



## Case Report

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# Heart rate variability follow-up during COVID-19 -a case report-

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**Background:** To detect an early increase in the inflammatory response might prove to be vital for mitigating the deleterious effects of the disease over time.

**Case:** A 52-year-old obese man with moderate asthma and hypertension, who developed COVID-19 and had moderate symptoms, used a wearable device to record heart rate variability (HRV) during his illness. He had low parasympathetic tone, which decreased daily until it reached almost 2 standard deviations (SD) below normal values at the end of the second week. His sympathetic tone increased from  $> 3$  SD to  $> 5$  SD.

**Conclusions:** These findings suggest an altered modulation of the sympathetic and parasympathetic nervous systems in COVID-19, such that the sympathetic tone is augmented and the parasympathetic tone is reduced. Population norms of COVID-19 infections should be further studied over the short-term and using 24 h HRV measurements.

**Keywords:** Ambulatory monitoring; Autonomic nervous system; Computer-assisted signal processing; COVID-19; Heart rate; Wearable electronic devices.

With the advent of wearable devices capable of easily measuring patients' respiratory rate, heart rate (HR), and heart rate variability (HRV), early signs of illness can potentially be identified. Patients' respiratory and HR are typically elevated by illness, whereas HRV is generally decreased [1].

Smart watches and wristbands are important accessories for fitness, but their application in healthcare is still in its early stages. Tanwar et al. [2] hypothesized that a consistent decline in the values of major HRV components could be attributed to the onset or worsening of SARS-CoV-2 infections.

Hasty et al. [3] reported that substantial decreases in HRV preceded elevations in C-reactive protein (CRP) levels in the ensuing 72 hours with a 90.9% positive predictive value and a 0.187 error rate (sensitivity: 83.3% and specificity: 75%). The ability to detect an early increase in the inflammatory response might prove to be vital for mitigating the deleterious effects of Coronavirus disease 2019 (COVID-19) over time. These authors demonstrated the potential value of short-segment intermittent HRV analyses in this patient population. However, there are very few studies in the literature related to HRV in patients with COVID-19, even though HRV has been identified as a useful noninvasive method for monitoring the clinical evolution of COVID-19.

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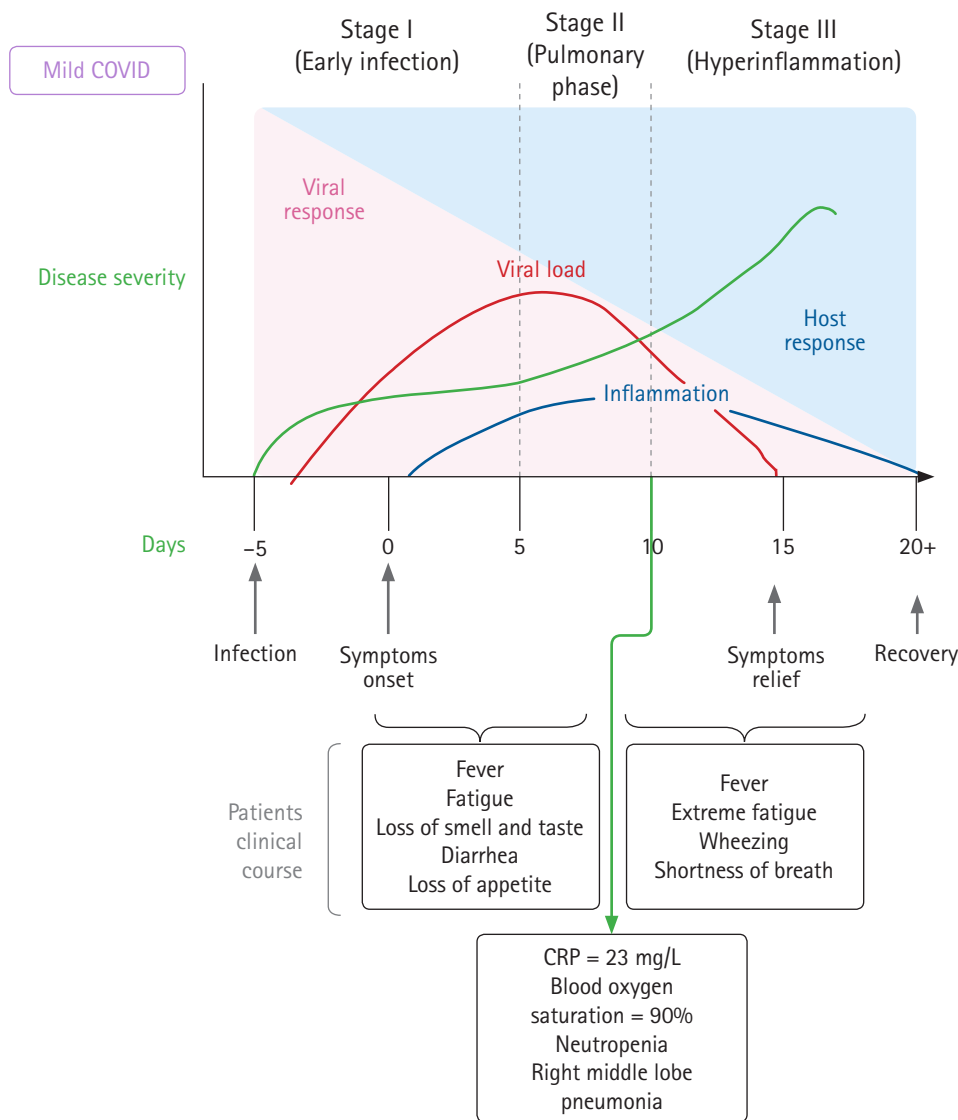
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In a prospective observational pilot study, Aragón-Benedí et al. [4] hypothesized that a depletion of the sympathetic nervous system and a predominance of parasympathetic activity reflected a compensatory anti-inflammatory response in severely ill COVID-19 patients.

We report the case of a 52-year-old patient with moderate asthma, hypertension, and obesity and a surgical history of a total thyroidectomy many years prior for a benign colloid goiter, who developed COVID-19 with moderate symptoms without the need for hospitalization. He used a wearable device (Polar 7<sup>®</sup>, developed by Polar Electro on 2007, USA) connected to a mobile application (CardioMood<sup>®</sup>, developed by CardioMood SA, Switzerland) to monitor HRV during his illness.

### Case Report

During the last few days of August 2020, the patient began experiencing symptoms and tested positive for COVID-19 using reverse transcription polymerase chain reaction. His symptoms started with fatigue, headache, body ache, and fever at approximately 38°C, followed by sore throat and congestion. He went to the hospital and was advised to maintain home isolation (Fig. 1). On the second day after the onset of symptoms, he lost his sense of smell and taste, had an immediate loss of appetite, and developed diarrhea. During the first week, all symptoms remained stable. By the morning of the sixth day, his fever had resolved. He had a fever relapse on day 7, along with extreme fatigue and diar-



**Fig. 1.** Patient clinical course. HRV was recorded from day 8 to 12 when symptoms worsened and the last record was on day 19, when the patient had almost recovered. CRP: C-reactive protein.

reha. By day 10, he developed wheezing and shortness of breath, which were evaluated in a hospital. Chest radiography showed an opacity in his right lung, his SaO<sub>2</sub> was 90%, and his laboratory results were altered, showing neutropenia and high CRP levels. He resumed his scheduled asthma treatment, though he was non-compliant and experienced multiple exacerbations. On day 11, his feet felt cold, and he reported paresthesia. He had a persistent fever of approximately 38°C. On day 12, his fever resolved spontaneously, and hospital admission was therefore not necessary.

He began monitoring his HRV during the second week of his illness, with a chest band device for HR monitoring (Polar 7<sup>®</sup>, developed by Polar Electro on 2007, USA). He had a mobile application and was able to obtain inter-beat intervals between all successive heartbeats (RR intervals). This device has been used for monitoring athlete training and have recently been validated for use in healthcare [5].

We obtained raw data (RR intervals) from measurements obtained during the second week of the patient's illness, when he had already been diagnosed with unilateral SARS-CoV-2 pneumonia, with a low-grade fever of approximately 38°C and an oxygen saturation of approximately 90%. Measurements were conducted at rest in the afternoon from days 8 to 12. Another measurement was performed a week later when home isolation was discontinued. The mobile application was used only for data collection. The Kubios<sup>®</sup> (Kubios Oy, Finland) standard software [6] (<https://pubmed.ncbi.nlm.nih.gov/24054542/>, cited by 458 articles by 2021) and ARTiiFACT<sup>®</sup> (developed by Tobias Kaufmann, Germany) software [7] (<https://pubmed.ncbi.nlm.nih.gov/21573720/>, cited by 74 articles by 2021), which have been cited by multiple previous reports, were used for HRV data analysis, and both yielded similar results. We also performed time-domain analysis using Python scripts to validate the results and to perform a visual exploratory analysis, plotting circles with the intent of showing the sympathetic nervous system (SNS) tone variations for each day. The working IPython notebook is available from <https://colab.research.google.com/drive/1qCL2tdfrdlejoXjsKVWQW9IEr-4Hxj0iR?usp=sharing>.

Normal distributions of data from each sample were tested and QQ plots (quantile-quantile: standard distribution quantiles vs. sample quantiles plot) were drawn using the ARTiiFACT<sup>®</sup> software (Fig. 2). All patient samples appeared to follow a normal Gaussian distribution, except for the sample from day 19, when it appears to be skewed to the left. This might have been caused by an artifact in the first few seconds of the sample (Fig. 3, day 19 sample).

The time series graphs of the RR intervals for each sample are

shown in Fig 3. The differences between the ill and normal states are immediately evident. The RR intervals were higher when the patient recovered.

## Discussion

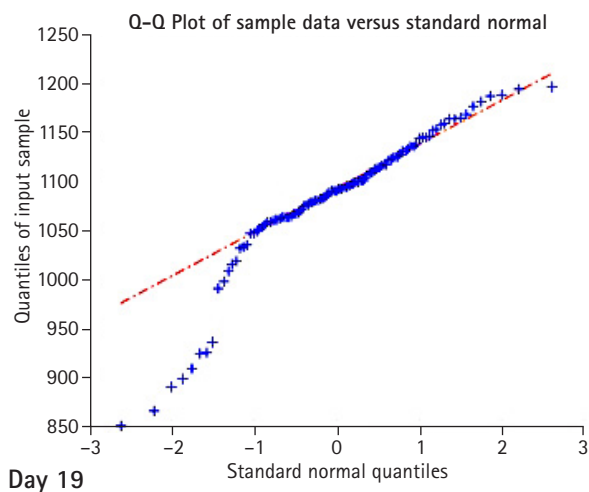
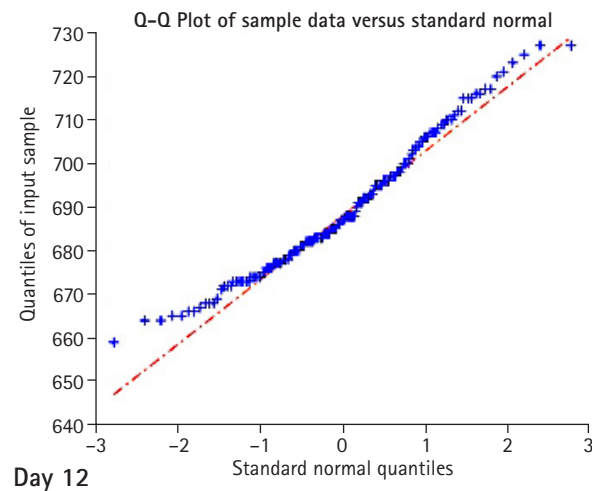
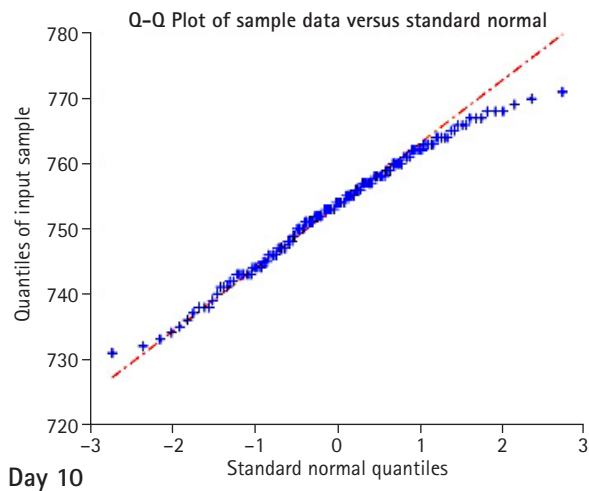
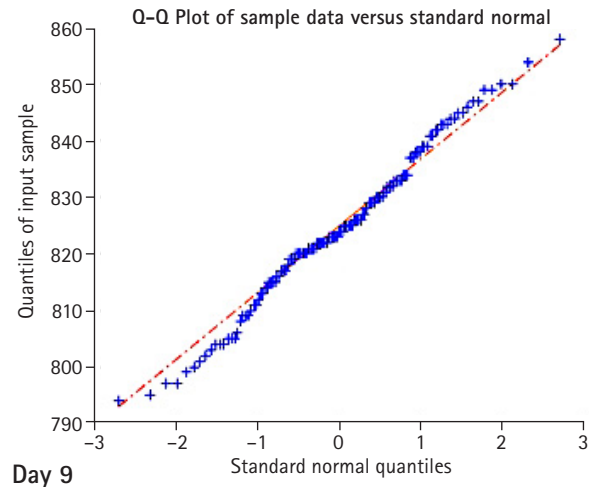
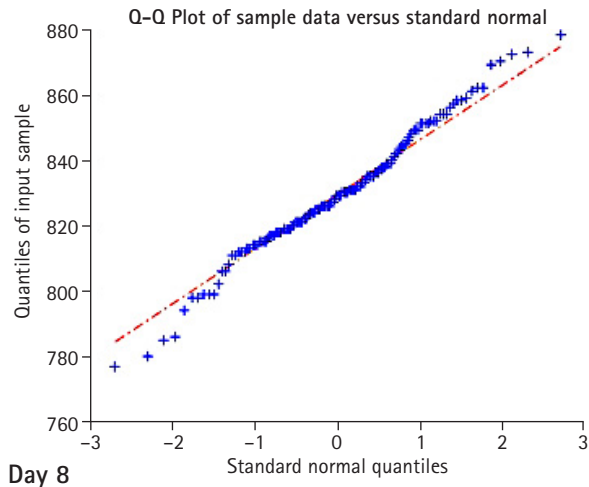
HRV is defined as the variation in the elapsed time between consecutive heartbeats, measured in milliseconds. A person's HRV is governed by two aspects of the autonomic nervous system: the sympathetic and parasympathetic branches [8].

The sympathetic branch regulates the body's reactions to mental and physical stress by releasing suitable hormones, thereby causing an increase in heart contractions and reducing HRV. Its counterpart, the parasympathetic branch, regulates the body when it must recover from a stressful state. To do this, the parasympathetic branch slows down the HR and thus increases HRV. Studies have shown that HRV can be used to predict morbidity caused by mental disorders such as depression and posttraumatic stress disorder or physical afflictions such as diabetes, concussions, and asthma. [9] Therefore, HRV is a good indicator of underlying health issues and is an important factor that can be used to reduce the likelihood of mortality.

Kleiger et al. [10] published a milestone study in the late 1980s that established HRV as an independent predictor of mortality in patients with acute myocardial infarction. For a historical perspective of HRV, refer to the comprehensive review conducted by Nicolini et al. [11].

In 1996, a consensus statement was issued by the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, specifying standards of measurement for time- and frequency-domain measures [12], providing a summary of the main HRV measures, and discussing methods of evaluation, duration of electrocardiogram (ECG) recording, and nomenclature. The duration of the recordings included in this case report was 2 min. There is evidence in the literature that 3 min recordings should be used for time- and frequency-domain methods, and 2 min recordings can be used for frequency-domain methods alone, although the task force recommended 5 min recordings. Recordings < 2 min are considered untrashort.

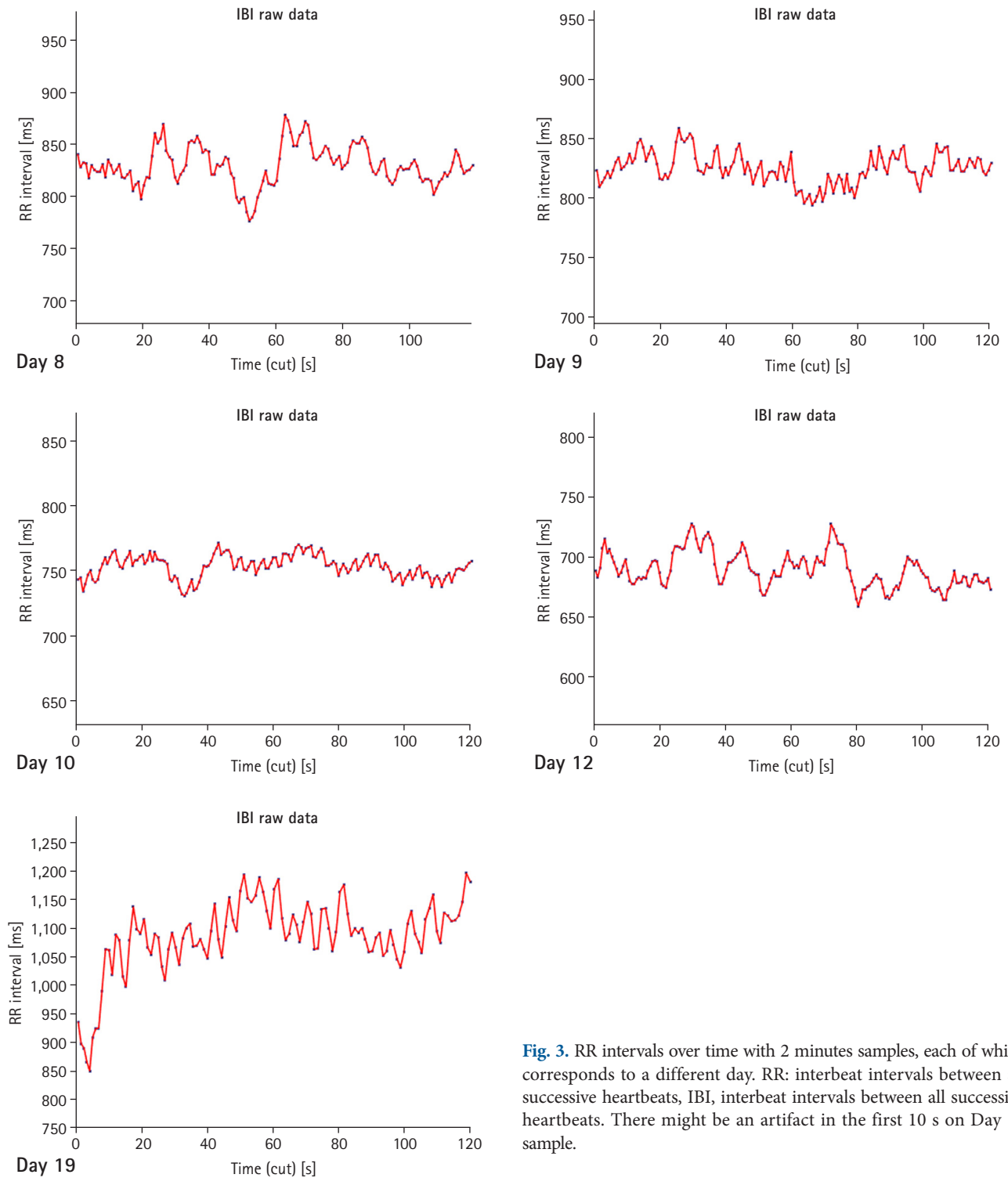
The discussion of HRV measurements has been centered on a reductionistic model of sympathovagal balance between the parasympathetic nervous system (PNS) and the SNS. The application of nonlinear dynamics to HRV calculations produces nonlinear measurements that might best capture system complexity. It is widely accepted that the SNS tone has an arrhythmogenic and pro-ischemic effect, while the PNS is protective. The concept of



**Fig. 2.** Q-Q Plot (quantile-quantile: standard distribution quantiles vs. sample quantiles plot). Q-Q Plot: quantile-quantile plot. Day 19 sample is skewed to the left (might be caused by an artifact in the first seconds of the sample. [Fig. 3., day 19 sample]).

autonomic modulation in a complex system is gaining support, although we will use a reductionist model centered on the autonomic tone and the heart to interpret our findings given the small number of measurements in this study. Time-domain calculations are used to quantify the variability between inter-beat intervals.

Optimal HRV is associated with health, adaptability, and resilience. HRV declines with age and increases with increased aerobic fitness. Women show relative PNS dominance, while men show relative SNS dominance. Autonomic nervous system dysfunction is a common systemic indicator of poor health [13].



**Fig. 3.** RR intervals over time with 2 minutes samples, each of which corresponds to a different day. RR: interbeat intervals between all successive heartbeats, IBI, interbeat intervals between all successive heartbeats. There might be an artifact in the first 10 s on Day 19 sample.

**Table 1** summarizes all our time-domain calculations using the ARTiiFACT<sup>®</sup> software. The mean RR interval shows parasympathetic cardiac activation when its value is higher. When actively ill with COVID-19, our patient had lower discharge values. All samples taking during the patient’s COVID-19 illness had similar mean RR intervals.

Results were similar regarding the root mean square of successive differences between RR intervals (RMSSD). This measurement reflects the beat-to-beat variation in HR, which is less influenced by respiratory sinus arrhythmia (RSA) than other time-domain parameters supposed to index vagal tone, and is used to estimate PNS-mediated changes in HRV. Our patient had

**Table 1.** Time and Frequency Domain Analysis Results Using ARTiiFACT Software

Parameters (unit)	Day 8	Day 9	Day 10	Day 12	Day 19	Reference values [14]			
	COVID-19 phase II				Recovered	Mean	SD	Median	Range
Mean RR (ms)	829.64	824.55	753.24	689.22	1083.01	926	90	933	785–1160
Median RR (ms)	829.00	824.00	754.00	687.00	1090.00				
Mean HR (bpm)	72.32	72.77	79.66	87.05	55.40				
SDNN (ms)	18.72	13.10	8.66	14.61	66.80	50	16	51	32–93
RMSSD (ms)	9.27	8.87	4.91	5.84	36.92	42	15	42	19–75
NN50 (ms)	0.00	0.00	0.00	0.00	23.00				
pNN50 (%)	0.00	0.00	0.00	0.00	20.72				
VLF (%)	59.38	63.14	40.89	43.34	56.49				
LF (%)	30.93	21.15	44.45	47.41	11.73				
HF (%)	9.69	15.72	14.66	9.24	31.78				
LF/HF (%)	3.19	1.35	3.03	5.13	0.37	2.8	2.6	2.1	1.1–11.6
LF [n.u.]	76.14	57.36	75.20	83.69	26.97	52	10	54	30–65
HF [n.u.]	23.86	42.64	24.80	16.31	73.03	40	10	38	16–60
VLF [abs] (ms <sup>2</sup> )	349.63	127.79	29.09	93.47	1250.27				
LF [abs] (ms <sup>2</sup> )	182.10	42.80	31.62	102.25	259.70	519	291	458	193–1009
HF [abs] (ms <sup>2</sup> )	57.08	31.81	10.43	19.93	703.39	657	777	385	82–3630
Recording length (s)	118.64	120.39	120.52	120.61	120.21				

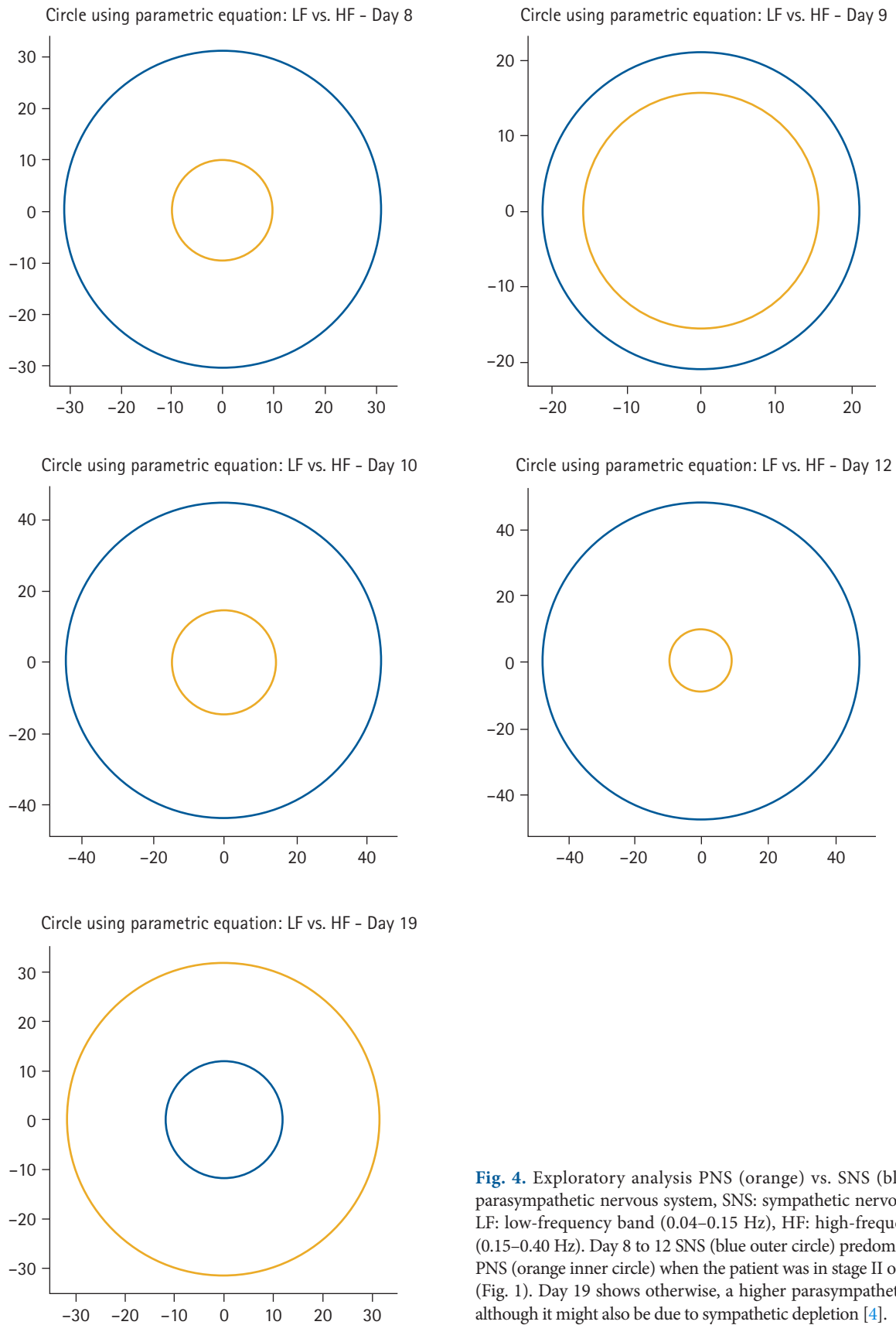
Absolute power is calculated as ms squared divided by cycles per second (ms<sup>2</sup>/Hz) and relative power is estimated as the percentage of total HRV power or in normal units (nu), which divides the absolute power for a specific frequency band by the summed absolute power of the LF and HF bands. This allows for a direct comparison of the frequency-domain measurements of two clients despite a wide variation in specific band power and total power among healthy, age-matched individuals. Inter-beat interval: time interval between successive heartbeats, NN intervals: inter-beat intervals from which artifacts have been removed, RR intervals: inter-beat intervals between all successive heartbeats, SD: standard deviation, HR: heart rate, SDNN: standard deviation of NN intervals, RMSSD: root mean square of successive interval differences, NN50: number of adjacent NN intervals that differ from each other by more than 50 ms (requires a 2-min epoch), pNN50: percentage of adjacent NN intervals that differ from each other by more than 50 ms, VLF: relative power of the very low-frequency band (0.0033–0.04 Hz), LF: relative power of the low-frequency band (0.04–0.15 Hz), HF: relative power of the high-frequency band (0.15–0.4 Hz), LF/HF: ratio of LF-to-HF power, LF [n.u.]: relative power of the low-frequency band in normal units, HF [n.u.]: relative power of the high-frequency band in normal units, VLF [abs]: absolute power of the very-low-frequency band, LF [abs]: absolute power of the low-frequency band, HF [abs]: absolute power of the high-frequency band.

a lower RMSSD when ill than when he had recovered. Our patient also had a lower standard deviation (SD) of normal-to-normal (NN) intervals (SDNN), which is the “gold standard” for medical stratification of cardiac risk since it is more accurate when calculated over a 24 h period. SDNN values < 50 ms are unhealthy or high risk, those between 50 and 100 ms indicate moderate risk, and values > 100 ms are considered normal. For short-term recordings taken at rest, the primary source of these variations is parasympathetically mediated respiratory baroreflex activity.

Frequency-domain measurements are used to estimate the distribution of the signal energy within four frequency bands, and are expressed as the relative or absolute power. The low-frequency band (LF: 0.04–0.15 Hz) is called the baroreceptor band because it reflects baroreceptor activity at resting conditions and is also influenced by low respiratory rates or deep breathing. The high-frequency band (HF: 0.15–0.40 Hz) is known as the respiratory band because it is influenced by RSA. It reflects PNS activity but cannot

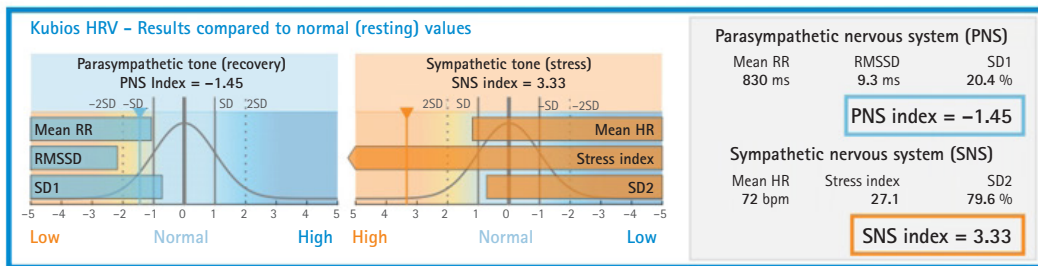
be considered a pure index of cardiac vagal control. It is highly correlated with time-domain measures, such as the RMSSD and the proportion of successive NN intervals > 50 ms (pNN50). Lower power of HF is correlated with stress, anxiety, or worry. The LF/HF ratio might be related to the SNS and PNS ratio, with a lower ratio reflecting PNS dominance and a higher ratio reflecting SNS dominance. Since this is a reductionist approach to the complex relationship between SNS and PNS, this assumption may be controversial. Our patient had higher LF values than HF values during his COVID-19 illness. The relationships between these two frequency-domain measurements are graphically summarized in Fig. 4. It is evident that the relationship was completely inverted when the patient had recovered.

Time-domain norms have been reviewed in previous short-term HRV studies and 24-h measurements [14]. These norms are used by the Kubios® software (developed by Kubios Oy, founded in 2016 in Kuopio, Finland as a spin-off company from University of Eastern Finland) to report results (Fig. 5). Our patient had a

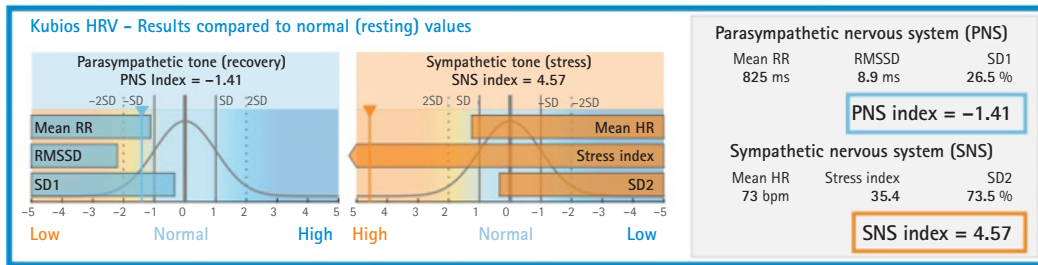


**Fig. 4.** Exploratory analysis PNS (orange) vs. SNS (blue). PNS: parasympathetic nervous system, SNS: sympathetic nervous system, LF: low-frequency band (0.04–0.15 Hz), HF: high-frequency band (0.15–0.40 Hz). Day 8 to 12 SNS (blue outer circle) predominates over PNS (orange inner circle) when the patient was in stage II of Covid-19 (Fig. 1). Day 19 shows otherwise, a higher parasympathetic activity, although it might also be due to sympathetic depletion [4].

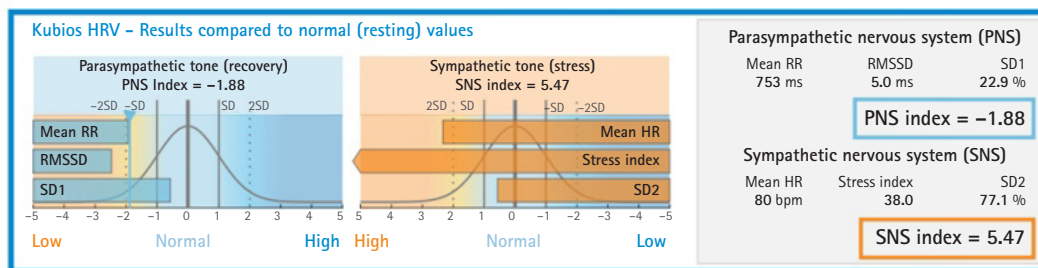
(A) Day 8 (fever, fatigue, lack of smell and taste, diarrhea)



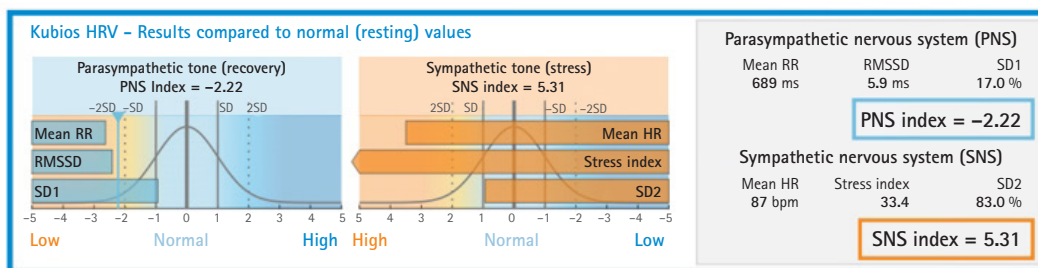
(B) Day 9 (fever, fatigue, lack of smell and taste, diarrhea)



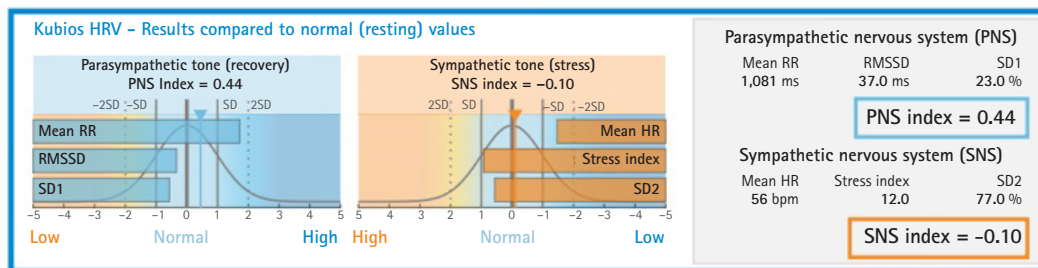
(C) Day 10 (fever, worsening of symptoms, hospital visit: CRP = 23 mg/L, SaO<sub>2</sub>=90%, neutropenia, right middle lobe pneumonia)



(D) Day 12 (fever, extreme fatigue, shortness of breath, wheezing)



(E) Day 19 (recovered)



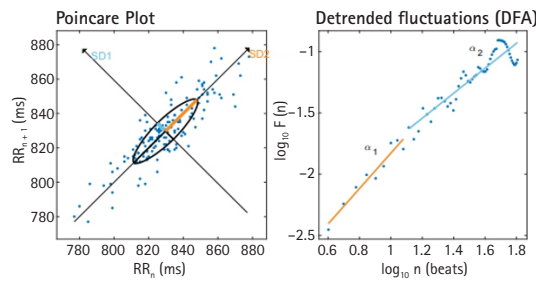
**Fig. 5.** Time-domain results using Kubios® software (2 min measurements). RR: interbeat intervals between all successive heartbeats, SD: standard deviations, HR: heart rate, RMSSD: root square of successive interval differences, PNS: parasympathetic branch of the nervous system, SNS: sympathetic branch of the nervous system, SD1: standard deviation (hence SD) of the distance of each point from the  $y = x$  axis, perpendicular to the line of identity, SD2: standard deviation of each point from the  $y = x + \text{average RR interval}$ , along the line of identity, Kubios software was developed by Kubios Oy, founded in 2016 in Kuopio, Finland as a spin-off company from University of Eastern Finland.



Day 8

Nonlinear results

Variable	Units	Value
Poincare Plot		
SD1	(ms)	6.6
SD2	(ms)	25.7
SD2/SD1		3.898
Approximate Entropy (ApEn)		0.819
Sample Entropy (SampEn)		1.482
Detrended Fluctuation Analysis (DFA)		
Short-term fluctuations, $\alpha_1$		1.447
Long-term fluctuations, $\alpha_2$		1.019

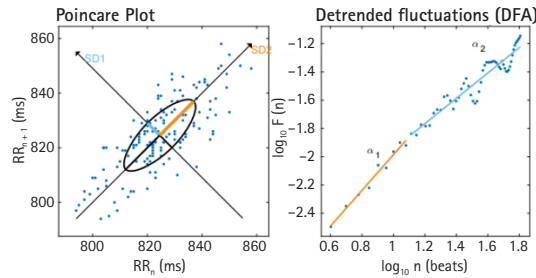


\* Results are calculated from the non-detrended selected RR series.

Day 9

Nonlinear results

Variable	Units	Value
Poincare Plot		
SD1	(ms)	6.3
SD2	(ms)	17.6
SD2/SD1		2.772
Approximate Entropy (ApEn)		0.851
Sample Entropy (SampEn)		2.054
Detrended Fluctuation Analysis (DFA)		
Short-term fluctuations, $\alpha_1$		1.265
Long-term fluctuations, $\alpha_2$		0.897

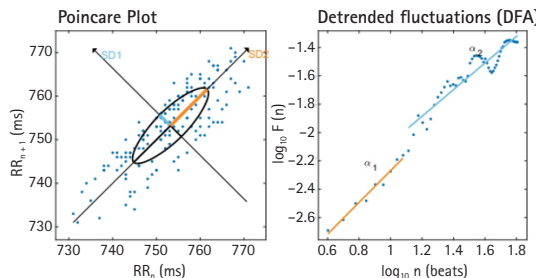


\* Results are calculated from the non-detrended selected RR series.

Day 10

Nonlinear results

Variable	Units	Value
Poincare Plot		
SD1	(ms)	3.5
SD2	(ms)	11.9
SD2/SD1		3.366
Approximate Entropy (ApEn)		0.812
Sample Entropy (SampEn)		1.635
Detrended Fluctuation Analysis (DFA)		
Short-term fluctuations, $\alpha_1$		1.119
Long-term fluctuations, $\alpha_2$		0.940

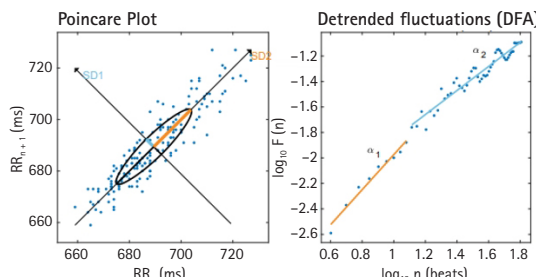


\* Results are calculated from the non-detrended selected RR series.

Day 12

Nonlinear results

Variable	Units	Value
Poincare Plot		
SD1	(ms)	4.2
SD2	(ms)	20.4
SD2/SD1		4.894
Approximate Entropy (ApEn)		0.833
Sample Entropy (SampEn)		1.362
Detrended Fluctuation Analysis (DFA)		
Short-term fluctuations, $\alpha_1$		1.376
Long-term fluctuations, $\alpha_2$		0.944

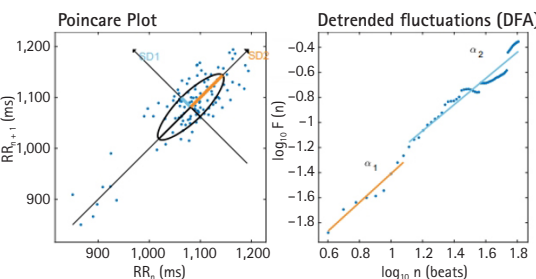


\* Results are calculated from the non-detrended selected RR series.

Day 19

Nonlinear results

Variable	Units	Value
Poincare Plot		
SD1	(ms)	26.3
SD2	(ms)	88.4
SD2/SD1		3.357
Approximate Entropy (ApEn)		0.792
Sample Entropy (SampEn)		1.469
Detrended Fluctuation Analysis (DFA)		
Short-term fluctuations, $\alpha_1$		1.148
Long-term fluctuations, $\alpha_2$		1.046



\* Results are calculated from the non-detrended selected RR series.

**Fig. 6.** Kubios®: Nonlinear Results. SD1, standard deviation (hence SD) of the distance of each point from the  $y = x$  axis, perpendicular to the line of identity; SD2: standard deviation of each point from the  $y = x + \text{average RR interval}$ , along the line of identity; Kubios software was developed by Kubios Oy, founded in 2016 in Kuopio, Finland as a spin-off company from University of Eastern Finland.

low parasympathetic tone during his COVID-19 illness, which decreased every day until it reached almost 2 SDs lower than normal at the end of the second week. Conversely, his sympathetic tone was very high and reached at > 3 SDs up to > 5 SDs from normal values. These results suggest that an alteration in the modulation of the SNS and PNS occurred, which apparently augmented sympathetic tone and decreased parasympathetic tone. The clinical value of short-term measurements of HRV in COVID-19 patients is yet to be established. However, in an observational pilot study of patients with COVID-19 on mechanical ventilation, Aragón-Benedí et al. [4] found that the normalized high frequency component (HFnu) was higher in the non-survivor group and was correlated with higher IL-6 levels. A cut-off value of 80 predicted mortalities with a sensitivity of 100%, specificity of 85.7%, positive predictive value of 87.5%, and negative predictive value of 100% was found. The non-survivor group had values > 80. The receiver operating characteristic curve demonstrated that the HFnu could predict mortality with an area under the curve of 0.980. Our patient had surpassed the threshold of 80 on day 12, although he did ultimately recover.

The medical stratification of cardiac risk was performed using 24 h HRV recordings. The results from the recordings that were < 5 min in length should be interpreted with caution and should not be compared with long recordings. The patient's values returned to normal one week after home isolation was discontinued (Fig. 5E).

Nonlinear measurements index the unpredictability of a time series. The Poincaré plot is a scatter plot of the RR interval against the prior interval. The area of the ellipse is the total HRV and is correlated with the baroreflex sensitivity, LF and HF power bands, and RMSSD. Researchers use it to visually search for patterns hidden within a time series. The SD of the distance of each point from the  $y = x$  axis, perpendicular to the line of identity (SD 1), and the SD of each point from the  $y = x + \text{average R-R interval}$ , along the line of identity (SD 2) values were much lower during the patient's illness than after recovery (Fig. 6). The SD 1/SD 2 ratio correlated with the LF/HF ratio.

Although we were able to obtain raw data from the CardiMood website (<https://www.cardiomood.com/>), we could only obtain the RR interval time series. Since we did not determine the sampling frequency rate, we were not able to replicate the same results using the RHRV package in R commander. The device we used was a photoplethysmography-based (PPG) biosensor, which is less accurate than ECG-based biosensors. Data were captured over a short period lasting 120 s, and the frequency-domain analyses may have been inaccurate for measurements < 300 s. According to Laborde et al. [15], a 5-min recording is recommended,

when possible, as it enables comparisons between clinical studies. Short-term values are only appropriate when a patient is breathing at a normal rate (11–20 bpm); however, we could not obtain data regarding the respiratory rate of our patient [13].

The value of HRV as a predictor of COVID-19 mortality is yet to be established. If HRV is considered a marker of autonomic nervous system modulation, the influence of erratic rhythm should be considered because it affects short-term time- and frequency-domain measures. Nonlinear measurements of HRV can detect a decrease in autonomic nervous system modulation and loss of complexity, which might imply a worse prognosis. Population norms should be further studied for patients with COVID-19 using short-term and 24 h HRV measurements. ECG-based wearable devices have been shown to be more accurate for HRV calculations than PPG-based devices, and some have been validated for clinical use [5]; therefore, we recommend their use in patients with COVID-19. These devices are widely available at a low cost and can be used to monitor the clinical evolution of patients with COVID-19 who are isolated at home. In desperate circumstances, where there is an insufficient number of hospital beds, this method might be useful for anticipating worsening symptoms and for admitting only those patients at risk of developing severe COVID-19 to the hospital. We strongly recommend further explorations of HRV in the COVID-19 population.

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## Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

## Author Contributions

Alejandro Figar Gutiérrez (Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Software; Writing – original draft; Writing – review & editing)

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