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Altered Heart Rate Variability Early in ICU Admission Differentiates Critically Ill Coronavirus Disease 2019 and All-Cause Sepsis Patients

IMPORTANCE: Altered heart rate variability has been associated with autonomic dysfunction in a number of disease profiles, in this work we elucidate differences in the biomarker among patients with all-cause sepsis and coronavirus disease 2019.

OBJECTIVES: To measure heart rate variability metrics in critically ill coronavirus disease 2019 patients with comparison to all-cause critically ill sepsis patients.

DESIGN, SETTING, AND PARTICIPANTS: Retrospective analysis of coronavirus disease 2019 patients admitted to an ICU for at least 24 hours at any of Emory Healthcare ICUs between March 2020 and April 2020 up to 5 days of ICU stay. The comparison group was a cohort of all-cause sepsis patients prior to coronavirus disease 2019 pandemic.

MAIN OUTCOMES AND MEASURES: Continuous waveforms were captured from the patient monitor. The electrocardiogram was then analyzed for each patient over a 300 seconds observational window that was shifted by 30 seconds in each iteration from admission till discharge. A total of 23 heart rate variability metrics were extracted in each iteration. We use the Kruskal-Wallis and Steel-Dwass tests ($p < 0.05$) for statistical analysis and interpretations of heart rate variability multiple measures.

RESULTS: A total of 141 critically ill coronavirus disease 2019 patients met inclusion criteria, who were compared with 208 patients with all-cause sepsis. Three nonlinear markers, including the ratio of standard deviation derived from the Poincaré plot, sample entropy, and approximate entropy and four linear features, including mode of beat-to-beat interval, acceleration capacity, deceleration capacity, and the proportion of consecutive RR intervals that differ by more than 50 ms, were all statistically significant ($p < 0.05$) between the coronavirus disease 2019 and all-cause sepsis cohorts. The three nonlinear features and acceleration capacity, deceleration capacity, and beat-to-beat interval (mode) were statistically significant ($p < 0.05$) when comparing pairwise analysis among the combinations of survivors and nonsurvivors between the coronavirus disease 2019 and sepsis cohorts. Temporal analysis of the main markers showed low variability across the 5 days of analysis compared with sepsis patients.

CONCLUSIONS AND RELEVANCE: In this descriptive statistical study, heart rate variability measures were found to be statistically different across critically ill patients infected with severe acute respiratory syndrome coronavirus 2 and distinct from bacterial sepsis.

KEY WORDS: coronavirus disease 2019; decompensation; heart rate variability; sepsis; severe acute respiratory syndrome coronavirus 2

The novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) has led to a large cascade of transmissions resulting in high numbers of individuals hospitalized for the coronavirus disease 2019 (COVID-19), an impact still being accounted for across

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the globe. A major target of the disease has been the respiratory components, resulting in acute respiratory insufficiency and failure. In patients who require mechanical ventilation, reported mortality rates exceed 50% (1, 2). However, COVID-19 is not only a respiratory disease. Cardiac, renal, hemodynamic, hematological, and neurologic manifestations were noted in critically ill COVID-19 patients (3–5). The multisystem injury and high mortality rate require means to identify patients at high risk.

Heart rate variability (HRV) is a naturally occurring phenomena, which takes different patterns in critical illness (6). HRV has long been associated to be a surrogate measure of cardiac autonomic tone (7–10). Analyzing complex dynamic features from the electrocardiogram (ECG) has been shown to indicate early cardiorespiratory complications (11, 12), autonomic dysfunction (13), sepsis (14), and death (15). These HRV measures, drawn from both temporal and frequency domain, have also been used in predictive models for early and rapid identification of deterioration and mortality in the ICU (16–20). However, the exploration of a comprehensive list of HRV metrics has not been investigated among COVID-19 patients. Therefore, in this study, we explore the association and implications of these components in critically ill COVID-19 patients, identifying features that differentiate survivors and nonsurvivors. Separately, using a descriptive statistical methodology, we study the similarities of these characteristics to non-COVID-19 all-cause sepsis patients in a multi-ICU, single healthcare system.

METHODS

The study was approved by the Emory University Institutional Review Board (Number STUDY00000302). All medical, surgical, neurocritical, transplant, and cardiac ICU admissions with COVID-19 between March 1, 2020, and April 31, 2020, within Emory Healthcare system were screened. Patients were selected to be included in the analysis if they were in the ICU for greater than 24 hours. Controls were identified as all-cause sepsis patients meeting Sepsis-3 criteria (21), between 2015 and 2017, a previously published patient series (20). Patients with less than 24 hours of ICU admission were excluded due to the presence of confounding workflow

factors from higher acuity. Continuous bedside monitoring data were extracted during the patient's ICU stay, and HRV measures were generated using a sliding window. The data were exported from the archival system, de-identified and analyzed using open source and proprietary statistical programs.

DATA ABSTRACTION

Continuous waveforms were captured from the General Electric bedside monitors across Emory affiliated hospitals, using the BedMaster system (Excel Medical Electronics, Jupiter, FL). The data archival infrastructure is available in 152 beds spanning medical, surgical, transplant, and cardiac ICUs across the health system. For this study, continuous ECG were captured from the bedside, each sampled at a sampling frequency of 240 Hertz. The ECG was then analyzed for each patient over a 300 seconds observational window that was shifted by 30 seconds in each iteration from admission till discharge. A total of 23 HRV metrics were extracted in each iteration using the “PhysioNet Cardiovascular Signal Toolbox” (22). The list of measures used in this study is numbered in **Supplemental Table 1** (<http://links.lww.com/CCX/A835>). Where any 300 seconds observational window had more than 20% of poor data quality, the segment was discarded from the analysis (23). We applied a series of signal processing-based methods, including band-pass filtering to preprocessing the waveform and to identify segments with poor data quality. We then applied a sensor-fusion approach that combines multiple ECG leads to identify optimal R-R peaks in the ECG that were then used to compute HRV (24).

STATISTICAL ANALYSIS

MATLAB (MathWorks, Natick, MA) was used to analyze the continuous ECG and extract relevant HRV features. The statistical analysis of this data was analyzed using Python Scikit-learn (25) and JMP (SAS Institute, Cary, NC) software. Differences among demographics were evaluated for statistical significance ($p < 0.05$) using the chi-square method for categorical and standard Student t test or one-way analysis of variance for continuous variables. We use the Kruskal-Wallis and Steel-Dwass tests ($p < 0.05$) for statistical analysis and interpretations of HRV multiple measures.

PATIENT LEVEL ANALYSIS

Due to the use of a 300 seconds sliding window, the average number of observations sampled per patients was in excess of 10,500. In order to estimate encounter level variability (pertaining to a single ICU stay), we derived the average value for each HRV measure. Since the goal of the study is to detect early markers of mortality, we limit the period of analysis to the first 5 days (120 hr) from ICU admission. Histograms were generated using Scikit-learn for each measure and separated by the class label.

TRAJECTORIES OF DISEASE

Temporal trajectories of each patient were generated to investigate differences in acuity and deterioration magnitude among COVID-19 survivors and nonsurvivors. Aggregate features of HRV (mean, minimum, maximum, etc.) were generated by uniformly sampling data across each 8-hour segment from admission until the fifth day. In-hospital mortality outcome was retrieved from the clinical record.

CONFOUNDING INFLUENCE OF WORKFLOW AND ICU STAY

In order to evaluate whether these characteristics manifest as a function of specific clinical workflow or varying

length of ICU stay, we performed a sensitivity analysis by selecting only the first 8 hours of monitoring, and differences were computed for statistical significance using above mentioned methods. Statistical tests were performed on the aggregate mean value across each feature in order to reduce bias due to high dimensionality.

RESULTS

A total of 778 hospitalized patients were identified in a clinical chart review for positive SARS-CoV-2 tests by use of quantitative reverse transcription polymerase chain reaction. From this cohort, 413 encounters were mapped to bedside monitors that were actively archiving data during the time of their hospitalization. We excluded 272 patients due to insufficient data or poor quality (> 20% missing data) data from the first 5 days of ICU admission, leaving a total of 141 patients who were analyzed. We identified 557 encounters, pre-COVID-19, who met sepsis-3 criteria during their ICU stay and had high-frequency bedside monitoring captured. Two-hundred eight of those encounters had sufficient data quality in the first 5 days of ICU stay and were eligible for the study. **Table 1** presents a description of the clinical and demographic characteristics of the cohort. Notably, among African Americans, the differences in mortality were

TABLE 1.
List of Patient Characteristics

Characteristics	Coronavirus Disease 2019			Sepsis (All Cause)		
	Survivor	Nonsurvivor	All	Survivor	Nonsurvivor	All
<i>n</i>	91	50	141	117	91	208
Age, mean ± SD	59 ± 15	71 ± 14 ^a	63 ± 16	59 ± 16	69 ± 16 ^a	63 ± 16
Females, <i>n</i> (%)	43 (47)	24 (48)	67 (48)	56 (48)	37 (41)	93 (45)
Mechanical ventilation, <i>n</i> (%)	68 (74)	44 (88) ^a	112 (79)	24 (17)	28 (31)	52 (25)
ICU length of stay (d), mean ± SD	29 ± 19	19 ± 18	26 ± 19	25 ± 18	17 ± 18	22 ± 19
Acute Physiology and Chronic Health Evaluation-II, mean ± SD	12 ± 18	14 ± 16	13 ± 17	9 ± 8	14 ± 13	10 ± 8
Race, <i>n</i> (%)						
African American	73 (80) ^b	35 (70) ^b	108 (76) ^b	36 (30) ^b	32 (35) ^b	68 (33) ^b
Asian	0	3 (6)	3 (2)	0	2 (1)	2 (1)
Caucasian	14 (15)	6 (12)	20 (14)	70 (60)	45 (49)	115 (55)
Multiple	0	0	0	1 (1)	0	1
Unknown	4 (4)	6 (12)	10 (7)	10 (9)	12 (13)	22 (11)

^aStatistical significance ($p < 0.001$) by nonparametric Mann-Whitney U test between survivors and nonsurvivors in each group.

^bStatistical significance ($p < 0.001$) by χ^2 test.

statistically significant by chi-square test within both the COVID-19 and all-cause sepsis cohorts ($p < 0.05$). Within both groups, the nonsurvivors were older on average compared with the survivors. More patients in the COVID cohort underwent mechanical ventilation than in the sepsis cohort (79% vs 25%; $p < 0.05$), with moderate effect size (Cohen's $d > 0.5$).

A basic description of the different HRV indices of the COVID-19 and sepsis group is detailed as a distribution histogram plot in **Supplemental Figure 1** (<http://links.lww.com/CCX/A836>). While the total number of encounters in the sepsis group is greater, there was significantly more data available per encounter in the COVID-19 group. **Supplemental Figure 2** (<http://links.lww.com/CCX/A837>) illustrates the data missingness as a function of monitoring time from admission till day 5 for sepsis and COVID-19 groups. Prior to inclusion criteria being applied, there were approximately 680,799 seconds (~8 d) of data points on average per encounter in the COVID-19 group, while 206,288 seconds (2.4 d) in the sepsis group.

Descriptive statistics of the HRV measures are detailed in **Table 2**. A list of statistically significant features derived from those HRV measures are included in **Supplemental Table 2** (<http://links.lww.com/CCX/A838>), along with their effect size (Cohen's d). Notably, both Kruskal-Wallis and Steel-Dwass tests for multiple comparisons show statistically significant separations between the COVID-19 and all-cause sepsis groups. Specifically, on seven specific markers, which consists of three nonlinear markers, including the ratio of standard deviation derived from the Poincaré plot (SD1:SD2), sample entropy (SampEn), and approximate entropy (ApEn) and four linear features, including mode of beat-to-beat interval (NN), acceleration capacity (AC), deceleration capacity (DC), and the proportion of consecutive RR intervals that differ by more than 50 ms (pNN50), were statistically significant between more than one binary combinations of the subgroups (comparing survivors and nonsurvivors in both the COVID-19 and sepsis cohorts). The three nonlinear features and AC, DC, and NN (mode) were statistically significant across all four combinations. A number of NN metrics show significant QRS complex elongation between COVID-19 and sepsis, with the NN (mean) appearing on average, greater among both COVID-19 subgroups than in sepsis survivors

TABLE 2.
Heart Rate Variability Measures Between Coronavirus Disease 2019 and All-Cause Sepsis

Heart Rate Variability Metric	Coronavirus Disease 2019		Sepsis	
	Mean	SE	Mean	SE
NNmean	606.12	2.05	590.13	5.15
NNmedian	605.60	2.07	589.41	5.23
NNmode	595.60	2.03	578.32	5.26
NNvariance	149.83	11.08	282.82 ^a	60.50
NNskewness	0.09	0.01	0.10	0.03
NNkurtosis	12.12	0.18	12.27	0.50
NNinterquartile range	22.38	0.33	28.83 ^a	1.17
SDNN	20.84	0.28	25.17 ^a	0.88
RMSSD	20.87	0.36	23.11	0.97
pnn50	0.06	0.00	0.08	0.01
ulf	147.44	6.32	205.95	19.18
vlf	321.02	9.50	542.36 ^a	44.32
lf	170.31	7.93	281.33 ^a	27.38
hf	234.70	9.02	336.94 ^a	31.92
lfhf	1.76	0.04	1.77	0.08
ttlplr	873.48	26.30	1,366.59 ^a	102.34
Acceleration capacity	-3.42	0.05	-4.59 ^a	0.18
Deceleration capacity	3.25	0.05	4.44 ^a	0.17
SD1	14.77	0.25	16.36	0.68
SD2	24.28	0.32	30.21 ^a	1.08
SD1:SD2	0.67	0.01	0.63 ^a	0.01
Sample entropy	1.25	0.01	1.29 ^a	0.02
Approximate entropy	0.98	0.00	0.98 ^a	0.01

NN = beat-to-beat interval.

^a $p < 0.01$ by both Kruskal-Wallis and Steel-Dwass multiple comparisons tests between coronavirus disease 2019 and sepsis cohorts.

and nonsurvivors. However, we note that the effect size comparison of COVID-19 and all-cause sepsis by Cohen's d (**Supplemental Table 2**, <http://links.lww.com/CCX/A838>) suggests that NN features (skewness, kurtosis, mean, median, SD, interquartile range [IQR], and mode) had a large effect size (Cohen's $d > 0.8$). ApEn, SampEn, frequency domain features (power

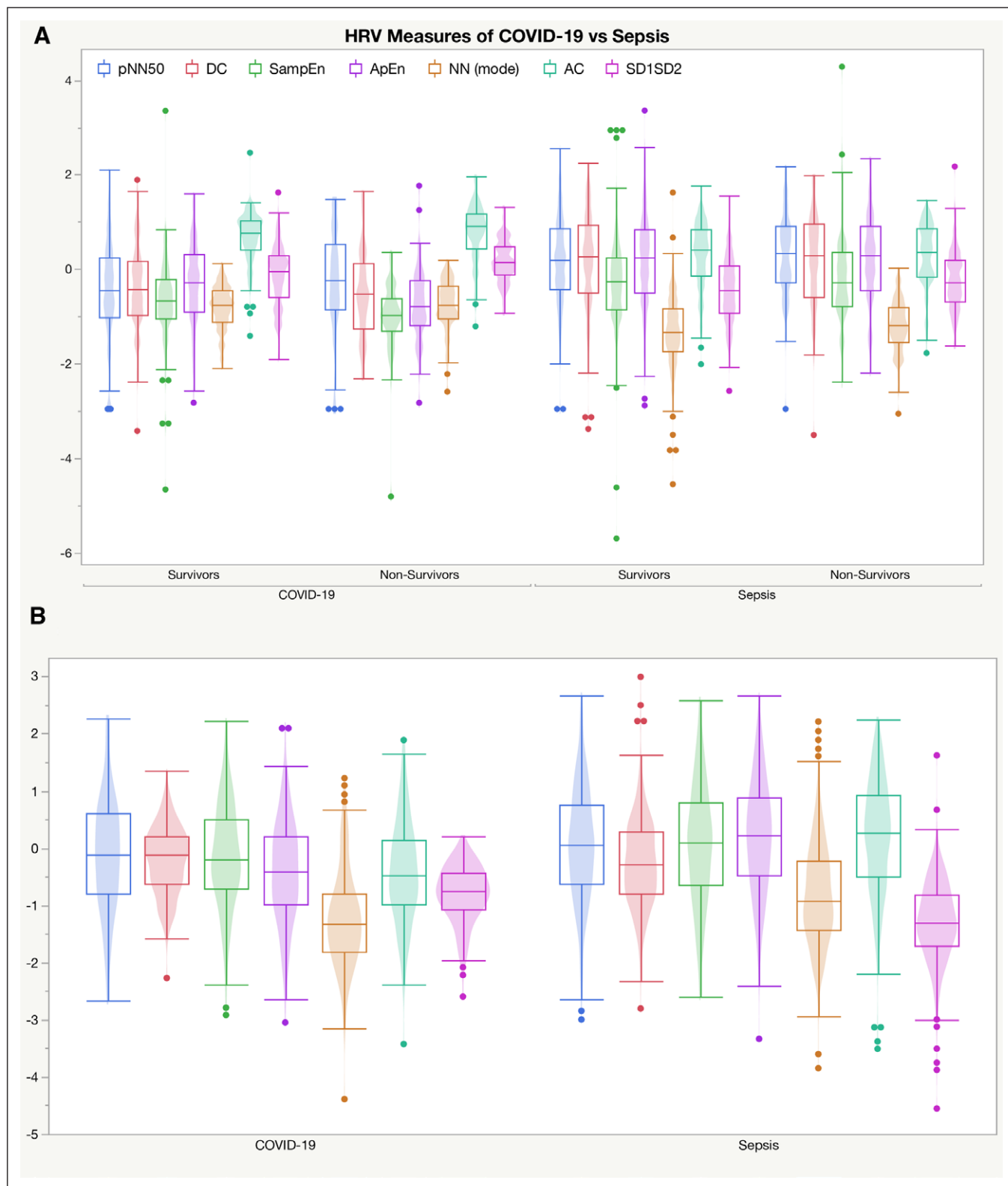


Figure 1. Selected illustration of key altered heart rate variability (HRV) measures between the coronavirus disease 2019 (COVID-19) and all-cause sepsis cohorts. **A**, *Box plots* with violin subcomponents characterizing the distribution within each group categorized by mortality. **B**, *A box plot* illustrating the differences among the same HRV measures when compared between COVID-19 and sepsis cohorts. AC = acceleration capacity, ApEn = approximate entropy, DC = deceleration capacity, NN = beat-to-beat interval, pNN50 = the proportion of consecutive RR intervals that differ by more than 50 ms, SampEn = sample entropy, SD1:SD2 = the ratio of standard deviation derived from the Poincaré plot.

in the low-frequency range [LF]:power in the high-frequency range [HF], power in very low frequency range [VLF], power in the ultra-low frequency range, LF, and HF) along with root mean square of successive differences (RMSSD), SD1:SD2 had moderate effect size (Cohen's $d > 0.5$).

Figure 1A illustrates a box plot of the six highly differentiating measures, with their respective distributions rendered by a violin plot, illustrating kernel density in the background. **Figure 1B** compares the same HRV markers without categorization by mortality. The COVID-19 cohort had generally lower pNN50, SampEn, ApEn, AC, beat-to-beat (mode), and SD1:SD2 than the sepsis cohort.

Figure 2A illustrates correlation matrix of each HRV measure value, correlations were observed among metrics relating to vagal tone (RMSSD, pNN50, HF, SD1). Nonlinear components consisting of SD1:SD2, SampEn, and ApEn were the most distinguishing factor between each subgroup and demonstrate a bimodal distribution within the COVID-19 survivors and nonsurvivors, which was not observed among the all-cause sepsis cohort.

AC and DC components were significantly different among the two broad groups, with COVID-19 groups having a lower DC but a greater AC median value compared with the sepsis groups. pNN50 in COVID 19 groups were on average lower in comparison to sepsis groups, where sepsis nonsurvivors had the largest pNN50 median. The correlation plot (Fig. 2A) further shows high correlations among the beat-to-beat (NN*) derived features and HRV components attributed to parasympathetic activity. AC shows negative correlation with many of the time-frequency and nonlinear features; however, no collinearity was found in ratios thought to represent sympathovagal balance (SD1:SD2, LF:HF, SampEn, ApEn). LF:HF ratio was found to have elevated median values between COVID-19 and all-cause sepsis; however, this is not distinguished when considering readings in nonsurvivors.

Figure 2B illustrates a chord diagram of the interactions among the HRV measures with statistical significance across COVID-19 and all-cause sepsis cohorts using the Kruskal-Wallis and Steel-Dwastests ($p < 0.01$). The three nonlinear measures, along with AC, DC, and NN (mode), had the greatest number of interactions (width of the link) among each of the four groups with a p value of less than 0.001. pNN50 had fewer strongly

significant interactions and could not differentiate COVID-19 nonsurvivors from survivors. SD1:SD2 had stronger statistical significance among sepsis survivors and COVID-19 nonsurvivors.

Temporal trajectories of values were accumulated over each 8-hour segment of data and projected from admission until day 5. **Figure 2C** illustrates the normalized temporal trajectories for the six most statistically significant HRV measures between the cohorts, the 95% CI is marked by the shaded region around each line. The mode of NN, pNN50, ApEn, and SampEn starts lower in the COVID-19 cohort and after 5 days remains lower than the sepsis cohort. While DC and SD1:SD2 begin higher in the COVID-19 cohort and end lower during the same timeframe. AC, DC, pNN50, NN (mode), the 95% CI is much tightly bound in COVID-19 patients. While among the nonlinear metrics, the 95% CI bound is much broader. Within all seven HRV measures, the sepsis cohort demonstrates dynamic fluctuations over their ICU stay that are not observed within the COVID-19 patients.

We further evaluated whether the differences observed within the HRV measures among COVID-19 patients and those with sepsis may be due to differences in clinical workflows or due to varying ICU length of stay. When analyzing data from only the first 8 hours of ICU stay, statistical significance ($p < 0.05$) was observed for differences across many of the same HRV measures (**Fig. 3**). The mode and IQR of the beat-to-beat variability were the most statistically significant ($p < 0.001$), followed by frequency domain features such as VLF, LF ($p < 0.01$). Entropy measures did not appear among the statistically significant, and pNN50 that was previously among the most statistically significant also did not appear in this evaluation. Standard deviation of successive RR intervals, AC, and DC measures were both included ($p < 0.05$).

DISCUSSION

By comparing retrospective cohorts of COVID-19 and non-COVID-19 all-cause sepsis patients, this study demonstrates a distinctively expressed subsets of nonlinear and time domain HRV measures. The results show statistical separation between sepsis and COVID-19 patients and also separates between survivors and nonsurvivors.

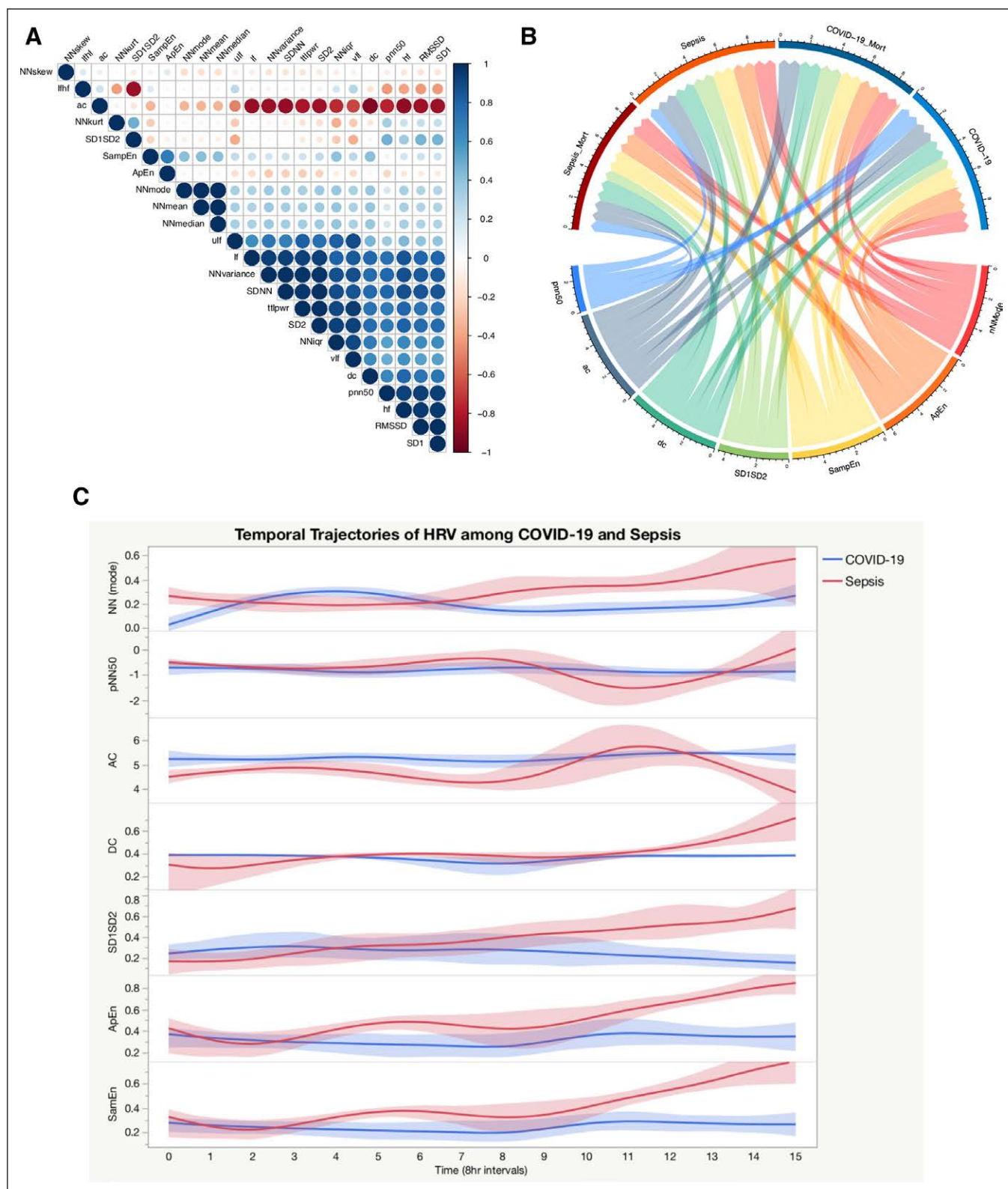


Figure 2. A, A correlation plot of all heart rate variability (HRV) measures, suggesting strong interactions between SDNN, pNN50, LF, VLF, and SD1, previously linked to parasympathetic components. **B**, A chord diagram illustrating interactions among HRV measures and the four unique classes of coronavirus disease 2019 (COVID-19) and sepsis survivors and nonsurvivors. The *upper* portion of the chord diagram lists the four subgroups, survivors and nonsurvivors of COVID-19 and sepsis. The *lower* portion illustrates the six HRV measures that demonstrated statistically significant separation between the groups. The size of the edge in the lower portion represents more statistically significant interactions across each group, along with the magnitude of the statistical significance, (*Continued*)

Figure 2. (Continued) i.e., $p < 0.001$ are weighted higher. **C**, Temporal trajectories among highly significant features distinguishing COVID-19 and sepsis cohorts. The 95% CI is illustrated as shades bounding each line. Unlike in the sepsis cohort, where a dynamic change is observed in these HRV measures, the COVID-19 group has more monotonic characterization. AC = acceleration capacity, ApEn = approximate entropy, DC = deceleration capacity, HF = power in the high-frequency range, LF = power in the low-frequency range, NN = beat-to-beat interval, pNN50 = the proportion of consecutive RR intervals that differ by more than 50 ms, RMSSD = root mean square of successive differences, SampEn = sample entropy, SD1:SD2 = the ratio of standard deviation derived from the Poincaré plot, ULF = power in the ultra-low frequency range, SDNN = standard deviation of successive RR intervals, VLF = power in very low frequency range.

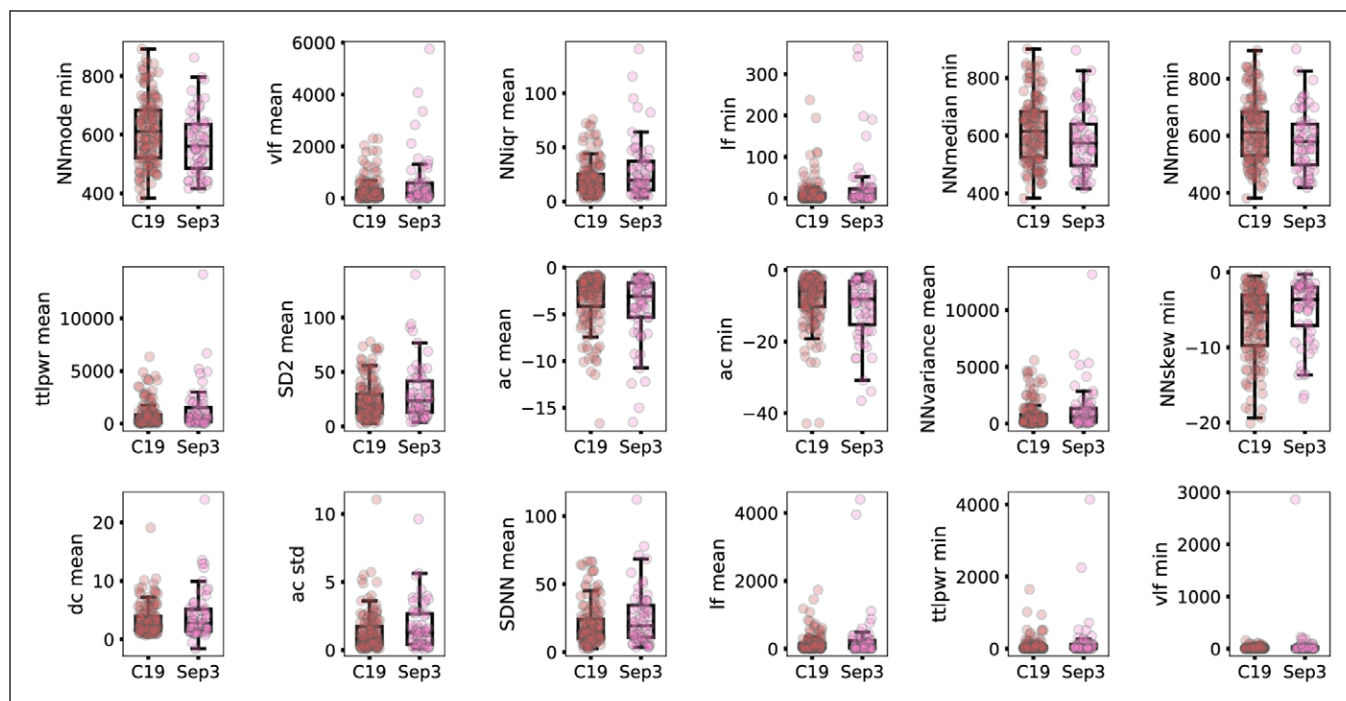


Figure 3. A box plot of select heart rate variability measures compared between coronavirus disease 2019 (COVID-19) and sepsis cohorts using data from the first 8 hr of ICU stay. These measures indicate similar overlap in statistical significance ($p < 0.05$) for beat-to-beat measures like beat-to-beat interval (NN) mode and interquartile range; however, the absence of entropy and pNN50, which appears to be more important later in the ICU stay. AC = acceleration capacity, DC = deceleration capacity, LF = power in the low-frequency range, min = minimum, pNN50 = the proportion of consecutive RR intervals that differ by more than 50 ms, SDNN = standard deviation of successive RR intervals, VLF = power in very low frequency range.

When comparing the differences of the cohorts from a demographic standpoint, there was statistical significance ($p < 0.05$) observed in race, with significantly more African Americans in the COVID-19 dataset, which is consistent with recent reports (26). There was no meaningful difference between mortality among ethnicities. No distinctive differences by sex were observed in outcomes, with about an equal number of male nonsurvivors (52%).

Out of the battery of HRV indices analyzed, only some were able to separate the groups (COVID-19 and sepsis) and subgroups (survivors and nonsurvivors) in

a statistically significant manner. The most statistically significant measure of HRV across multiple groups was ApEn, SampEn, and SD1:SD2. ApEn derived from methods of information theory is a measure of the degree of nonstationarity, and higher values indicate poor irregularity and thus suggest a poor parasympathetic tone. SampEn, is a similar measure of signal complexity as ApEn, however, a more robust one, when considering shorter observational time. Both SampEn and ApEn were lower in the COVID-19 cohort than in all-cause sepsis, indicating a reduced dynamic in heart rate modulation.

Of the significant time domain HRV indices we measured (Supplemental Table 2, <http://links.lww.com/CCX/A838>), pNN50, AC, DC, and NN (mode) strongly distinguished COVID-19 patients from all-cause sepsis. Cardiovascular complications within COVID-19 have been documented in many recent works (27–29). In our results, we see on average a greater NN value (lower heart rates) within COVID-19 patients when compared with all-cause sepsis. Apart from NN (mode), most beat-to-beat metrics show a higher baseline distance among COVID-19 patients. IQR of NN shows that COVID-19 profiles among survivors and nonsurvivors are closer to all-cause sepsis nonsurvivors indicating a potential increase in risk for mortality.

pNN50 has long been a predictor of poor cardiac physiology (30). In our analysis, we see that after day 2 (seventh block, pNN50, Fig. 2), the mean pNN50 distinguishes from earlier periods and has a distinct difference progressively during the ICU stay. COVID-19 seems to be significantly associated with decreased DC, while AC was higher (Fig. 1). Increased AC and decreased DC have specifically been shown to be predictive of mortality in myocardial infarction (31) and heart failure (32), and both AC and DC components were implicated in inflammatory mediation (33) and indicate significant vagal activation (34). In particular, decreased DC has been shown to be linked with impaired peripheral nervous system activity (35). Interestingly, evaluating temporal trajectories also emphasize distinct characteristics between the groups, while the trajectory of values among the COVID-19 group did not change significantly over time, in contrast, a greater degree of temporal dynamics was observed in the sepsis cohort (Fig. 2).

The ratio of SD1:SD2 derived from the Poincaré plot, a visual geometric measure of self-similarity in periodic functions. SD1 has been correlated with the baroreflex sensitivity and measures short-term changes modulated by respiratory sinus arrhythmia (RSA) associated with parasympathetic activity (36). The SD1:SD2 ratio is a measure of autonomic balance, whereby decreased SD1:SD2 ratio indicates an elevated sympathetic tone and suppressed parasympathetic activity (37). It was interesting to note that in our dataset, the COVID-19 group had a marginally higher SD1:SD2 ratio than all-cause sepsis, in contrast to findings from DC, pNN50, SampEn, and ApEn that indicate a lower

parasympathetic tone. An elevated SD1:SD2 may indicate a broad and complex dynamics between the sympathetic and parasympathetic arms and/or medication influence being reflected in COVID-19.

There are several pathophysiological explanations for the differences shown between COVID-19 and sepsis patients. One option relates to a direct cardiac injury. Indeed, cardiac manifestations in COVID-19 patients are common (5). A direct injury could theoretically damage the cardiac pacemaker or the conduction system, resulting in changes of HRV. A second option to be considered is an injury to the autonomic system. Many of the parameters found to differentiate the groups in this cohort were previously correlated with changes in the sympathovagal tone (12, 13). The level of neurotropism of SARS-CoV-2 remains unclear, and specifically whether or not it could invade parasympathetic fibers via the gastrointestinal tract or the lungs.

A third option could be related to the binding of SARS-CoV-2 to angiotensin-converting enzyme (ACE) 2, resulting in the loss of the protective pathway against a dysregulated autonomic system (38). The loss of ACE2 function has been associated with binding to the SARS-CoV-2 virus driven by endocytosis and initiation of the proteolytic cleavage and processing. ACE2 regulates the renin-angiotensin system (RAS) system by converting angiotensin I and angiotensin II into angiotensin 1–9 and angiotensin 1–7, respectively (39, 40). Loss of function of the ACE2 receptor, and thus an unregulated angiotensin II has been associated with hypertension and cardiovascular autonomic dysfunction (41). In a cohort of 12 COVID-19 patients, circulating angiotensin II was found to be significantly elevated when compared with controls and showed linear relationship with viral load (42). Angiotensin II exerts several actions on the sympathetic arm of the autonomic nervous system, facilitating increased sympathetic outflow and neurotransmission. It also acts on the baroreflex mechanism to modulate blood pressure (43, 44), and therefore by surrogate influence the cardiac non-stationarity. Finally, the targeting of the respiratory system by the SARS-CoV-2 virus impacts breathing rate, and thus the RSA, which in turn modulates high-frequency activities of the cardiac system.

Although it is plausible that the COVID-19 disease process would drive the HRV differences by one of the aforementioned means, there are other parameters that need to be further addressed. Notably, the COVID-19

cohort in this report had a higher Acute Physiology and Chronic Health Evaluation-II score, a higher rate of mechanically ventilated, and a higher rate of vasopressor use. These variables add complexity to this multifactorial analysis. The use of vasoactive agents, and especially catecholamine agents, are bound to have an effect on HRV to some extent due their direct sympathetic action (6). Degree of acuity and mechanical ventilation are likely to have an impact on HRV, via various mechanisms (e.g., inflammatory signaling related to acuity of illness and changes in intrathoracic pressure as a result of mechanical ventilation, respiratory variability), yet a direct impact was not clearly demonstrated yet (45). In order to further study the specific effect of these parameters, future studies will be required to better identify the impact of such variables on HRV in the general critically ill population and further in specific groups such as patients with sepsis and COVID-19.

The combination of the seven nonlinear and temporal HRV measures indicates potential sympathovagal imbalance within this pilot study, with various degrees of interaction between the sympathetic and parasympathetic arms. Among COVID-19 patients, there was more pathologic regularity observed both overall and temporally. This indicates potential suppressed parasympathetic activity that may be driven by interference with the RAS system. Parallel influences from respiratory components affecting the RSA further contribute to a dysfunctional autonomic regulation of the cardiac system. These cues, as shown within this analysis, can be distinctive between the cohorts, including between survivors and nonsurvivors, and therefore potentially predictive of mortality.

When we performed a sensitivity analysis consisting of only the first 8 hours of monitoring data, we found that the differences of 18 HRV markers were statistically significant (Fig. 3). Notably, some of the more pathologic measures of HRV, such as SampEn and pNN50, did not emerge as statistically different during the first 8 hours, while it was among the most significant features over the 5-day analysis period. This may be due to the worsening clinical status of the patient that may be observed for patients during more lengthy ICU stays, while patients who would have been discharged prior to the ICU stay may have had less pathologic ranges. Further evaluation is needed to fully understand the dynamics of these HRV measures as a function of ICU stay and various workflows.

There are a number of limitations of this study, including the fact that only 141 COVID-19 patients were eligible for inclusion. Furthermore, the analysis was performed on a cohort from multiple hospitals and units, yet still from a single health system in a single metropolitan. COVID-19-related mortality in our health system was lower than prior reports that could affect generalizability. This study was an observational cohort study performed retrospectively, and therefore causality analysis is limited. Specifically, this study did not examine the correlation between the HRV metrics and interventions used to treat the patients. Specifically, future focus should be on the influence of mechanical ventilation, sedation, and vasopressor. Additional work needs to be done to evaluate the performance of these measures prospectively. Developing methods to automatically capture these data and generate point-of-care biomarkers is an active area of ongoing work (46, 47).

CONCLUSIONS

HRV is broadly implicated across patients infected with SARS-CoV-2 and admitted to the ICU for critical illness. These biomarkers may suggest a degree of autonomic dysfunction that can be longitudinally expressed. Key subsets of measures were identified across time, frequency, and nonlinear domains. The results highlight potential biomarkers that could separate COVID-19 patients from all-cause sepsis patients. More importantly, these results prove preliminary data to allow early separation of survivors and nonsurvivors. Temporal trajectories of these markers further suggest significant decoupling as the disease progresses, with salient decoupling noticeable as early as at ICU admission. While the results of this study are early, we establish the premise that these higher dimensional features of heart rate can be associated with poor outcomes among COVID-19 patients.

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