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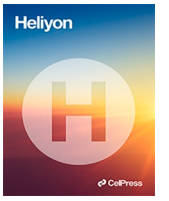

Research article

Heart rate variability and mortality in critically ill COVID-19 pneumonia patients

Chalermchai Komaenthammasophon [a,b], Monvasi Pachinburavan [a], Ronpichai Chokesuwattanaskul [b,c,*]

[a] Division of Critical Care Medicine, Department of Medicine, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand
[b] Division of Cardiology, Department of Medicine, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, Thailand
[c] Center of Excellence in Arrhythmia Research, Cardiac Center, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand

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ABSTRACT

Background: Heart rate variability (HRV) has prognostic value for predicting mortality in both cardiovascular and sepsis patients. Decreased HRV has been associated with increased mortality and morbidity. However, the prognostic significance of HRV in critically ill patients COVID-19 pneumonia still remains unknown. The current study aimed to (1) evaluate prognostic utility of HRV parameters on outcomes in patients with severe COVID-19 pneumonia and (2) assess the correlation between HRV parameters and inflammatory markers.

Methods: Consecutive critically ill patients with COVID-19 pneumonia admitted to a tertiary referral intensive care unit from October 2021 to June 2022 in Bangkok, Thailand were enrolled. HRV parameters over the 24 h following intensive care unit admission were recorded using telemetry and analyzed using the Holter program (Philips Holter 2010 Plus/1810 Series). Receiver-operating characteristic (ROC) curve analysis was used to determine optimum threshold cutoffs of various HRV parameters. Formal comparisons of in-hospital mortality between patients with and without a decrease in HRV were performed using Cox regression after adjusting for potential confounders.

Results: A total of 65 patients were enrolled in the study. Patients were classified into two groups: survivors (n = 44, 68 %) and non-survivors (n = 21, 32 %). The standard deviation of normal-to-normal intervals (SDNN) was significantly lower in non-survivors than in survivors (70.30 vs. 105.95; p = 0.03). The SDNN predicted in-hospital mortality with an area under the ROC curve of 0.67 (95 % CI 0.55–0.79). At a cutoff of 70 ms, the SDNN showed a sensitivity and specificity of 0.48 and 0.86. The low SDNN group (<70 ms) demonstrated higher median ferritin, IL-6, and hs-C-reactive protein levels than did the normal SDNN group, although such differences did not reach statistical significance (1139.0 vs. 508.4; p = 0.137 and 91.2 vs. 64.4; p = 0.352, respectively). After adjusting for potential confounders in the multivariable model, the adjusted hazard ratio for in-hospital mortality in those with SDNN <70 ms was 3.70 (95 % CI 1.34–10.24).

Conclusion: A decrease in SDNN, a commonly used HRV parameter, was associated with mortality and inflammatory biomarkers in critically ill patients with COVID-19 pneumonia.

* Corresponding author. King Chulalongkorn Memorial Hospital, Bangkok, Thailand.
E-mail addresses: c.komaen@gmail.com (C. Komaenthammasophon), monvasi@gmail.com (M. Pachinburavan), drronpichaic@gmail.com (R. Chokesuwattanaskul).

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1. Introduction

The corona virus disease 2019 (COVID-19) pandemic, caused by the SARS-CoV-2 coronavirus, has been one of the most challenging health care problems worldwide. Published studies have described clinical manifestations, intensive care unit (ICU) admission rates, and mortality rates across several countries. Differences in ICU admission and mortality rates between countries have been attributed to distinct epidemiologic profiles of patients, comorbidities, vaccination rates, and preparedness of each country in responding to the COVID-19 pandemic [1–3].

Since its introduction in 1965, heart rate variability (HRV) has been used to provide prognostic information for patients with both cardiovascular and non-cardiovascular conditions. HRV can be measured in three domains: a time domain, a frequency domain, and non-linear measures [4]. The time domain is the easiest to obtain and interpret. Time-domain parameters, such as the standard deviation of all normal-to-normal intervals (SDNN) and the standard deviation of the averages of normal-to-normal intervals (SDANN) in all 5-min segments of the entire recording can be measured using basic telemetry and Holter monitoring [5]. In chronic heart failure patients with a New York Heart Association class II–IV disease and median follow up time of 22 months, SDNN was independently associated with a 2.5-fold increase in the relative risk of death, irrespective of age and left ventricular ejection fraction [6]. Likewise, among bone marrow transplant patients, those with sepsis had lower HRV than did those with neutropenia alone without sepsis. In addition, alterations in HRV developed at an average of 35 h prior to signs and symptoms of sepsis [7].

Cytokine storm plays an important role in the severity of COVID-19 [8]. Dysregulated systemic and local tissue cytokines have been associated with the severity and symptoms of COVID-19. Moreover, fluctuating levels of inflammatory cytokines can affect the autonomic nervous system. HRV, which reflects autonomic nervous system activity, differed significantly between COVID-19-infected patients and healthy controls [9]. Furthermore, studies have shown an association between increasing C-reactive protein (CRP) levels and decreasing HRV in COVID-19 patients [10].

HRV has also been associated with the severity of COVID-19. Indeed, one study showed that SDANN and SDNN were significantly lower in patients with severe COVID-19 infection than in those without severe symptoms [9]. Moreover, longer delays before an increase in HRV was observed in the severe group were associated with a slower recovery from COVID-19 pneumonia [11]. Since HRV parameters are readily accessible in many clinical settings, detecting a decline in HRV could potentially aid in forecasting a worse prognosis for COVID-19 patients. Enhanced vigilance through closer monitoring and timely interventions may mitigate the rapid advancement of the disease. Also, data on the prognostic utility of HRV in ICU-admitted COVID-19 patient remains scarce.

The current study aimed to (1) evaluate prognostic performance of HRV parameters on clinical outcomes in patients with severe COVID-19 pneumonia and (2) assess the associations between HRV parameters and inflammatory markers.

2. Materials and methods

2.1. Patient population

This study was conducted at the ICU of King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Consecutive patients aged $\geq$18 years confirmed to have COVID-19 via reverse transcription-polymerase chain reaction and diagnosed with pneumonia via chest roentgenogram and/or chest computed tomography were eligible for inclusion. All included participants were mechanically ventilated or on high-flow nasal cannula. The exclusion criteria included pacemaker rhythm and persistent/permanent atrial fibrillation. Patients received standard therapy for severe covid-19 pneumonia, including systemic corticosteroid and supportive care. All patients received intravenous remdesivir. Concomitant care and all other interventions will be as directed by the treating clinician, including choice of sedative agent, depth of sedation, and use of neuromuscular blocking agents. Therefore, our patient cohort can be applicable to settings where patients receive both supportive and specific therapy for COVID-19, rather than solely supportive treatment. The study protocol and ethical considerations were approved by the institutional review board on human research (King Chulalongkorn Memorial Hospital IRB committee, approval No. 951/64.) A waiver of consent was granted by the institutional review board to work on de-identified data.

2.2. Electrocardiographic assessment

A digital 12-lead electrocardiogram (ECG) was acquired using continuous telemetry monitoring (Philips IntelliVue, The Netherlands). The standard default settings were a speed of 25 mm/s with a voltage of 10 mm/mV. ECG data were analyzed using the Holter program (Philips Holter 2010 Plus/1810 Series; Philips Medical Systems, MA, USA).

The SDNN, standard deviation of the averages of NN intervals in all 5-min segments of the entire recording (SDANN5), and root mean square of the sum of the squares of differences between adjacent normal-to-normal intervals (RMSSD) were computed and used as HRV parameters for primary analysis, according to European Society of Cardiology (ESC)/European Heart Rhythm Association (EHRA)/Asia Pacific Heart Rhythm Society (APHRS) recommendations [12].

Telemetry electrocardiogram monitoring was performed upon ICU admission using standard ICU monitors. HRV data derived from the dynamic ECG during the first 24 h following admission was extracted and analyzed. ECG telemetry data were reviewed by two experienced cardiologists blinded to the patient's diagnosis and outcome data. When conflicting interpretations in ECG rhythm discordance analysis emerged, a third physician blinded to clinical data was brought in to adjudicate.

2.3. Sample size determination

Using Freedman's method, we hypothesized that a >25 % reduction in HRV parameters would be found in approximately one third of enrolled patients and that the survival probability would be 30 % in this group and 70 % in the group with no decrease in HRV. Under these assumptions, enrolling 64 patients would provide 90 % power to detect a hazard ratio (HR) of 3.4 or greater at a two-sided significance level of 5 %.

2.4. Outcomes

The primary study outcome was in-hospital mortality in patients with severe COVID-19 pneumonia after ICU admission. Secondary outcomes were ICU-free days at 28 days, ventilator-free days (VFDs) at 28 days, ICU length of stay (ICULOS), hospital length of stay (HosLOS), total positive pressure ventilation days (PPVD), and plasma concentrations of inflammatory markers hs-CRP, ferritin, and IL-6.

2.5. Statistical analysis

After dividing the participants into two groups, namely survivors and non-survivors, baseline demographic data were compared. Categorical variables were reported as frequency (percentage) and compared using Fisher's exact or a chi-square test as appropriate. Continuous variables were expressed as mean ± SD or median (25th to 75th percentile) and compared using an independent *t*-test or a Wilcoxon rank sum test as appropriate. Receiver-operating characteristic (ROC) curves were constructed to assess the association between each HRV parameter and in-hospital mortality. The optimum cutoff point for further evaluation was determined by selecting the nearest point to the top right-hand corner on the ROC curve. The area under the resulting ROC curve at this dichotomized point was used to determine the ability of HRV to predict mortality. Associations between the selected cutoff point in HRV and mortality were then evaluated using the Kaplan–Meier method and compared using a log-rank test. Cox regression was used to calculate the relative

Table 1
Baseline characteristics. Data are presented as mean ± SD, median (Q1-Q3), or N (%).

Baseline characteristics	All participants (n = 65)	Survivors (n = 44)	Non-survivors (n = 21)	p value
Age, year	68 ± 18.0	67 ± 18.6	68 ± 17.1	0.84
Male sex, n (%)	37 (56.9)	20 (45.5)	17 (80.9)	0.01
BMI (kg/m^2)	24.54 ± 7.13	25.96 ± 7.71	21.57 ± 4.64	0.02
Comorbidity, n (%)				
Diabetes mellitus	27 (41.5)	17 (38.6)	10 (47.6)	0.49
Hypertension	36 (55.4)	26 (59.1)	10 (47.6)	0.38
Dyslipidemia	34 (52.3)	22 (50.0)	12 (57.1)	0.59
Lung disease	10 (15.4)	6 (19.0)	4 (13.6)	0.72
Active cancer	10 (15.4)	4(9.1)	6 (28.6)	0.07
Prior CAD	11 (16.9)	8 (18.2)	3 (14.3)	1.00
Previous MI	11 (16.9)	8 (18.2)	3 (14.3)	1.00
Previous PCI	6 (9.2)	5 (11.4)	1 (4.8)	0.66
Prior Stroke	18 (27.7)	10 (38.1)	8 (22.7)	0.20
CKD				
GFR < 60	25 (38.5)	17 (38.6)	8 (38.1)	0.97
Dialysis dependent	7 (10.8)	5 (11.4)	2 (9.5)	1.00
NYHA class III or IV, n (%)	16 (24.6)	12 (27.3)	4 (19)	0.55
APACHE II score	14.06 ± 5.16	13.27 ± 5.26	15.71 ± 4.64	0.07
SOFA score	5.00 ± 2.59	4.66 ± 2.57	5.71 ± 2.55	0.13
PF ratio, median (Q1-Q3)	182.0 (124.0–273.8)	203.4 (137.5–284.1)	155.0 (120.5–233.0)	0.19
Inotropic drug, n (%)	28 (43.1)	14 (31.8)	14 (66.7)	0.008
AKI	22 (33.8)	10 (22.7)	12 (57.1)	0.006
Inflammatory biomarkers				
Ferritin, median (Q1-Q3)	601.0 (243.0–1,598.0)	437.6 (147.0–885.3)	1,440.5 (1,044.5–5,880)	<0.001
IL-6, median(Q1-Q3)	63.3 (14.5–270.0)	37.1 (8.6–174.4)	107.2 (38.7–1,401.5)	0.01
hs-CRP, median (Q1-Q3)	73.9 (21.1–166.7)	53.4 (12.7–139.4)	102.21 (71.0–193.0)	0.01
Treatment, n (%)				
Methylprednisolone	29 (44.6)	19 (43.2)	10 (47.6)	0.73
Dexamethasone	57 (87.7)	38 (90.5)	19 (86.4)	1.00
Anticoagulant	32 (49.2)	20 (45.5)	12 (57.1)	0.38
Muscle relaxant	20 (30.8)	9 (20.5)	11 (52.4)	0.01
Propofol	24 (36.9)	11 (25.0)	13 (61.9)	<0.001
Opioid	39 (60.0)	20 (45.5)	19 (90.5)	<0.001
Gaba-agonist	25 (38.5)	13 (29.5)	12 (57.1)	0.03
Lactate	2.24 ± 1.67	2.05 ± 1.84	2.66 ± 1.15	0.18
Albumin	3.08 ± 0.54	3.17 ± 0.56	2.88 ± 0.43	0.04

Abbreviation: AKI = acute kidney injury; BMI = body mass index; CAD = coronary artery disease; CKD = chronic kidney disease; GFR = glomerular filtration rate; MI = myocardial infarction; NYHA= The New York Heart Association; PCI = percutaneous coronary intervention.

risk of mortality in those with reduced HRV, and adjusted models were developed to assess how potential confounders influenced the mortality risk associated with HRV. All analyses began upon ICU admission. Patients who did not die were censored upon hospital discharge. Analyses were performed using IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. and Stata Statistical Software: Release 17, College Station, TX: StataCorp LLC., with a two-sided p value of <0.05 indicating statistical significance.

3. Results

A total of 78 subjects were screened. After the excluding 13 patients with atrial fibrillation, 65 participants were enrolled in the study. The mean (SD) age of study participants was 68 (17.1) years, among whom 56.9 % were men. Moreover, 21 (32.3 %) patients died in the hospital and were classified as non-survivors. Baseline demographic, comorbidities and clinical characteristics in survivors and non-survivors are summarized in Table 1. Age was comparable between survivors and non-survivors. Non-survivors comprised significantly more males and had a significantly lower body mass index than did survivors. Common comorbidities were well-balanced in both groups. Non-survivors had higher levels of inflammatory biomarkers, especially ferritin, and lactate than did survivors. Disease severity represented by the APACHEII score, SOFA score, and PF ratio did not differ between the groups. All key clinical and outcome variables have no missing data.

3.1. HRV and mortality

We then determined the association between mortality and HRV parameters SDNN, SDANN5, and RMSSD. SDNN, one of the most commonly used HRV parameters, was significantly lower in non-survivors than in survivors (70.3 vs. 105.95; $p = 0.03$). All other HRV parameters were lower in non-survivors, albeit not significantly (Table 2).

3.2. Prognostic performance of SDNN

Using ROC curve analysis (Fig. 1), we determined that a cutoff of SDNN of 70 ms was the optimal threshold, with an AUC of 0.67 (95 % CI 0.55–0.79), a sensitivity of 0.47, and specificity of 0.86 for mortality prediction. As shown in Fig. 2, patients with a SDNN <70 ms had significantly higher in-hospital all-cause mortality rates than did those with a SDNN >70 ms (log-rank $p = 0.01$).

In Cox regression models, those with a SDNN <70 ms had a HR of 2.78 (95 % CI 1.17–6.59) for in-hospital mortality. After adjusting for other potential confounding clinical factors, the adjusted HR was 3.7 (95 % CI 1.34–10.24; $p = 0.01$; Table 3).

The variables in the Cox regression models were age, sex, patient with cardiac disease, use of inotropic drugs, and AKI status. These parameters were selected by using the p value less than 0.05 from univariate analysis. In order to demonstrate the reliability of the outcome, we conduct regression analysis by varying the independent variable to examine the correlation between HRV and mortality. When modifying the model with a different set of covariates, the association between low SDNN and higher mortality rates remains evident compared to patients with high SDNN. The Cox regression model with different independent variables in addition to HRV is shown in Supplementary Table 1.

3.3. SDNN and secondary outcome

For secondary clinical outcomes, no significant difference was observed in ICU-free days at 28 days, ICULOS, HosLOS, VFDs at 28 days, and total PPVD between the SDNN <70 ms and SDNN ≥ 70 ms groups. The median, 25th and 75th percentile values of ferritin, IL-6 and hs-CRP were all higher in SDNN <70 ms group but these differences were not statistically significant (Table 4).

4. Discussion

Our study demonstrated an association between SDNN and mortality in patients with severe COVID-19 pneumonia. All HRV parameters (SDNN, SDANN5, and RMSSD) were lower in non-survivors than in survivors. Our results showed that SDNN was the HRV parameter that best predicted mortality in patients with severe COVID-19 pneumonia. A 24-h SDNN of <70 ms was associated with a higher mortality rate among patients with severe COVID-19 pneumonia. Moreover, the low SDNN group showed higher levels of inflammatory markers than did the high SDDN group.

The integration of the renin–angiotensin system with ACE2 enzyme residing within the brain stem influences baroreflex sensitivity. Indeed, studies have shown that SARS-CoV-2, which invades the host brainstem cell by affixing to ACE2 and altering angiotensin II (Ag II) to angiotensin concentration ratio, can alter baroreflex sensitivity [10,13–15]. HRV parameters can indicate viral proteins in the

Table 2
Median (Q1-Q3) heart rate variability parameters among the participants grouped according to mortality.

HRV parameters	All participants (n = 65)	Survivors (n = 44)	Non-survivors (n = 21)	p value
SDNN (msec)	99.4 (68.10–135.20)	105.95 (84.58–141.55)	70.30 (42.95–113.50)	0.03
SDANN5 (msec)	76.9 (45.25–103.55)	82.0 (57.33–106.25)	51.50 (38.45–95.70)	0.08
RMSSD (msec)	51.7 (28.75–121.25)	55.65 (34.70–117.15)	39.50 (22.05–131.10)	0.30

Abbreviation: msec = millisecond.

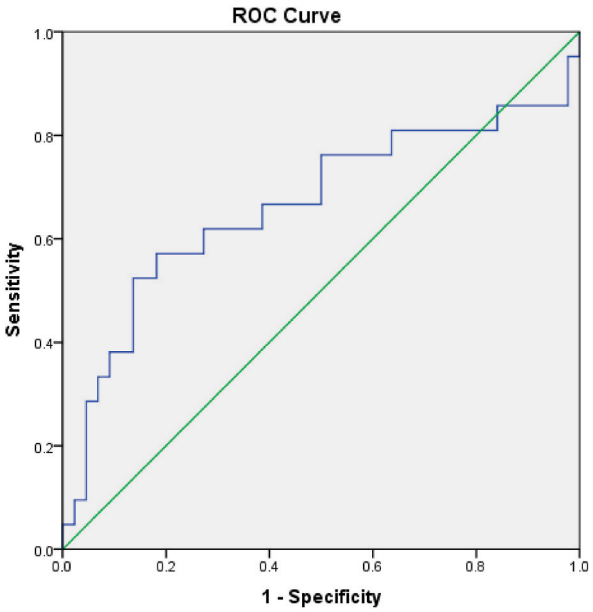

Fig. 1. ROC curve for the ability of SDNN to predict mortality.

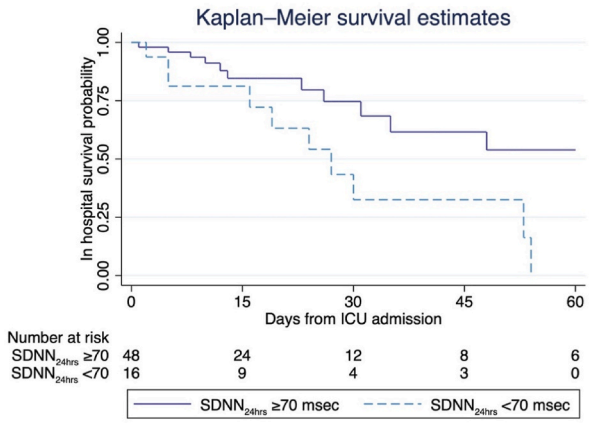

Fig. 2. Kaplan–Meier curve showing survival probability in study participants with a SDNN ≥70 or <70 ms in the 24 h following ICU admission.

Table 3
Univariable and multivariable hazard ratios for factors associated with in-hospital mortality using Cox regression. APACHE II score was not modeled given that AKI is a component of the score.

	Univariable		Multivariable	
Characteristic	HR (95 % CI)	p	HR (95 % CI)	p
SDNN <70 ms	3.69 (1.33–10.21)	0.01	3.70 (1.34–10.24)	0.01
Male vs. female	2.89 (0.97–8.6)	0.06	4.83 (1.37–17.08)	0.02
BMI (per km/m^2 increase)	0.91 (0.84–0.98)	0.01	0.91 (0.82–1.01)	0.07
Active cancer	2.33 (0.9–6.04)	0.08	4.58 (1.31–15.97)	0.02
AKI	2.4 (1.01–5.72)	0.048	7.87 (2.16–28.59)	0.002
Albumin (per 1 g/dL increase)	0.22 (0.08–0.62)	0.004	0.23 (0.06–0.86)	0.03

brainstem that affect baroreflex sensitivity. Changes in HRV usually preceded clinical signs [16]. HRV reflects the autonomic modulation of heart rhythm and frequency [17]. In fact, reduced HRV has been observed in patients with autonomic dysfunction, mental disorders, and critical illnesses. Moreover, low HRV indicates reduced ability to adaptively respond to illness [18]. Due to the aforementioned reasons, not only direct invasion by SARS-CoV-2 into the central autonomic nervous system, but also the results of

Table 4
Secondary outcomes overall and by SDNN group.

Outcome	Total	SDNN <70 (n = 16)	SDNN ≥70 (n = 49)	p value
ICU-free day at 28 day, median (IQR)	14 (0–24)	0 (0–23.75)	17.0 (0–24.5)	0.14
HosLOS, median (IQR)	17 (10–30.5)	18.0 (9.25–29.50)	17.0 (10.0–32.0)	0.95
28VFD, median (IQR)	28 (4.5–28)	22.0 (1.75–28.0)	28.0 (10.0–28.0)	0.27
Total PPVD, median (IQR)	9 (4.5–24)	11.5 (5.25–26.25)	9.0 (4.0–22.5)	0.74
Ferritin, median (IQR)	601.0 (243.0–1598.0)	1139.0 (601.0–2492)	508.4 (192.9–1466.8)	0.14
IL-6, median (IQR)	63.3 (14.5–270.0)	104.9 (18.7–327.3)	54.7 (14.4–270.0)	0.61
hs-CRP, median (IQR)	73.9 (21.1–166.7)	91.2 (41.2–193.9)	64.4 (19.1–138.8)	0.35

Abbreviation: LOS = length of stay; PPVD = positive pressure ventilation days; VFD = ventilatory-free days.

inflammatory cytokines are the presumptive mechanism for HRV alterations. Therefore, HRV can be used as a surrogate for impaired autonomic function and be associated with poor clinical outcomes in critically ill patients.

To discover the interplay between HRV, measured using 20-min ECG monitoring, and COVID-19 infection, Gruionu et al. compared HRV in three groups of patients: those hospitalized for COVID-19, those with cardiovascular disease, and healthy volunteers. Notably, they demonstrated that HRV in patients with COVID-19 was similar to that observed in cardiovascular disease patients but different from that observed in healthy volunteers [19]. COVID-19 patients had a higher HRV and time-domain HRV variables, including SDRR, RMSSD, and SDSD compared to those with healthy volunteers. A distinct feature of the current study is that we included more severe COVID patients and performed longer telemetry monitoring than did Gruionu et al. The longer monitoring period in our study allows us to determine the actual HRV spectrum that can sometimes have a diurnal variation. The brief HRV monitoring period in the study by Gruionu et al. might not have eliminated the confounding influence of diurnal HRV pattern.

Our study has several strengths. First, this has been the first study to investigate the association between HRV and mortality, as well as the prognostic characteristics of various HRV parameters, in patients with severe COVID-19 pneumonia. Secondly, in terms of clinical application, HRV is a non-invasive modality that is part of routine care for critically ill patients; hence, it incurs no additional cost. The proposed cutoff can be adopted into routine practice to guide clinicians in determining which patients should be more closely monitored given that changes in HRV are a harbinger of clinical deterioration. In addition, HRV parameters were obtained only from telemetry without direct patient exposure. Therefore, health care workers had no COVID-19 exposure risk throughout the study period. Lastly, the information provided by the current study can serve as a basis for future studies aiming to assess the relationship between other viral infections and HRV to predict clinical outcomes. Furthermore, our enrolled subjects had higher mortality rates (33 %) than did those included in recent clinical trials, which reported a mortality rate of approximately 20%–30 % [20,21]. The high-risk patients included in our study emphasizes the utility of HRV changes as a prognostic marker in the critically ill population.

Our study has a major limitation that is noteworthy. The number of participants was rather small (65 patients) given that we selectively enrolled very critically ill patients, leading to insufficient statistical power for measuring some secondary clinical outcomes and subjecting to unmeasured confounders. The generalizability of this study may be limited to those who are critically ill patients. However, despite the small number of subjects, our result can still demonstrate the obvious HRV alteration in severe COVID-19 pneumonia patients. Another limitation is that this study did not exclude cardiac patients and patients on inotropic and/or vasopressor which could affect HRV parameters. However, multivariate analysis still showed HRV robustness after adjusting for all possible clinical confounders.

In conclusion, the current study found that a decrease in HRV parameters (SDNN) was significantly associated with higher mortality rates in severe COVID-19 pneumonia patients. Moreover, a decrease in HRV parameters (SDNN) was associated with increasing inflammatory markers, particularly hs-CRP.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article. For more detailed data including protocol and individual data set of this study are available on request from the corresponding author, [Chokesuwattanaskul R.] upon reasonable request. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Ethics declarations statements

This study was reviewed and approved by The Institutional Review Board of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand with the approval number COA No. 0089/2022.

Informed consent was not required for this study because working on only de-identified data and observational study without any intervention to the patients.

CRediT authorship contribution statement

Chalermchai Komaenthammasophon: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Monvasi Pachinburavan:** Validation, Supervision, Conceptualization. **Ronpichai Chokesuwattanaskul:** Writing – review & editing, Writing –

original draft, Supervision, Project administration, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34842.

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