5.1%), while the hypothermic patients had the highest prevalence (8.5%, $p = 0.005$). Hypothermics also had the highest prevalence of CVAs (10%, $p = 0.001$). Inpatient 30-day mortality rate was significantly different between subphenotypes ($p = 0.02$): 8.6% mortality rate for hypothermics, 8.5% for hyperthermic slow resolvers, 7.2% for normothermics, and 5.9% for hyperthermic fast resolvers (Table 1).

Association of Subphenotypes With Inflammatory Responses

There were significant differences in levels of inflammatory markers between subphenotypes. The hyperthermic slow resolvers had the highest CRP, with a mean of 137 mg/L (95% CI, 132–142 mg/L), followed by hyperthermic fast resolvers (121; 95% CI, 117–126), normothermics (97; 95% CI, 93–101), and lowest levels in hypothermics (95; 95% CI, 89–101) ($p < 0.001$). The hyperthermic slow resolvers also had the highest levels of IL-6 and ferritin, while normothermic patients had the lowest levels ($p < 0.001$) (**Fig. 2**; and **Appendix Table 2**, http://links.lww.com/CCM/G926). The mean non-log-transformed levels of IL-6 were 19 pg/mL (13.9–24 pg/mL) in hyperthermic slow resolvers, 14 pg/mL (10.5–17.5 pg/mL) in hyperthermic fast resolvers, 12 pg/mL (8.6–15.5 pg/mL) in normothermic, and 13.5 pg/mL (8.4–18.6 pg/mL) in hypothermic. The missingness of the biomarkers by subphenotype and over the course of the study are presented in **Appendix Tables 3** and **4** (http://links.lww.com/CCM/G926).

Association of Subphenotypes With Coagulation Disturbances

D-dimer levels were significantly different between the subphenotypes ($p < 0.001$), with the hypothermic patients having the highest levels, followed by normothermics, and then the hyperthermic subphenotypes. Hypothermic patients also had the highest levels of fibrin monomers ($p < 0.001$) (Fig. 2; and Appendix Table 2, http://links.lww.com/CCM/G926).

TABLE 1.
Clinical Characteristics Compared Between Temperature Trajectory Subphenotypes

Characteristics	Study Cohort	Hyperthermic Slow Resolvers	Hyperthermic Fast Resolvers	Normothermic	Hypothermic	*p*
n	5,903	1,452	1,469	2,126	856	
Age, yr	61 (49–73)	58 (46–69)	60 (49–72)	60 (49–73)	69 (56–80)	< 0.001
Sex, female	2,952 (50)	664 (45.7)	698 (47.5)	1,172 (55.1)	418 (48.8)	< 0.001
Race						< 0.001
Black	3,012 (51)	910 (62.7)	684 (46.6)	1,050 (49.4)	368 (43)	
White	1,972 (33.4)	329 (22.7)	531 (36.1)	732 (34.4)	380 (44.4)	
Other	919 (15.6)	213 (14.7)	254 (17.3)	344 (16.2)	108 (12.6)	
Hispanic ethnicity	460 (7.8)	130 (9)	125 (8.5)	154 (7.2)	51 (6)	0.09
Comorbidities						
Congestive heart failure	899 (15.2)	216 (14.9)	187 (12.7)	308 (14.5)	188 (22)	< 0.001
Pulmonary disease	970 (16.4)	203 (14)	242 (16.5)	370 (17.4)	155 (18.1)	0.02
Hypertension	3,530 (59.8)	862 (59.4)	884 (60.2)	1,235 (58.1)	549 (64.1)	0.02
Diabetes mellitus	1,958 (33.2)	534 (36.8)	483 (32.9)	652 (30.7)	289 (33.8)	0.002
Renal disease	1,250 (21.2)	326 (22.5)	298 (20.3)	401 (18.9)	225 (26.3)	< 0.001
Liver disease	240 (4.1)	65 (4.5)	47 (3.2)	91 (4.3)	37 (4.3)	0.3
Hospital outcomes						
Venous thromboembolism	418 (7.1)	74 (5.1)	106 (7.2)	165 (7.8)	73 (8.5)	0.005
Cerebrovascular accident	453 (7.7)	103 (7.1)	84 (5.7)	180 (8.5)	86 (10)	0.001
Renal replacement therapy	399 (6.8)	141 (9.7)	81 (5.5)	121 (5.7)	56 (6.5)	< 0.001
Mechanical ventilation	707 (12)	248 (17.1)	142 (9.7)	225 (10.6)	92 (10.7)	< 0.001
Vasopressors	705 (11.9)	243 (16.7)	138 (9.4)	231 (10.9)	93 (10.9)	< 0.001
Inotropes	82 (1.4)	28 (1.9)	9 (0.6)	30 (1.4)	15 (1.8)	0.02
Sequential Organ Failure Assessment	3 (1–6)	3 (2–7)	3 (1–5)	2 (1–5)	3 (2–6)	< 0.001
Length of stay, d	6 (3–10)	7 (4–13)	5 (3–9)	5 (3–9)	6 (3–11)	< 0.001
Mortality	438 (7.4)	124 (8.5)	87 (5.9)	153 (7.2)	74 (8.6)	0.02

All values are presented as *n* (%) or median (interquartile range). Inotropes are defined as dobutamine and milrinone. Mortality represents 30-d inpatient mortality. *p* values signify the results of comparisons between subphenotypes through χ^2 or analysis of variance testing, as appropriate.

The hypothermic and normothermic patients had increased odds ratio (OR) of CVAs (OR, 1.42; 95% CI, 1.02–1.97 and OR, 1.58; 95% CI, 1.20–2.09, respectively) when controlling for demographics, comorbidities, and SOFA score with the hyperthermic fast resolvers serving as the reference group (**Fig. 3**; and **Appendix Table 5**, http://links.lww.com/CCM/G926). The hyperthermic slow resolvers had decreased odds of VTEs (OR, 0.66; 95% CI, 0.49–0.90) compared with the hyperthermic fast resolvers. The association of subphenotypes with biomarker abnormalities persisted when testing biomarker levels measured between 72 and 168 hours of hospitalization (**Appendix Fig. 3**, http://links.lww.com/CCM/G926).

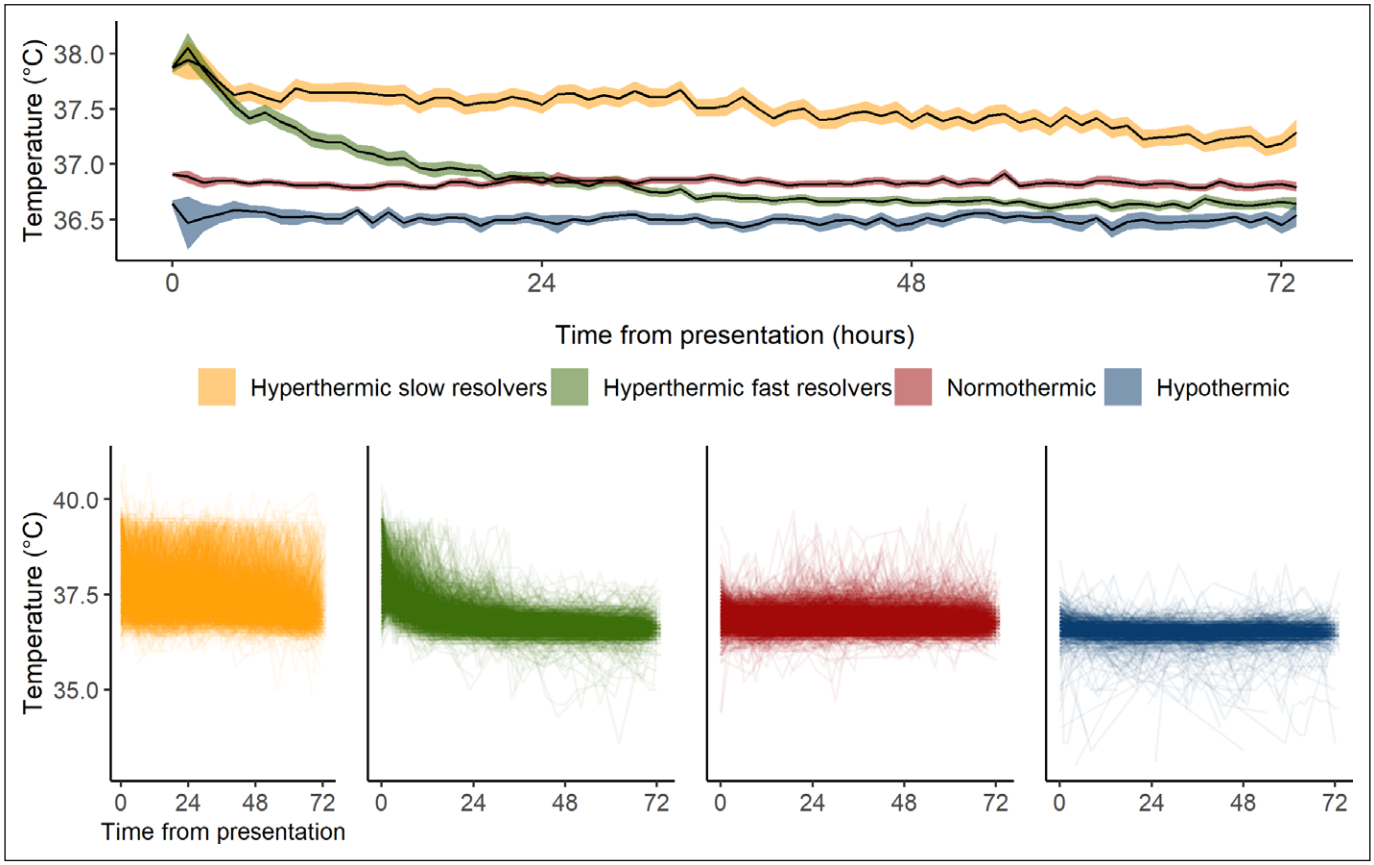

Figure 1. Temperature trajectory subphenotypes in patients with coronavirus disease 2019 (COVID-19). Applying a validated algorithm to oral temperature measurements from the first 72 hr of hospitalization, four temperature trajectory subphenotypes were identified in a multicenter cohort of 5,903 hospitalized COVID-19 patients: hyperthermic slow resolvers (n = 1,452, 25%), hyperthermic fast resolvers (1,469, 25%), normothermics (2,126, 36%), and hypothermics (856, 15%). The *top graph* presents the mean temperature measurement at each hour for each subphenotype with the *shaded regions* representing the 95% CI around the mean. The *bottom graphs* display the individual trajectories of each patient in the four subphenotypes.

Association of Subphenotypes With Organ Dysfunction

The markers of end-organ dysfunction were significantly different between the subphenotypes. The hypothermic subphenotype had the highest BNP and lactic acid ($p < 0.001$) (Fig. 2; and Appendix Table 2, http://links.lww.com/CCM/G926). Hyperthermic slow resolvers had the highest creatinine ($p < 0.001$). Both hyperthermic slow resolvers and normothermic patients had significantly higher OR of requiring vasopressors (OR, 1.75; 95% CI, 1.29–2.37 and OR, 1.43; 95% CI, 1.06–1.93, respectively) compared with hyperthermic fast resolvers. The hyperthermic slow resolvers had significantly higher OR of renal replacement therapy (1.55; 95% CI, 1.08–2.22), mechanical ventilation (1.69; 95% CI, 1.24–2.29), and 30-day inpatient mortality (1.58; 95% CI, 1.13–2.19) (Fig. 3; and Appendix Table 5, http://links.lww.com/CCM/G926).

Given the significant association between sex and trajectory subphenotype, we tested the interactions between sex and subphenotype in association with outcomes. We found that in hyperthermic slow resolvers, males had significantly decreased OR for mechanical ventilation (0.49; 95% CI, 0.26–0.90; $p = 0.02$) and decreased OR of vasopressor use (0.43; 95% CI, 0.23–0.80; $p = 0.008$) compared with females.

Change in Subphenotype Prevalence Over Time

The percentage of patients who were classified as hyperthermic slow resolvers decreased over the course of the pandemic, from 53% of patients in March 2020; 23% of patients by August 2020; and less than 15% by 2021 (**Fig. 4**). There was a contemporaneous increase in dexamethasone use: less than 5% receiving dexamethasone from March to May 2020, 14% in June 2020, and over 60% in the subsequent months.

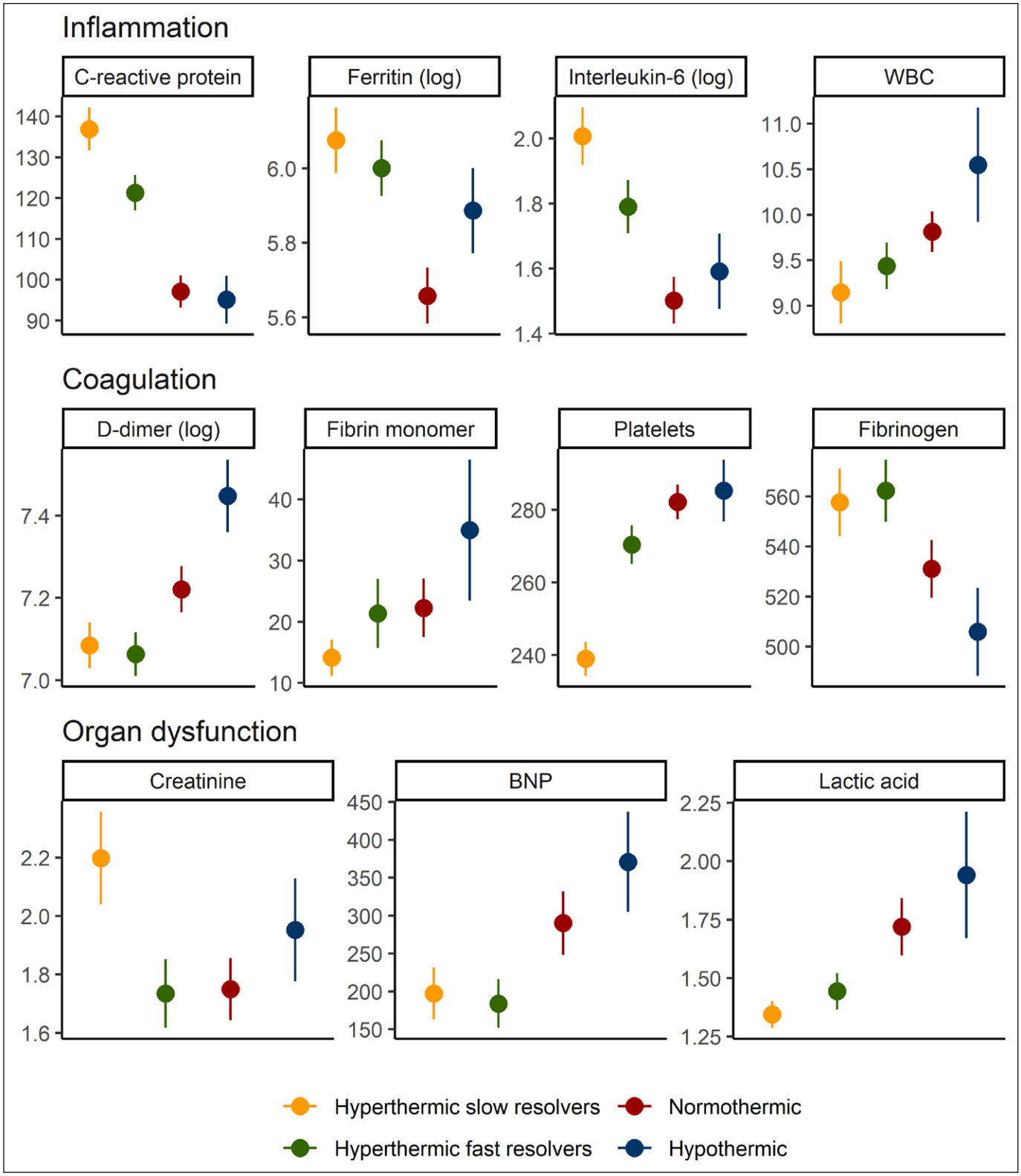

Figure 2. Biomarker levels compared between temperature trajectory subphenotypes. Biomarker levels (most abnormal values in the first 72 hr of hospitalization) were compared between the temperature trajectory subphenotypes using analysis of variance testing. All biomarkers that remained significant after Bonferroni correction for multiple testing ($p < 0.001$) are presented above. The hyperthermic slow resolvers had the highest levels of inflammatory markers (*top row*) including C-reactive protein, ferritin, and interleukin-6 (IL-6) but had relatively lower WBC counts. The hypothermics had abnormal coagulation markers (*middle row*), with the highest levels of D-dimer and fibrin monomers, high platelet count, and relatively lower fibrinogen. The hypothermics also had the highest brain natriuretic peptide (BNP) and lactic acid levels. Of the biomarkers presented, IL-6, fibrinogen, fibrin monomers, and lactic acid were missing in greater than 50% of study patients.

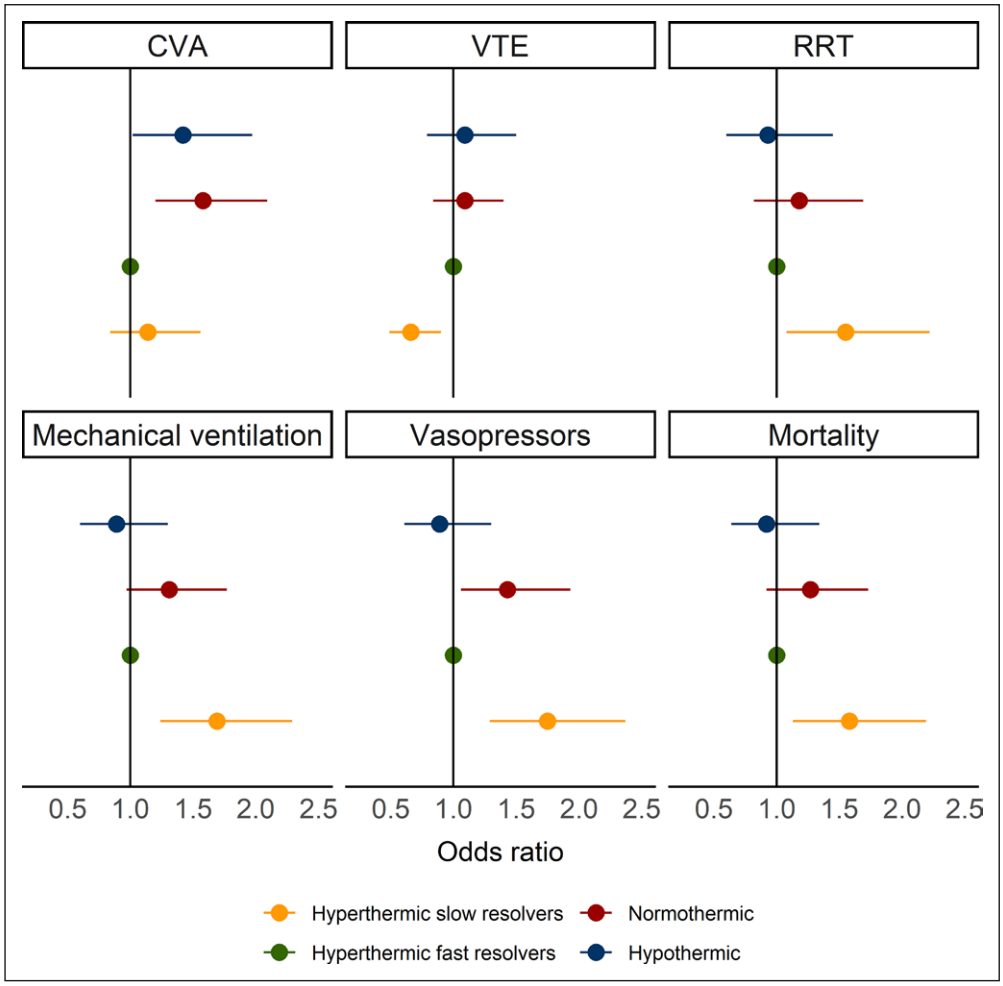

Figure 3. Odds ratio (OR) for hospital outcomes compared between temperature trajectory subphenotypes. The temperature trajectory subphenotypes were evaluated for association with venous thromboembolic events (VTEs), cerebrovascular accidents (CVAs), renal replacement therapy (RRT), mechanical ventilation, vasopressors, and 30-d inpatient mortality. Logistic regression was performed to evaluate these outcomes controlling for age, sex, race, comorbidities, and maximum Sequential Organ Failure Assessment score in the first 72-hr of hospitalization. The hyperthermic fast resolvers were selected as the reference group based on our prior work, as this subphenotype has consistently demonstrated the lowest mortality rates. Hypothermics and normothermics had increased OR of CVAs (OR, 1.42; 95% CI, 1.02–1.97 and OR, 1.58; 95% CI, 1.20–2.09, respectively). Hyperthermic slow resolvers had lower odds of having VTEs (OR, 0.66; 95% CI, 0.49–0.90). Hyperthermic slow resolvers had significantly higher OR of requiring RRT (1.55; 95% CI, 1.08–2.22), vasopressors (1.75; 95% CI, 1.29–2.37), mechanical ventilation (1.69; 95% CI, 1.24–2.29), and 30-d inpatient mortality (1.58; 95% CI, 1.13–2.19) compared with hyperthermic fast resolvers.

We hypothesized that increasing dexamethasone use was associated with the decreasing prevalence of hyperthermic slow resolvers, and we evaluated this association through propensity score matching with inverse probability weighting. The 2,217 treated patients (i.e., patients in the post-RECOVERY trial period who received dexamethasone in the first 72 hr of hospitalization) were matched to 899 control patients (i.e., patients in the pre-RECOVERY trial period who did not receive dexamethasone). The propensity model had acceptable distributional overlap of propensity scores, well-balanced covariates, and no disproportionally weighted patients (**Appendix Figs. 4** and **5,** http://links.lww.com/CCM/G926). After inverse probability weighting, dexamethasone treatment was associated with a significant reduction in probability of hyperthermic slow resolvers membership (27% reduction; 95% CI, 23–31%; $p < 0.001$). We performed the following sensitivity analyses:

1) We included patients treated with any corticosteroid within the first 72 hours and found that treatment with any corticosteroid was associated with a significant reduction in probability of hyperthermic slow resolver membership (26%, $p < 0.001$).
2) We restricted the treated and control cohort to patients requiring supplemental oxygen and found that dexamethasone was associated with a significant reduction in hyperthermic slow resolver membership (29%, $p < 0.001$).
3) We limited the treatment cohort to patients receiving dexamethasone in the first 24 hours of hospitalization and found a significant reduction in hyperthermic slow resolvers membership (31% reduction, $p < 0.001$).

The changes in proportions of other subphenotypes and treatments over the study period are presented (**Appendix Figs. 6** and **7** and **Appendix Table 6**, http://links.lww.com/CCM/G926).

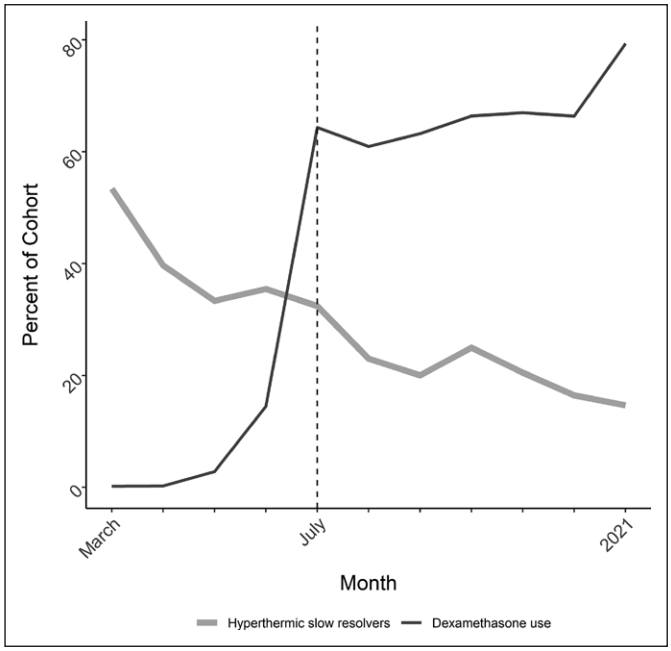

Figure 4. Change in use of dexamethasone and prevalence of hyperthermic slow resolvers over the pandemic. Given the widespread increase in use of dexamethasone around the publication of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial in July 2020, we hypothesized that we would see a contemporaneous decrease in the prevalence of the hyperinflammatory temperature subphenotype (the hyperthermic slow resolvers). Dexamethasone use (as a percentage of admitted patients per month that received the medication) and the prevalence of hyperthermic slow resolvers per month are presented over the course of the study. Dexamethasone use steadily increased over the course of the pandemic with a large rise in July coinciding with the publication of the RECOVERY trial (marked by the *dashed black line*). The percentage of patients with the hyperthermic slow resolver temperature pattern steadily decreased over the course of the pandemic, from over 50% in March 2020 to less than 15% by 2021.

Early Identification of Subphenotypes

Patients were classified into temperature trajectory subphenotypes using temperature data from the first 4 hours (i.e., presenting temperature) and the first 24 hours of hospitalization (**Appendix Fig. 8**, http://links.lww.com/CCM/G926). There was poor agreement (51%) between the presenting temperature and the 72-hour model. There was 74% agreement in subphenotype classification between the 24-hour and 72-hour models. The accuracy incrementally improved with higher frequency of temperature measurements within the 24-hour period (**Appendix Fig. 9**, http://links.lww.com/CCM/G926).

DISCUSSION

We present the novel discovery of a hypercoagulable temperature trajectory subphenotype and a hyperinflammatory subphenotype in COVID-19. Using longitudinal body temperature, we discovered that the hypothermic subphenotype had marked abnormalities in coagulation biomarkers and the highest prevalence of VTEs and CVAs. As far as we know, this is the first study to demonstrate a direct clinical association between body temperature and coagulation abnormalities in COVID-19. The hyperthermic slow resolvers had elevated CRP, ferritin, and IL-6 and higher frequency of cardiovascular failure requiring vasopressors and respiratory failure requiring mechanical ventilation. The hyperthermic slow resolvers had significantly higher mortality compared with hyperthermic fast resolvers. Interestingly, we also observed that the prevalence of the hyperthermic slow resolvers drastically decreased over the course of the pandemic.

COVID-19 disease is associated with significant perturbations to the hematological system and often results in a hypercoagulable state (29). However, it is still unclear which subgroups of COVID-19 patients would benefit most from higher intensity anticoagulation (30, 31). Prior studies have suggested a link between lower temperatures and coagulation abnormalities (32–34). In our study, the hypothermic subphenotype had elevated D-dimer and fibrin monomer levels. Importantly, this subphenotype had significantly higher unadjusted prevalence of VTEs and CVAs. The prevalence of CVAs remained significant even when controlling for age, comorbidities, and severity of illness. Given the marked elevation in levels of D-dimer and fibrin monomers, we hypothesize that hypothermic patients may need more aggressive screening for VTEs and that the true prevalence may be underdiagnosed. Further research is needed to evaluate whether hypothermic patients benefit from therapies targeting specific perturbations in hemostasis.

The host response to COVID-19 is heterogeneous, and patients may demonstrate both pro- and anti-inflammatory responses (3, 35–37). Given this heterogeneity, anti-inflammatory therapies may benefit certain groups, while harming others (38). Although there is no gold standard definition of hyperinflammation, hyperthermic slow resolvers demonstrated several abnormalities consistent with a hyperinflammatory

state (39–43). CRP and ferritin have been commonly used to define COVID-19–associated hyperinflammation, and hyperthermic slow resolvers had the highest levels of both biomarkers (40). Sinha et al (10) have reported on using IL-6 and vasopressor need to identify an acute respiratory distress syndrome hyperinflammatory subphenotype. Hyperthermic slow resolvers had elevated IL-6 levels and the highest frequency of vasopressor use. These findings are consistent with our prior observations in hyperthermic slow resolvers with *Staphylococcus aureus* bacteremia and all-cause septic shock, in which we found that this subphenotype had persistent elevations in inflammatory cytokines (17). Future research should investigate whether this subphenotype would benefit from anti-inflammatory therapies including tocilizumab. Interestingly, there were significant interactions between sex and the hyperthermic slow resolver subphenotype. Specifically, females had increased OR for mechanical ventilation and vasopressor use in this subphenotype. This suggests that the increased risks of poor outcomes associated with hyperthermic slow resolvers may be predominantly in females following this temperature pattern. Further research is needed to study the complex interactions between sex and body temperature responses to infection.

Over the course of the pandemic, we have seen drastic shifts in standards of care. In our center, we observed that the percentage of inpatients receiving dexamethasone increased from less than 5% in the beginning of the pandemic to over 60% after publication of the RECOVERY trial. Interestingly, we found a contemporaneous decrease in the prevalence of hyperthermic slow resolvers. Prior studies have shown that dexamethasone can change temperature patterns and may benefit hyperinflammatory phenotypes (44–46). Given that the hyperthermic slow resolvers are a hyperinflammatory subphenotype, we hypothesize that the use of dexamethasone is contributing to the shifting of this temperature pattern. However, the decreasing prevalence of hyperthermic slow resolvers began before the publication of the RECOVERY trial, and thus cannot be completely explained by dexamethasone usage. This shift in temperature patterns could also be due to other changes in clinical practices (such as the use of remdesivir, which increased in parallel with the use of dexamethasone), changes in demographics of infected patients, and changes in the pathogen itself. Further research is necessary to investigate whether corticosteroids affect temperature patterns through immunological changes.

The study has several limitations. First, the retrospective nature limits the capacity for causal inferences. For instance, our results suggest that dexamethasone contributed to the observed changing temperature patterns over the course of the pandemic, but there could be other interventions such as IV fluids that contribute to changes in temperature trajectories. Second, the biomarkers were collected as clinically indicated resulting in missing data. Importantly, missing data varied by subphenotype, suggesting that the clinical decision to check the biomarker may have been influenced by the differential presentations of these subphenotypes. Third, the temperature trajectory model currently requires 72 hours of temperature data and cannot be accurately determined by the initial measurements at presentation, which may limit immediate clinical implementation. As supported by our data, future work investigating higher frequency temperature measurements may allow early identification of these subphenotypes.

CONCLUSIONS

Using subphenotypes derived from the universally available measurement of temperature, we found that hyperthermic slow resolvers were hyperinflammatory and at high risk for respiratory failure, shock, and mortality, while hypothermics were hypercoagulable with marked coagulation abnormalities. Future work should investigate whether temperature trajectory subphenotypes have differential responses to treatment.

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