Ultrashort Heart Rate Variability for Early Risk Stratification in Pneumonia Patients: Preliminary Analysis

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ABSTRACT **Background:** Pneumonia patients are susceptible to autonomic nervous system changes. Ultrashort heart rate variability (usHRV) is the measurement of cyclic changes in heart rate over a period < 5 minutes.

Objectives: To describe usHRV in patients with pneumonia and assess the correlation with mortality.

Methods: We conducted a retrospective analysis, which included patients diagnosed with pneumonia in the emergency department (ED). UsHRV indices were calculated from a 10-second ED electrocardiogram and correlated with mortality utilizing logistic and Cox regressions.

Results: The study comprised 240 patients. Mortality rates over 30, 90, and 365 days were 13%, 18%, and 30%, respectively. usHRV frequency-domain parameters had significant univariate correlations with mortality. Normalized low frequency (LF) and high frequency (HF) were correlated with 30-, 90-, and 365-day mortality in an opposite direction (odds ratio [OR] 0.094, $P = 0.028$ vs. OR 4.589, $P = 0.064$; OR 0.052, $P = 0.002$ vs. OR 6.975, $P = 0.008$; OR 0.055, $P < 0.001$ vs. OR 7.931, $P < 0.001$; respectively). Survival analysis was conducted for a follow-up median period of 5.86 years (interquartile range 0.65–9.77 years). Univariate Cox proportional hazard regression revealed time-domain indices with significant correlation with survival (SDNN and RMSSD; hazard ratio [HR] 1.005, 1.005; $P = 0.032$, $P = 0.005$; respectively) as well as frequency-domain parameters (normalized LF, HF, LF/HF ratio, and total power; HR 0.102, 5.002, 0.683, 0.997, respectively; $P < 0.001$).

Conclusions: usHRV may predict mortality in pneumonia patients and serve as a novel risk stratification tool.

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KEY WORDS: autonomic nervous system, emergency department, heart rate variability, pneumonia, risk stratification

Pneumonia is a respiratory infectious disease of the lung's parenchyma and is the leading cause of visits to the emergency department (ED) among infectious diseases. In the United States, pneumonia is the third leading cause of hospital admissions, responsible for 544,000 hospitalizations annually. Despite improved diagnostic and management strategies, the mortality rate has remained steady for the last several decades [1].

Pneumonia may present with nonspecific electrocardiogram changes, such as T-wave inversion or deflection of the ST segment, as well as electrocardiogram alterations, similar to those described in pulmonary embolism [2]. Heart rate regulation is controlled by the autonomic nervous system (ANS), which is significantly affected by respiration. Heart rate variability (HRV) represents the changes in time intervals between consecutive heartbeats and has been shown to be a method for ANS activity quantification [3]. The evaluation of the HRV can be performed on various lengths of time: long-term (24 hours), short-term (5 minutes), and ultrashort-HRV ([usHRV] under 5 minutes), with short-term HRV considered the gold standard [4]. Long-term HRV studies have demonstrated correlations between all-cause mortality and heart attacks, strokes, and sepsis [5-7].

HRV analysis has focused on time and frequency domain indices. The time-domain supplies quantification measurement of variability of the sinus interbeat interval and the amount of it in a fixed measure of time. Standard deviation of interbeat interval between consecutive NN beats (SDNN) is calculated by sinus beats after removal of irregular sinus beats and is mainly affected by the activity of the sympathetic and parasympathetic nervous system. In short-term analysis, the origin of the SDNN variability is derived from parasympathetic activity, which is the result of respiratory sinus arrhythmia (RSA) [3,8]. RSA reflects the activity and synchronization of HRV with respiratory

which, in normal physiological condition, affects gas exchange via perfusion/ventilation matching [9]. Root mean square of successive difference between normal heart beats (RMSSD) reflects the variation between heartbeats and provides evaluation to vagal tone changes. This parameter is greatly affected by the parasympathetic ANS more than SDNN, and less affected by respiration [3,10].

Frequency-domain represents the quantification of the relative ratio of the particular changes in the HRV wave. Low frequency (LF), the area between 0.04 and 0.15 Hz, reflects the activity of baro-receptors and is influenced by both sympathetic and parasympathetic nervous systems, as well as the baro-reflex. High frequency (HF), the area between 0.15 and 0.40 Hz, reflects the activity of parasympathetic system and represents the parameter for sinus diversity related to respiration. In exhalation, the vagus nerve is inhibited, which causes an increase in heart rate. In contrast, in inhalation acetylcholine is secreted, which leads to re-excitation of vagus nerve and results in a decrease in heart rate. The LF/HF ratio attempts to represent the relation between the sympathetic and parasympathetic nervous systems [3,10].

Confusion, urea, respiratory rate, blood pressure and age over 65 (CURB-65), pneumonia severity index (PSI), and severe community acquired pneumonia (SCAP) scores have been utilized worldwide in the ED setting as prognostic tools for patients presenting with community acquired pneumonia. Notably, the one year-community acquired pneumonia severity index (CAPSI) score has shown superiority over CURB-65, PSI, and SCAP as an ED prognostic tool [11].

The role of HRV as a method for risk stratification in pneumonia patients has recently been examined in coronavirus disease 2019 (COVID-19) pneumonia patients, with short-term low HRV (SDNN and RMSSD) predicting both survival and the need for intensive care unit admission in the first week after presentation in the ED [12]. In patients with sepsis, a high (≥ 1) LF/HF ratio showed better survival-over-time when compared with low (< 1) LF/HF ratio [13]. HRV has been assessed in patients with systemic sclerosis and demonstrated impairment in cardiac autonomic function [14]. Additional studies dealing with the relationship between HRV, particularly usHRV, and pneumonia are scarce. We aimed to describe usHRV in patients with pneumonia and evaluate their prognostic significance.

PATIENTS AND METHODS

STUDY DESIGN AND POPULATION

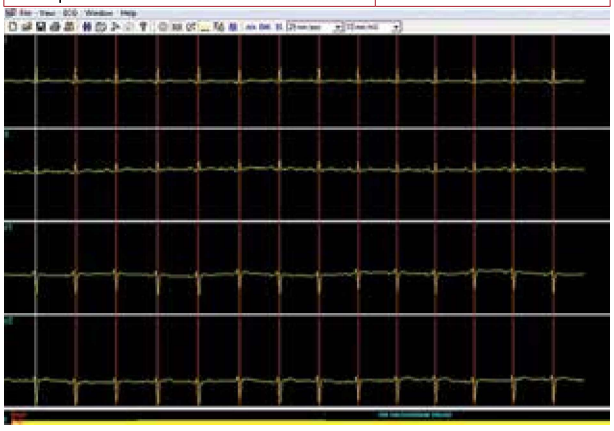
We conducted a retrospective single center analysis based on the Rambam Health Care Campus (Haifa, Israel) database of all ED visits during the years 2010–2015. Patients aged 18 years and older who were diagnosed with pneumonia based on clinical, laboratory, and radiographic findings, were considered. Excluded were patients who did not have an usHRV record from their ED visit, as well as electrocardiograms with irregular heartbeats (e.g., atrial fibrillation or flutter, premature beats) or low resolution. The institutional review board approved this study (approval key 0603-16-RMB). Since all the data were retrospectively collected, individual informed consent was not required.

DATA COLLECTION

All ED visits and discharge letters from the study period were screened for a diagnosis of pneumonia, utilizing MDClone (Beer-Sheva, Israel) computer software. Medical records of potential eligible patients were reviewed to verify eligibility. Patient demographics as well as ED vital signs, including blood pressure, pulse, oxygen saturation, and temperature were obtained. Patient mental status and respiratory distress were documented based on ED physician reports. Laboratory results, including complete blood count and chemistry panel were also assessed. Patient's date of death, if prior to data acquisition (June 2019) was collected with the MDClone software. Electrocardiograms were recorded with Norav Medical electrocardiogram LAN mobile wireless system [Figure 1].

Figure 1. Heart rate variability measurement

HRV result	Results
Time domain	
RR#	13
Max RR (ms)	714
Min RR (ms)	664
Average RR (ms)	684
Average HR (bpm)	87
SDNN (ms)	15.90
SDANN (ms)	–
RMSSD (ms)	10.21
HRV trangle indes	4.33
NN50	0.00
pNN50	0.00
Frequency domain	Power (ms^2)
ULF (0–0.003 Hz)	–
VLF (0.003–0.04 Hz)	–
LF (0.04–0.15 Hz)	484.60
HF (0.15–0.4 Hz)	130.21
Total power	721.10



ELECTROCARDIOGRAM AND HRV ANALYSIS

Patients arrived at the Rambam ED and underwent a 10-second resting electrocardiogram (LAN Green–Mobile wireless model; Norav Medical, Yokneam, Israel) while lying motionless in a supine position for at least 30 seconds. The electrocardiogram electrodes were placed in anatomical positions according to standard procedure using a designated precordial electrocardiogram lead positioning system (Tapuz Medical, Caesarea, Israel). Resting electrocardiogram files were visualized with a viewing software (Resting electrocardiogram version 5.62, Norav Medical) and analyzed with a custom version of the HRV analysis software able to import 10 second recording (HRV version 5.62). usHRV parameters, were computed automatically utilizing this software. In addition, electrocardiograms were manually checked and recordings with disturbances, which could potentially affect accurate measurement of usHRV, such as excessive noise, low resolution, and sudden baseline instability or spikes, were excluded from the analysis. This study focused on average, minimal, and maximal RR intervals, as well as linear time-domain variables (including SDNN, RMSSD, and HTI). Frequency-domain parameters, representing the area under the spectral peaks within 0.04–0.15 Hz (LF), 0.15–0.4 Hz (HF), and 0.01–0.4 Hz (total power [TP]), were also considered. Both absolute (ms^2) and normalized LF and HF components were evaluated (e.g., HF (normalized unit [nu]) = absolute HF/TP).

ENDPOINTS

Outcomes included all-cause mortality, within 30 and 90 days, as well as 1 year. Survival analysis was also performed.

STATISTICAL ANALYSIS

The study database was analyzed with R software, version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria). Comparisons between groups were performed with Mann-Whitney U or Fisher's exact tests. Correlations between variables and outcomes were assessed with univariate logistic regression (LR) and presented as odds ratio (OR) with *P* values. Survival analysis was performed with Cox regression. $P < 0.05$ was considered significant.

RESULTS

Of 4764 patients diagnosed at Rambam's ED with pneumonia within the study period, 350 were randomly selected; 110/350 were excluded due to incomplete medical records or missing

Table 1. Study population characteristics, in relation to emergency department discharge status

	Hospitalized (n=182)	Discharged (n=58)	*P*-value
Age (years)	67.14 ± 17.05	52.80 ± 18.74	**< 0.001**
Sex: male	124 (68.13%)	39 (67.24%)	> 0.999
Ethnicity: Jewish	109 (78.99%)	36 (81.82%)	0.830
Hospital acquired pneumonia	70 (38.46%)	8 (13.79%)	**< 0.001**
Systolic BP (mmHg)	134.92 ± 26.64	136.84 ± 22.54	0.327
Diastolic BP (mmHg)	74.01 ± 13.07	80.07 ± 16.44	**0.016**
Pulse (beats per minute)	95.06 ± 18.90	86.17 ± 17.87	**0.004**
Temperature (PO; °C)	37.25 ± 0.83	37.18 ± 0.69	0.752
Room air saturation (%)	93.32 ± 5.01	95.70 ± 3.45	**< 0.001**
Respiratory distress	90 (49.45%)	11 (18.97%)	**< 0.001**
Altered mental status	22 (12.09%)	4 (6.90%)	0.338
WBC (10^3/μl)	14.35 ± 9.43	10.84 ± 4.08	**0.008**
Hemoglobin (g/dl)	12.03 ± 2.04	13.20 ± 1.81	**< 0.001**
Platelets (10^3/μl)	258.02 ± 133.02	249.42 ± 91.34	0.961
Glucose (mg/dl)	156.98 ± 89.37	118.43 ± 45.82	**< 0.001**
Sodium (mmol/L)	136.20 ± 5.62	137.03 ± 2.85	**0.018**
Creatinine (mg/dl)	1.50 ± 1.72	1.05 ± 0.76	**0.001**
BUN (mg/dl)	28.22 ± 24.63	16.38 ± 7.59	**< 0.001**
Unilateral consolidation on chest X-ray	152 (83.52%)	45 (77.59%)	0.328
PR (ms)	165.55 ± 40.36	155.38 ± 35.58	0.059
QRS (ms)	89.24 ± 17.68	88.07 ± 13.83	0.988
QTC (ms)	433.30 ± 32.33	414.93 ± 25.31	**< 0.001**

BP = blood pressure, BUN = Blood urea nitrogen, PO = Per Os, WBC = white blood cell count

Bold signifies statistical significance

Table 2. All-cause mortality univariate logistic regression: 30, 90, 365 days

	30-day		90-day		365-day	
	Odds ratio (95% confidence interval)	*P*-value	Odds ratio (95% confidence interval)	*P*-value	Odds ratio (95% confidence interval)	*P*-value
Maximal RR (ms)	0.997 (0.994–1.000)	0.077	0.998 (0.995–1.000)	0.108	0.999 (0.997–1.001)	0.513
Minimal RR (ms)	0.997 (0.994–1.000)	0.074	0.997 (0.994–0.999	0.059	0.998 (0.996–1.000)	0.295
Average RR (ms)	0.997 (0.993–1.000)	0.068	0.997 (0.994–1.000)	0.066	0.998 (0.996–1.000)	0.297
SDNN (ms)	0.994 (0.971–1.009)	0.567	0.998 (0.982–1.010)	0.842	1.001 (0.990–1.011)	0.789
RMSSD (ms)	0.996 (0.979–1.006)	0.601	0.999 (0.988–1.008)	0.981	1.001 (0.993–1.008)	0.754
HTI	0.948 (0.749–1.143)	0.617	0.975 (0.806–1.145)	0.777	0.929 (0.790–1.072)	0.341
LF absolute (ms^2)	0.997 (0.993–1.000)	0.131	0.995 (0.992–0.998)	**0.013**	0.996 (0.993–0.998)	**0.004**
HF absolute (ms^2)	0.996 (0.991–1.000)	0.064	0.997 (0.993–1.000)	0.099	1.000 (0.997–1.002)	0.935
LF normalized (nu)	0.094 (0.010–0.728)	**0.028**	0.052 (0.007–0.331)	**0.002**	0.055 (0.011–0.253)	**< 0.001**
HF normalized (nu)	4.589 (0.956–24.674)	0.064	6.975 (1.715–31.344)	**0.008**	7.931 (2.463–27.230)	**< 0.001**
LF/HF ratio	0.943 (0.681–1.188)	0.673	0.819 (0.576–1.057)	0.193	0.712 (0.518–0.916)	**0.019**
Total power (ms^2)	0.997 (0.995–0.999)	**0.038**	0.997 (0.995–0.999)	**0.005**	0.998 (0.996–0.999)	**0.020**

HF = high frequency, HTI = HRV triangular index: integral of the NN interval histogram divided by the height of the histogram, LF = low frequency, RMSSD = root mean square of successive differences between normal heartbeats; RR = interval between two R waves; SDNN = standard deviation of interbeat interval between consecutive NN beats
Bold signifies statistical significance

Table 3. Survival analysis, univariate Cox proportional hazard regression

Variable	Hazard ratio	95% confidence interval		*P*-value
		Low	*High*	
Maximal RR (ms)	1.000	0.999	1.001	0.891
Minimal RR (ms)	0.999	0.998	1.001	0.263
Average RR (ms)	0.999	0.998	1.001	0.542
SDNN	1.005	1.000	1.011	**0.032**
RMSSD	1.005	1.001	1.009	0.005
HTI	1.032	0.951	1.120	0.447
LF absolute (ms^2)	0.995	0.993	0.997	**< 0.001**
HF absolute (ms^2)	0.998	0.996	1.000	0.071
LF normalized (nu)	0.102	0.040	0.259	**< 0.001**
HF normalized (nu)	5.002	2.423	10.330	**< 0.001**
LF/HF ratio	0.683	0.559	0.835	**< 0.001**
Total power (ms^2)	0.997	0.996	0.998	**< 0.001**

HF = high frequency, HTI = HRV triangular index: integral of the NN interval histogram divided by the height of the histogram, LF = low frequency, RMSSD = root mean square of successive differences between normal heartbeats, RR = interval between two R waves, SDNN = standard deviation of interbeat interval between consecutive NN beats
Bold signifies statistical significance

electrocardiogram tracings as well as irregular electrocardiogram rhythm. The final study cohort included 240 patients, with a male majority (68%); 61% of patients were Jewish, 15% Arab, and 24% of other ethnicity; 189 (79%) were categorized as community acquired while the remaining 21%, as healthcare acquired; 182 patients required hospitalization for in-patient antibiotic treatment. Patient clinical, laboratory, radiographic, and electrocardiographic parameters, in relation to hospital admission status, are detailed in Table 1.

Thirty-one (13%) patients died within 30 days, while 43 (18%) died up to 90 days after diagnosis (all-cause mortality). After 1 year of follow-up, 73 patients (30% of the study population) had died. Univariate LR analysis of usHRV parameters is detailed in Table 2. Notably, several frequency domain indices, were found to be significantly correlated with mortality. For 30-day mortality, normalized LF and TP had significant correlations (OR 0.094, 0.997; $P = 0.028$, 0.039; respectively). Regarding 90-day mortality, absolute, and normalized LF (OR 0.995, 0.052; $P = 0.013$, 0.002), as well as normalized HF and TP (OR 6.975, 0.997; $P = 0.008$, 0.005; respectively), were found to have significant correlations. Last, as for 1-year all-cause mortality, similar frequency-domain parameters, with the addition of LF/HF ratio (OR 0.712, $P = 0.019$), were found to have statistically significant correlations.

Survival analysis was conducted for a follow-up median period of 5.86 years (interquartile range 0.65–9.77 years). Univariate Cox proportional hazard regression for usHRV indices is presented in table 3. Noticeably, in addition to frequency-domain parameters, time-domain indices were also found to have significant correlation with survival (SDNN and RMSSD; hazard ratio 1.005, 1.005; $P = 0.032$, 0.005; respectively).

DISCUSSION

In this retrospective study of patients arriving at the ED with pneumonia, we found several usHRV parameters obtained from 10-second ED electrocardiograms, which correlated with 30-day, 90-day, and 1-year all-cause mortality. Specifically, frequency-domain indices, including LF (normalized) and TP were associated with decreased risk of mortality. HF (normalized) was associated with increased risk of mortality in 90 days and 1 year.

Furthermore, in a median follow up of 5.86 years, survival was correlated with LF, HF, LF\HF ratio and TP, as well as time-domain indices, SDNN and RMSSD.

Multiple studies have identified several mortality risk factors for patients with pneumonia, including age, race, sex, co-morbidities, severity of illness and type of pneumonia [15].

Infectious disease in general and pneumonia in particular are associated with a balance of pro- and anti-inflammatory processes, leading to the immune response. Pneumonia causes fever, tachypnea, tachycardia, and hypoxia, which reflect sympathetic modulation leading to expected alteration in HRV.

RSA is HRV in synchrony with respiration and has been used as an index for vagal activity along with SDNN [9]. The association between HRV and respiration function, has been documented in a study of patients presenting with obstructive sleep apnea (OSA). LF and the LF/HF ratio have been found to be increased in severe OSA, while HF decreased. These findings are in alliance with our results and may indicate the sympathetic activity is dominant in both the day and the night [16]. It might be explained by constant hypoxia at night and fatigue during the day.

A systematic review and meta-analysis of HRV and inflammation proposes, which indices of HRV, specifically SDNN, and HF, can be used to index activity of the neurophysiological pathway responsible for adaptive regulating inflammatory processes in human [17,18].

SDNN and HF have been shown to be independent predictors of sepsis and septic shock severity [19]. SDNN has also been demonstrated to be a risk factor for death in septic patients, even after adjusting for severity scores [20]. Additional studies have shown particular alteration and dysfunction of ANS in ICU patients presenting with multiple organ dysfunction syndrome (MODS) [21]. Similar to our results, admission HRV was found to be a good marker of infected pancreatic necrosis, MODS, and severe acute pancreatitis [22].

LIMITATIONS

Our study had several limitations. First, we had no proper documentation of respiratory rate at presentation, which has an effect on the ANS. Second, our research was a single center retrospective analysis. Last, co-morbidities such as congestive heart failure, ischemic heart disease, chronic lung diseases, and other clinical conditions known to affect the HRV analysis, as well as drugs such as beta-blockers, calcium channel blockers, and inotropic drugs, were not considered.

CONCLUSIONS

Our study is one of the first to report the correlation between HRV and patients with pneumonia. Particular usHRV indices, specifically frequency-domain, might be utilized as a prognostic tool in pneumonia patients on ED presentation. These preliminary results will be assessed in a more robust study, to both validate the risk stratification method and improve it.

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Capsule

A tumorigenic infection

The tumor-associated microbiome can contribute to tumor development and progression. **Udayasuryan** and colleagues found that *Fusobacterium nucleatum*, an oral commensal that can become an opportunistic pathogen, promotes tumor progression-associated activity in pancreatic ductal adenocarcinoma (PDAC) cells. Infection with *F. nucleatum* induced the release of cytokines that promoted proliferation, migration, and invasion in human PDAC cell lines, but not in normal human pancreatic epithelial cells. An antibody targeting one of the secreted cytokines inhibited the proliferation of PDAC cells.

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Capsule

Gut disease and bone loss

Inflammatory bowel disease represents a group of disorders marked by chronic inflammation of the gastrointestinal tract. In many individuals, this disease can also affect parts of the body outside of the gut, including the skin, kidneys, liver, and bone. **Peek** and colleagues investigated the association between systemic inflammation and bone loss using mouse models of gastrointestinal inflammation. The authors found increased numbers of osteoclast precursor cells, the cells that initiate bone eating and remodeling, and pro-osteoclastogenic cytokines within the bone. Alterations in cell surface receptors involved in osteoclast function, including the pro-osteoclastogenic co-receptor myeloid DNAX activation protein 12-associating lectin (MDL-1), provided a therapeutic target for monoclonal antibodies. Treating mice with antibodies reduced osteoclast numbers and the bone loss associated with intestinal inflammation.

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