Early detection of patient deterioration in patients with infection or sepsis

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Chapter 8

48-hour continuous heart rate variability as early warning for patient deterioration in emergency department patients with sepsis: preliminary results of the SepsiVit study.

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ABSTRACT

BACKGROUND

One in five patients presenting to the emergency department (ED) with infection or sepsis deteriorate. However, how deterioration can be detected early remains unknown. Continuous heart rate variability (HRV) analysis has the potential to detect whether a patient is progressing towards deterioration. The objective of the SepsiVit study was to evaluate whether continuous HRV measurement during the first 48 hours of hospitalization could provide an early warning signal for patient deterioration.

METHODS

We performed this prospective observational study in adult patients presenting with suspected infection or sepsis to the ED of our tertiary care teaching hospital. Patients with at least two systemic inflammatory response syndrome (SIRS) criteria were included. The patient's ECG signal was continuously recorded during the first 48 hours of hospitalization using a mobile bedside patient monitor (Philips IntelliVue MP70). HRV features in time, frequency and non-linear domains were calculated from the raw ECG signal. The primary outcome was patient deterioration within 72 hours from admission, defined as the development of acute kidney injury, liver failure, respiratory failure, intensive care unit admission or in-hospital mortality. We analyzed the data from an outcome-oriented and a data-driven perspective. For the latter, we used group-based trajectory modeling to analyze the trajectories emerging from the 48-hour HRV features in relation to the primary outcome.

PRELIMINARY RESULTS

122 patients were included between January 2017 and May 15, 2018, of which 24 patients were excluded because of insufficient measurements. The remaining 98 patients were used in the analysis; 38% of these patients deteriorated. On average 16 hours of the recorded data was suitable for HRV analysis; patient discomfort from the wires between patient and bedside monitor caused early dropout. From the outcome-oriented perspective, deteriorating patients had less variability in the time and non-linear domains and higher normalized high frequency (HF_{norm}) components and lower normalized low frequency (LF_{norm}) components. The data-driven perspective confirmed that trajectories with less variability were associated with a higher risk of patient deterioration. Overall, the HF_{norm} model was the best predictor of patient deterioration.

PRELIMINARY CONCLUSIONS

Deteriorating patients showed different trajectories in HRV features during the first 48 hours of hospitalization compared to non-deteriorating patients. A lower HRV was associated with an increased risk of patient deterioration. The frequency domain features best distinguished between deterioration and non-deterioration, especially the HF_{norm}. After validation of our results in the completed cohort of 171 patients, clinical application of continuous HRV analysis would require wearable monitors and a comprehensible composite representation of the risk of deterioration for individual patients.

INTRODUCTION

One in five patients presenting to the emergency department (ED) with infection or sepsis, deteriorate; most frequently within 48 hours from hospital admission[1,2]. However, it is unknown how early signs of patient deterioration can be monitored and predicted in infection or sepsis[3,4]. Traditionally, the diagnosis and monitoring of sepsis are based on infrequently measured discrete absolute values of vital signs, non-specific symptoms and scoring systems. In clinical practice, the crossings of certain thresholds of these vital signs are used to confirm the diagnosis and to monitor the response to treatment. These thresholds are derived from epidemiological research. However, thresholds for the *'average'* patient may not apply to or be beneficial for individual patients because of the heterogeneous patient population and the unpredictability of an individual's response to treatment[5]. Although vital signs of patients are continuously measured in the ED or intensive care unit (ICU), the majority of the measured data is discarded by only using discrete absolute values[5-7]. This discarded data may hold valuable information regarding early signs of patient deterioration. Monitoring changes in vital signs over time is called variability analysis[6,8].

The host response to infection is a complex non-linear system, like many other biological systems. Complex non-linear systems are composed of a virtually infinite number of interconnected variables, which are constantly changing. Complex systems have emergent properties that none of the individual parts possess and that disappear upon decomposition of the system into smaller parts. Small perturbations of individual variables in the system may be magnified or dampened depending on the state of the system, which may cause unpredictably large changes known as the *'Butterfly effect'*[5,9]. The emergent properties help explain unexpected rapid deterioration or clinical improvement without readily identifiable cause[5]. Despite large degrees of variability in individual variables, the system as a whole will naturally settle in a remarkably small number of stable states[6]. Continuous variability analysis can theoretically track the *'state of the system'* over time. Furthermore, variability analysis can be used to determine prognosis and response to treatment of individual patients contrary to traditional epidemiological thresholds[6]. Therefore, continuous variability analysis has the potential to determine whether an individual patient is progressing towards a state of health or towards deterioration.

Variability analysis can be performed on many types of vital signs. Heart rate variability (HRV) is the most studied, since HRV can be measured readily, easily, and non-invasively with bedside equipment commonly available. Furthermore, HRV is the most accurate variability measurement[10]. Although HRV has been studied in septic adults, it is most studied and successfully applied in neonates[5]. The leading bedside clinical application of HRV in neonates uses a proprietary composite measurement of HRV that predicts an increased likelihood of deterioration in the subsequent 24 hours[5,11]. In critically ill adults, HRV was mostly studied in small pilot studies and in ICU patients with sepsis and septic shock[5]. In these studies, reduced HRV was associated with the diagnosis of sepsis, impending shock and patient deterioration[5]. Barnaby *et al* found a HRV threshold discriminating between deterioration and no deterioration in a small study with 15 patients[12]. A study by Pontet *et al* in adult ICU patients suggested that a reduced HRV upon ICU admission could be useful in identifying septic patients at risk for developing multiple organ failure[13]. The question remains whether a reduction in HRV is also present in patients presenting to the ED with infection or sepsis, especially since most of these patients appear to be less severely ill than ICU patients.

Furthermore, it is unknown whether reduced HRV can be used as an early warning signal for impending patient deterioration in the ED population[7].

OBJECTIVE

The objective of the SepsiVit study was therefore to evaluate whether continuous HRV measurement during the first 48 hours of hospitalization in patients presenting to the ED with suspected infection or sepsis could provide an early warning signal for patient deterioration[7].

METHODS

STUDY PROTOCOL AND DATA COLLECTION

The protocol of the SepsiVit study was previously published[7]. Briefly, adult medical patients presenting to the ED of an academic tertiary care teaching hospital with suspected infection and at least two systemic inflammatory response syndrome (SIRS) criteria were included[7,14]. Patients were excluded in case of: (1) known pregnancy, (2) when the patient was not admitted to the hospital from the ED or transferred to a location outside our hospital (e.g. another hospital, nursing home, long-term care facility, etc.) or (3) when the patient had a cardiac transplantation. The patient's vital signs (ECG, heart rate, respiratory rate, blood pressure) were continuously measured during the first 48 hours of hospital admission using a mobile bedside patient monitor (Philips IntelliVue MP70 System with Multi-Measurement Module; Philips, Eindhoven, The Netherlands). The patient monitor was connected to a laptop computer with custom-made software to read the raw data from the monitor at the highest sample frequency supported by the monitor and store it in a database. In the current preliminary analysis, we analyzed the HRV features calculated from the ECG signal of the first 122 participants of the SepsiVit study (January 2017 – May 15, 2018).

ENDPOINTS AND DEFINITIONS

The primary endpoint for this study was patient deterioration within 72 hours from ED admission. We defined patient deterioration as the development of organ dysfunction, ICU admission or in-hospital mortality. For organ dysfunction, we distinguished between acute kidney injury (AKI), liver failure and respiratory failure, as defined below. For AKI, the Kidney Disease Improving Global Outcomes guideline criteria were used[15]. Liver failure was defined as total bilirubin level >34.2 μmol/L (2.0 mg/dL) and either alkaline phosphatase or a transaminase level greater than two times normal[16]. Respiratory failure was defined as the need for mechanical ventilation or either hypoxemia (PaO2 <8.0 kPa) or hypercapnia (PaCO2 >6.5 kPa) in the arterial blood gas analysis or a peripheral oxygen saturation <90% when breathing ambient air or <95% with at least 2 L/min of oxygen supplementation[17]. In-hospital mortality was defined as all-cause mortality during the patient's stay in the hospital. The Sepsis-2 criteria (2001 international sepsis definitions conference) were used to define sepsis, severe sepsis or septic shock, i.e. two or more systemic inflammatory response syndrome criteria and suspected/confirmed infection[14].

ETHICS AND INFORMED CONSENT

This study was carried out in accordance to the Declaration of Helsinki, the Dutch Agreement on Medical Treatment Act and the Dutch Personal Data Protection Act. The Institutional Review Board of the University Medical Center Groningen ruled that the Dutch Medical Research Involving Human Subjects Act is not applicable for this study and granted a waiver (METc 2015/164). All subjects provided written informed consent. All participants received standard care according to the hospital's protocols and the attending physician's discretion.

DATA PROCESSING

Before the raw ECG data could be used for the analysis of HRV features, it needed to be preprocessed. Preprocessing consisted of several steps (Figure 1): (1) Filtering of baseline wander, noise, power line and movement artifacts from the raw signal, (2) R-peak detection, (3) detection and correction of ectopic heart beats, (4) detection and correction of atrial fibrillation and other non-sinus rhythm. These preprocessing steps and the calculation of HRV features were performed by an automated algorithm developed by members of our research staff blinded to the clinical outcomes of the patients and implemented in Matlab (version R2017b, The MathWorks, Natick, Massachusetts, USA) to prevent subjective bias in the HRV analysis[7]. Technical details of the algorithm can be found in Appendix B on page 127.

Since ectopic heart beats and other non-sinus rhythm beats may result in a significant overestimation of the HRV, these beats needed to be corrected. The influence of non-sinus rhythm varies for each HRV feature, therefore there is no one-size-fits-all or best solution to detect and correct non-sinus beats[18-22]. In our algorithm, we differentiated between (1) ectopic heartbeats, (2) atrial fibrillation and (3) other non-sinus rhythms. Ectopic beats are heart beats that do not originate from the sinus node of the heart[22]. Numerous algorithms exist for the detection and correction of ectopic heart beats[18-20,23]. We chose a parsimonious algorithm and classified a beat as ectopic when its R-R interval differed more than 20% from the previous R-R interval and corrected for them by interpolation (technical details in Appendix B on page 127). After correcting the R-R intervals for ectopic heart beats, atrial fibrillation was detected using the algorithm developed by Tuboly *et al*[24]. Patients with sepsis are prone to develop cardiac dysrhythmias, most commonly atrial fibrillation. Only episodes of at least 5 minutes were considered clinically relevant[25,26]. The Tuboly algorithm also classified R-R intervals with non-sinus rhythm. The parts classified as non-sinus rhythm contain arrhythmias that are neither ectopic beats nor atrial fibrillation, but may originate from other arrhythmias or artifacts that were not filtered by the previous steps. Both R-R intervals classified as atrial fibrillation or non-sinus rhythm were deleted before the calculation of the HRV features, since interpolation would result in artificial changes to the HRV features[19].

After preprocessing the data, we used the corrected R-R interval series of each patient to calculate the HRV features. For the calculation of the HRV features, the R-R interval series were split into 30-minute non-overlapping windows. We chose 30-minute windows as reasonable trade-off between the amount of data, analysis resolution and the amount of data lost by missing measurements in a window. For each resulting window, we assessed the quality of the window. Windows meeting one or more of the following criteria were excluded and treated as missing data, since HRV features cannot be reliably calculated over them: (1) windows without R-R intervals, (2) windows containing less than 80% R-R interval data in 30

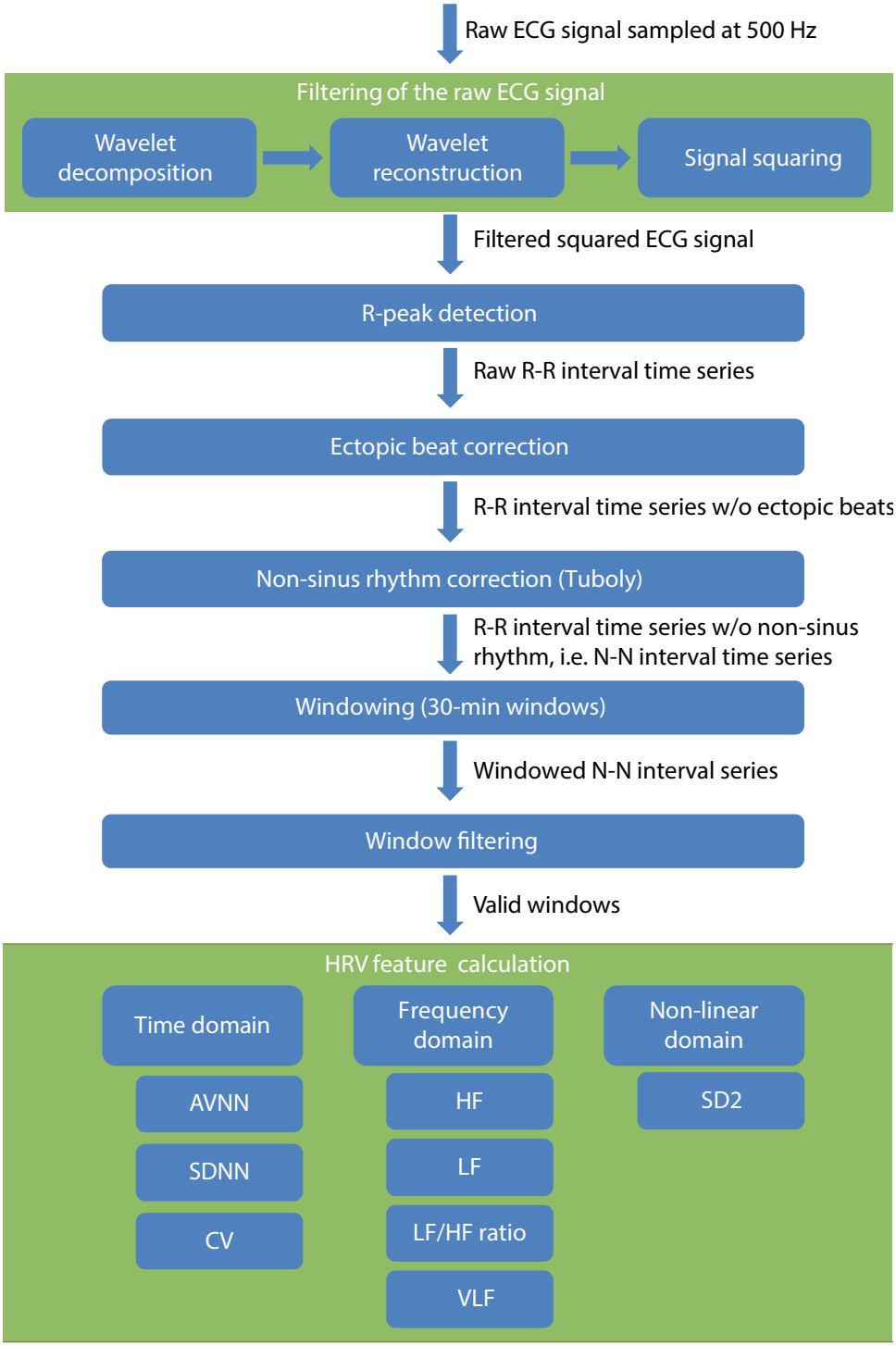

FIGURE 1. Automated raw ECG data processing and HRV feature (defined in Table 1) calculation flow-chart.

TABLE 1. Definitions of the calculated HRV features

Domain	Description
HRV feature	
Time	**Statistical calculations** of consecutive R-R intervals, **measurements of variation over time**[6].
AVNN (s)	The average (AV) normal to normal (N-N) interval[27]. The N-N interval is the R-R interval between two consecutive sinus beats on the ECG[28]. The AVNN represents the **average time between two sinus rhythm heartbeats**. The AVNN is the inverse of the heart rate in beats per minute.
SDNN (s)	The standard deviation (SD) of N-N interval. The SDNN reflects the **variability caused by all cyclic components in the period of the ECG recording**[27].
CV	The coefficient of variation of N-N intervals. The **ratio of SDNN to AVNN.**
Frequency	Time series of physiological data may be considered the sum of sinusoidal oscillations with distinct frequencies. The amplitude or power of each sine or cosine wave determines its contribution to the biological signal. T**he frequency domain of HRV evaluates the power of frequencies contributing to the underlying signal**[6]. This is **analogous to a prism that refracts light into its component wavelengths**[29]. The frequency domain is analyzed for three predefined frequency bands: high frequency (HF, 0.15 – 0.4 Hz), low frequency (LF, 0.04 – 0.15 Hz) and very-low frequency (VLF, 0.003 – 0.04 Hz)[27].
HF_{norm} (%)	**Normalized high frequency power.** The HF band reflects parasympathetic nervous system activity, corresponds to the heart rate variations due to the respiratory cycle and exhibits a circadian rhythm with higher values at night[6,29].
LF_{norm} (%)	**Normalized low frequency power.** The physiological mechanisms responsible for LF activity are subject of debate. The LF band is influenced by both sympathetic and parasympathetic nervous system activity and by blood pressure regulation via the baroreceptors. The latter is believed to be mainly responsible for the LF band in resting conditions[29]. Furthermore, it is believed that the parasympathetic nervous system has more influence on the LF band than the sympathetic nervous system[6].
LF/HF ratio	**Ratio between low frequency power and high frequency power**[6].
VLF (ms2)	**Very low frequency power**. The physiological mechanisms responsible for VLF activity are uncertain. The hearts intrinsic nervous system appears to generate the VLF rhythm and the sympathetic nervous system seems to modulate its amplitude and frequency. Furthermore, VLF activity may be generated by physical activity, thermo-regulation, renin-angiotensin and endothelial influence on the heart[6,29].
Non-linear	HRV can also be analyzed using non-linear features; one of them is a Poincaré plot. The Poincaré plot is a scatter plot of each R-R interval as a function of the previous R-R interval. This plot provides visual information about the R-R variability in the data[29]. The shape of the plot can be used to classify the data into various classes[30]. Healthy patients show a comet-shaped configuration in the Poincaré plot, reflecting an increasing R-R interval dispersion at lower heart rates[30]. Furthermore, the plot can be quantitatively analyzed using the feature described below. This quantitative method of analysis is based on the **notion of different temporal effects of changes in the sympathetic and parasympathetic modulation of the heart rate on the subsequent R–R intervals** without being sensitive for changes in heart rate[31].
SD2 (s)	**The standard deviation of the continuous long-term R-R interval variability in the Poincaré plot**. This feature quantifies the continuous long-term variation of the signal[32] .

minutes, (3) windows containing more than 20% atrial fibrillation or non-sinus rhythm, (4) windows containing more than 10% (interpolated) ectopic heart beats, (5) windows with an average heartbeat of less than 40 beats/min. Over the remaining windows, we calculated HRV features in three different domains: the time domain, frequency domain and non-linear domain (Table 1). Patients with at least six hours of measurements, i.e. twelve 30-min windows, were included in the final analysis as this was considered the minimum measurement time to find trajectories in vital signs related to patient outcome.

STATISTICAL ANALYSIS

Continuous data were reported as median with interquartile range (IQR) and analyzed using the Mann-Whitney U test. Categorical data were summarized as counts with percentages and analyzed using the Chi-square test. These statistical analyses were performed using IBM SPSS Statistics for Windows V.23.0 (IBM Corp, Armonk, New York, USA). A two-tailed p-value of <0.05 was considered significant.

How HRV features develop over time in patients with infection or sepsis is unknown. Therefore, we analyzed the data from two different perspectives: (1) outcome-oriented perspective and (2) a data-driven perspective. For the outcome-oriented perspective, plots with the mean values and their 95% confidence intervals summarized data over time for each feature grouped by patient outcome (deteriorated versus non-deteriorated). The outcome-oriented perspective was analyzed using Matlab (version R2017b, The MathWorks, Natick, Massachusetts, USA). For the data driven perspective, the data was analyzed independent of patient outcomes. In this perspective, groups of patients were created based on the patient's HRV features following a similar trajectory (i.e. pattern over time) using a technique called group-based trajectory modeling (GBTM). This is a particular type of latent class analysis following a data-driven approach, which provides the capacity to identify trajectories that emerge from the data, rather than defining trajectories before the statistical analysis. This method provides an exploratory capacity to identify previously unrecognized trajectories and identify factors that predict or alter distinctive time-based progression[33]. We performed the GBTM analysis in six steps: (1) start the analysis using a base model with two groups with quadratic growth trajectories. GBTM will try to separate the patients into two groups based on two trajectories that follow a distinct quadratic pattern. GBTM derives these trajectories based on the data. The goodness of fit of the model can be expressed using the Bayesian information criterion (BIC), where a lower BIC represents a better fit. Patients are assigned to a specific group by GBTM based on the maximum posterior-probability, i.e. the trajectory that best fits the data of the patient. (2) Extend the model by adding one additional group with quadratic growth trajectories at a time until the BIC is no longer reduced by adding more groups to the model or the predefined maximum of six groups was reached. (3) Using the model with the lowest BIC, optimize the growth terms by higher (cubic) or lower (linear, intercept) order growth terms until all highest order growth terms in the model are significant. (4) Perform a logistic regression analysis using the optimized model from step 3 with the group classification as outcome to identify significant covariates that influence group membership. This was done by adding age, gender and comorbidities as parameters to the logistic regression model. The least significant parameter was removed from the regression model, until all parameters were significant or no parameters were left. (5) Add the significant covariates from the logistic regression model as risk to the model. These covariates increase the risk of a specific patient for a certain trajectory and significantly influence the group assignment. Therefore, these covariates need to be included in the model. (6) Calculate the area under the receiver operator curve (AUROC) using the final model's most probable group membership versus observed patient deterioration for each HRV feature using predefined hypotheses. All analyses regarding GBTM were performed using Stata (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, Texas, USA) with the Traj plug-in[34,35].

PROTOCOL DEVIATIONS

The analysis of the data in the study deviated from the originally published study protocol at several points due to new insights during the study's execution, each of these deviations are described in detail below[7].

The time-frame within which the primary outcome, patient deterioration, was measured was not made explicit originally. Before starting the analysis, we specified the first 72 hours from admission as the observed time-frame for patient deterioration. Since the study only measured vital signs measured during the first 48 hours of hospitalization, we believed that it was unlikely that these measurements could predict deterioration after the first 72 hours of hospitalization. Furthermore, previous studies have shown that if sepsis patients deteriorate, it is most likely that deterioration occurs within the first 48 hours from admission[1,2,36]. In addition, previous studies showed that HRV may worsen 24-35 hours before clinical symptoms become apparent, at least for onset of sepsis[37,38]. Therefore, we also included a 24-hour period after the end of the measurements for the detection of patient deterioration.

In addition to the correction for ectopic beats, we realized that other arrhythmias, mainly atrial fibrillation, would also lead to a serious overestimation of the HRV[18-22]. Therefore, we decided to add a detection and correction step for these arrhythmias to the data preprocessing algorithm by applying the Tuboly algorithm[24].

Additionally, we added the average normal-to-normal (AVNN) to the time domain features, since it is the inverse of the heart rate. Therefore, this feature will be easy to understand for the clinician. As a parameter of variability, we furthermore added the ratio between the SDNN and AVNN, also known as the coefficient of variation (CV). Since we realized that sepsis and the body's response to sepsis are probably complex and non-linear, we also added a non-linear HRV feature to the analysis (Table 1)[6,10].

The t-test described in the protocol was replaced by the data-driven GBTM, described above, since GBTM is more applicable for modeling trajectories in longitudinal data over performing (repeated) t-tests with group means.

RESULTS

By May 15th 2018, 122 of the required 171 patients had been included in the SepsiVit study. Of them, 24 were excluded since they had less than 6 hours of measurements. The remaining 98 patients were included in the final analysis. In the remainder, we report the preliminary results of the SepsiVit study based on the data of these 98 patients (Table 2). Of these patients, 37 patients (38%) deteriorated within 72 hours from admission. Of these deteriorated patients, 19 (51%) developed acute kidney injury, 4 patients (11%) developed liver failure, 22 patients (60%) developed respiratory failure, one patient (3%) required ICU admission and no patients died within 72 hours from admission. Patients who deteriorated had a higher median age (65 years versus 61 years) and more chronic obstructive pulmonary disease (COPD; 19%; p<0.001) compared to patients who did not deteriorate. They also had a significantly higher sepsis severity (p = 0.001).

TABLE 2. Baseline characteristics of the study population

	Overall	Not deteriorated	Deteriorated	p Value
Number of patients [n (%)]	98 (100)	61 (62.2%)	37 (37.8%)	-
Demographics				
Age [median (IQR)]	62 (52-73)	61 (48-72)	65 (54-76)	<.001
Male [n (%)]	53 (54.1%)	32 (52.5%)	21 (56.8%)	.835
Comorbidity [n (%)]				
Cardiac disease	14 (14.3%)	9 (14.8%)	5 (13.5%)	.865
Chronic obstructive pulmonary disease	7 (7.1%)	0 (0.0%)	7 (18.9%)	<.001
Diabetes	26 (26.5%)	18 (29.5%)	8 (21.6%)	.391
Chronic liver disease	6 (6.1%)	4 (6.6%)	2 (5.4%)	.818
Chronic kidney disease	15 (15.3%)	9 (14.8%)	6 (16.2%)	.845
Organ transplant	27 (27.6%)	18 (29.5%)	9 (24.3%)	.578
Malignancy	31 (31.6%)	20 (32.8%)	11 (29.7%)	.752
Sepsis severity [n (%)]				
Sepsis	68 (69.4%)	50 (82.0%)	18 (48.6%)	.001
Severe sepsis	28 (28.6%)	11 (18.0%)	17 (45.9%)	
Septic shock	2 (2.0%)	0 (0.0%)	2 (5.4%)	

ECG RECORDING QUALITY

The quality of the ECG signal was assessed for each 30-min window of the total 48-hour recording period (Figure 2) based on the classification criteria described above. On average 16 hours of the data per patient could be used for HRV analysis. Patients who deteriorated had more valid data (32%) compared to non-deteriorated patients (28%). The largest loss of data was the result of empty windows caused by an early dropout of the patient from the study, 41% of the windows in the non-deterioration group and 33% in the deterioration group (Figure 2). Based on the feedback from the patients and nurses, early dropout was almost exclusively caused by discomfort of the patient and perceived limited mobility due to the wires of the patient monitor. They reported that the wires were uncomfortable during the night and experienced the need to be disconnected for a bathroom visit or a walk around as a burden. Early dropout occurred mostly around 24 hours after admission. Another 22% of the windows were excluded from analysis because they contained no data or less than 80% ECG signal, the amount of excluded windows for this reason was equal for both groups. Common causes for loss of signal included bathroom visits and leaving the bed for procedures and examinations or strolling around.

TIME DOMAIN HRV FEATURES

Deteriorating patients had a lower AVNN (i.e. a higher heart rate, Figure 3A) and less variability in their heart rate indicated by a lower SDNN (Figure 3B) and CV (Figure 3C) in the outcome-oriented perspective. In the data-driven perspective, the group-based trajectory models also distinguished between a high and a low group for these three parameters (Figure 3B, E and H). Patients that followed the low trajectories of these features had a higher risk of deterioration (Figure 3C, F and I). The AVNN trajectories did not significantly distinguish between deterioration and non-deterioration, indicated by the overlapping confidence intervals of the risk of deterioration (Figure 3B and C). This is confirmed by the area under the receiver operating characteristics curve (AUROC = .56; Figure 4A) for AVNN. In contrast, the SDNN (AUROC = .69) and CV (AUROC = .63) trajectories were significant but not very strong predictors of patient deterioration (Figure 4A).

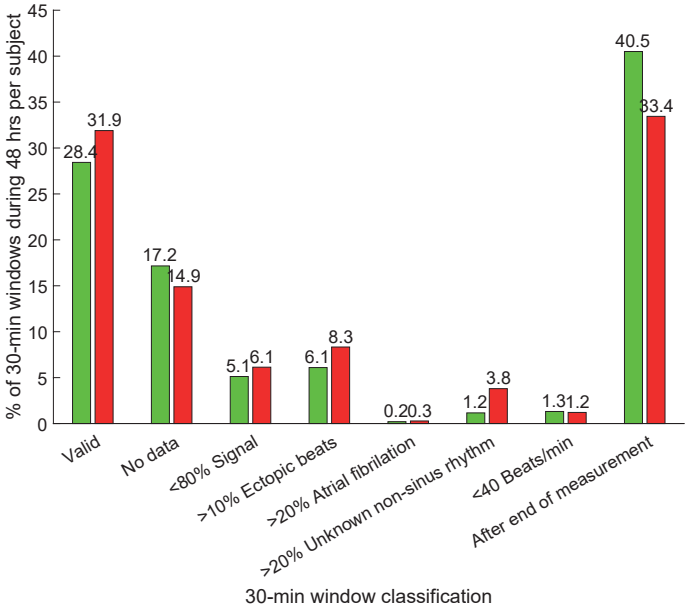

FIGURE 2. Quality classification of the 30-min windows of the analyzed patients (N=98) grouped by patient outcome. The quality for each of the 96 windows per subject was assessed according to the criteria shown on the x-axis. The mean quality was grouped by non-deteriorating (green) and deteriorating (red) patients.

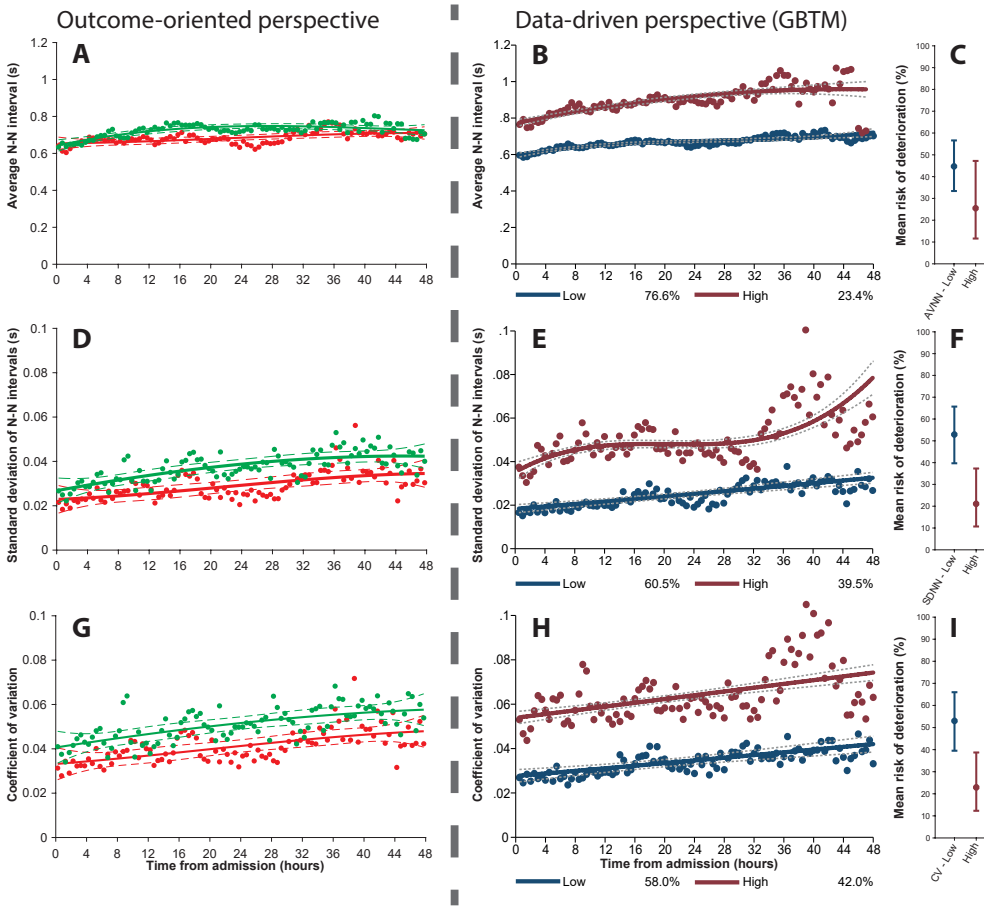

FIGURE 3. Time domain features during the first 48 hours from admission in the outcome-oriented and data-driven perspectives. The mean value of the time domain HRV features (Table 1) grouped by non-deteriorating (green) and deteriorating patients (red) in the outcome-oriented perspective (A, D, G): Average N-N interval (A), standard deviation of N-N interval (D), coefficient of variation (G). The trajectories (B, E, H) from the group-based trajectory modeling (GBTM) corresponding to the HRV parameter in the outcome-oriented perspective (A, D, G): Average N-N interval (B), standard deviation of N-N interval (E), coefficient of variation (H). Below the figures (B, E, H) are the legends for the groups identified by GBTM, the percentages represent the percentage of all patients (N=98) attributed to each group by GBTM. The mean risk of deterioration (C, F, I) for each of the groups identified by GBTM, including 95% confidence intervals for the mean: AVNN, Average N-N interval (C); SDNN, standard deviation of N-N interval (F) and CV, coefficient of variation (I). In all panels, dots represent the mean observed value. In panel A, B, D, E, G and H, solid lines represent fit lines and dotted lines represent 95% confidence intervals of the fit lines.

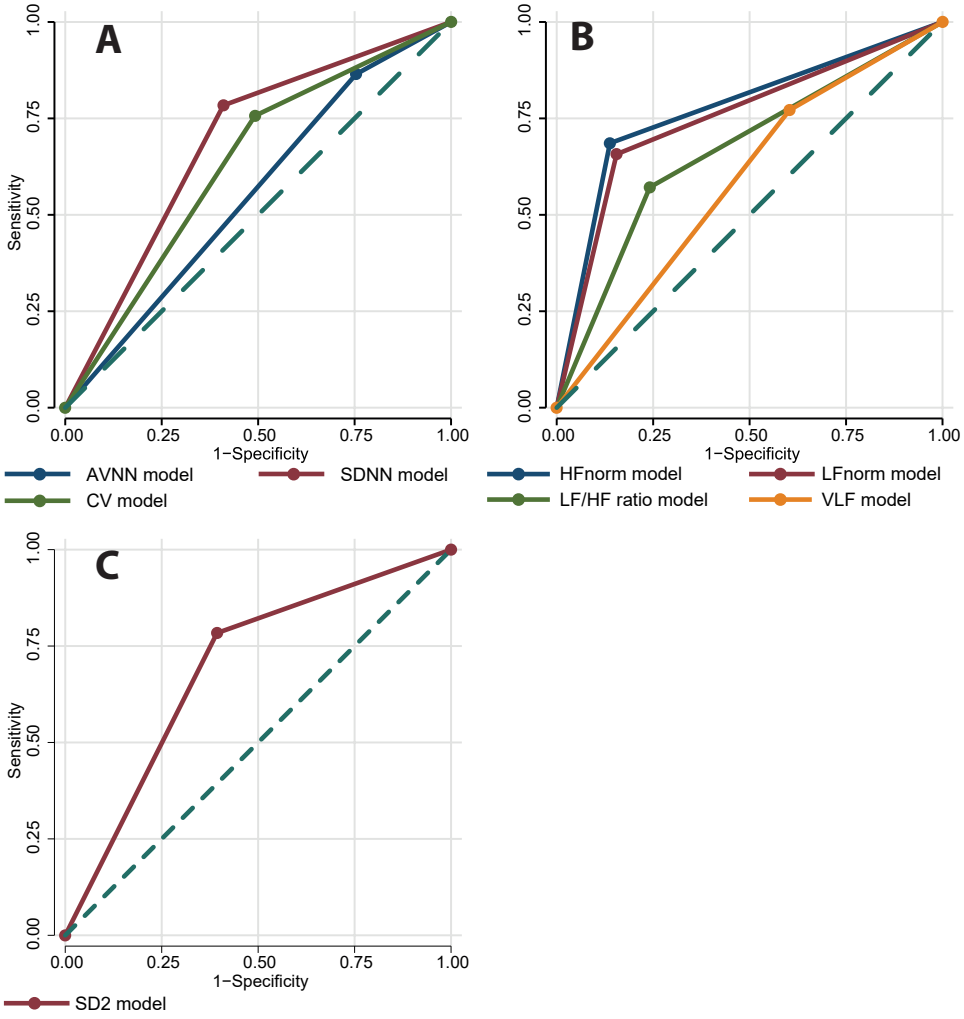

FIGURE 4. Receiver operating characteristics curves (ROC) for patient deterioration for each of the three heart rate variability domains based on the group-based trajectory models from the data-driven perspective. (A) ROC curves for the models in the time domain (Table 1). AVNN (average N-N interval; blue line), SDNN (standard deviation of N-N intervals; red line), CV (coefficient of variation; green line). (B) ROC curves for the models in the frequency domain. HF_{norm} (normalized high frequency; blue line), LF_{norm} (normalized low frequency; red line), LF/HF ratio (ratio between the normalized high and low frequency components; green line), VLF (very low frequency; orange line). (C) ROC curve for the model in the non-linear domain. SD2 (standard deviation of the continuous long-term R-R interval variability in the Poincaré plot; red line). In all panels, the dotted line represents the reference line at an area under the curve of 0.5.

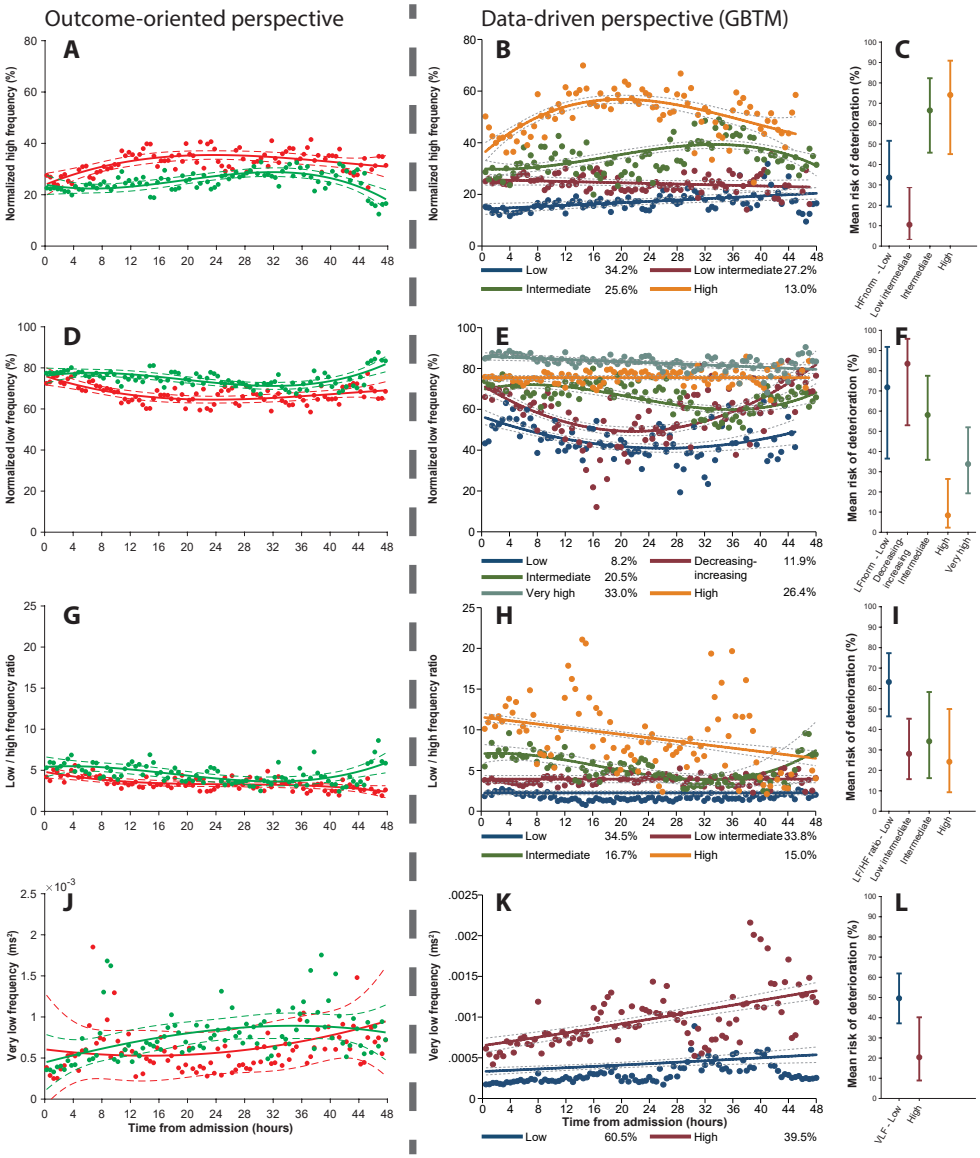

FIGURE 5. Frequency domain features during the first 48 hours from admission in the outcome-oriented and data-driven perspectives. The mean value of the frequency domain HRV features (Table 1) grouped by non-deteriorating (green) and deteriorating patients (red) in the outcome-oriented perspective (A, D, G, J): normalized high frequency components (A), normalized low frequency components (D), low/high frequency ratio (G), very low frequency components (J). The trajectories (B, E, H, K) from the group-based trajectory modeling (GBTM) corresponding to the HRV parameter in the outcome-oriented perspective (A, D, G, J): normalized high frequency components (B), normalized low frequency components (E), low/high frequency ratio (H), very low frequency components (K). Below the figures (B, E, H, K) are the legends for the groups identified by GBTM, the percentages represent the percentage of all patients (N=98) attributed to each group by GBTM. The mean risk of deterioration (C, F, I, L) for each of the groups identified by GBTM, including 95% confidence intervals for the mean: HF_{norm}, normalized high frequency components (C), LF_{norm}, normalized low frequency components (F), LF/HF ratio, low/high frequency ratio (I), VLF, very low frequency components (L). In all panels, dots represent the mean observed value. In panel A, B, D, E, G, H, J and K, solid lines represent fit lines and dotted lines represent 95% confidence intervals of the fit lines.

FREQUENCY DOMAIN HRV FEATURES

In the frequency domain, deteriorating patients showed higher normalized high frequency components (HF_{norm}; Figure 5A) and associated lower normalized low frequency components (LF_{norm}, Figure 5D) in the outcome-oriented perspective. The low / high frequency ratio (LF/HF ratio; Figure 5G) and very low frequency (VLF; Figure 5J) component did not differ between deteriorating and non-deteriorating patients.

The GBTM models in the data-driven perspective, identified many different trajectories for HF_{norm} (Figure 5B), LF_{norm} (Figure 5E) and the LF/HF ratio (Figure 5G). (NB HF_{norm} and LF_{norm} are highly related since they were normalized). Both features appear to have a certain optimum, were the patients following the low intermediate trajectory of the HF_{norm} (Figure 5C), and those following the high trajectory of LF_{norm} (Figure 5F), had the smallest risk of deterioration. For both features, trajectories around the edges of the spectrum yield an increased risk of deterioration. It should be noted that some of the groups were small and had large confidence intervals. The HF_{norm} (AUROC = 0.74; Figure 4) model best predicted patient deterioration, followed by LF_{norm} (AUROC = 0.72). The LF/HF ratio did not improve the prediction (AUROC = 0.64) and the VLF failed to distinguish deteriorating from non-deteriorating patients (AUROC = 0.58).

NON-LINEAR DOMAIN HRV FEATURES

In the non-linear domain, we analyzed the standard deviation of the continuous long-term N-N interval variability in the Poincaré plot (SD2). In the outcome-oriented perspective, deteriorating patients had a lower SD2 (Figure 6A), indicating less long-term variability in their heart rate. In the data-driven perspective, the GBTM model distinguished a low and high trajectory group for SD2 (Figure 6B). Patients following the low trajectory, i.e. low long-term variability, had a much higher risk of deterioration (Figure 6C). The SD2 model was a fair predictor of patient deterioration (AUROC = 0.70; Figure 4C).

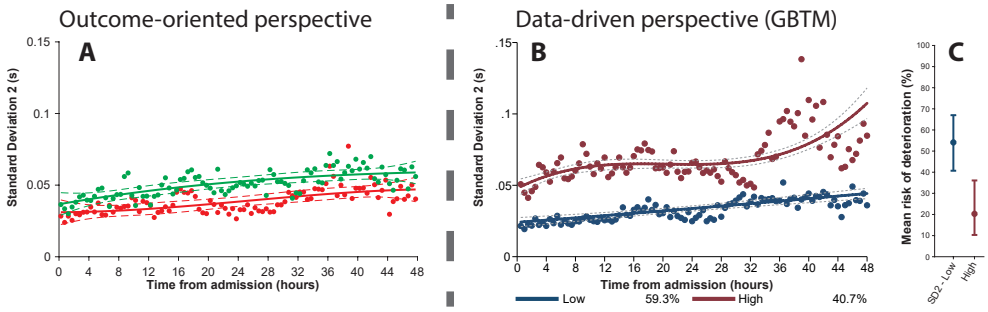

FIGURE 6. Non-linear domain feature during the first 48 hours from admission in the outcome-oriented and data-driven perspectives. The mean value of the non-linear domain HRV feature (Table 1) grouped by non-deteriorating (green) and deteriorating patients (red) in the outcome-oriented perspective: standard deviation of the continuous long-term R-R interval variability in the Poincaré plot (A). The trajectories from the group-based trajectory modeling (GBTM) corresponding to the HRV parameter in the outcome-oriented perspective (A): standard deviation of the continuous long-term R-R interval variability in the Poincaré plot (B). Below the figure (B) is the legend for the groups identified by GBTM, the percentages represent the percentage of all patients (N=98) attributed to each group by GBTM. The mean risk of deterioration (C) for each of the groups identified by GBTM, including 95% confidence intervals for the mean: SD2, standard deviation of the continuous long-term R-R interval variability in the Poincaré plot (C). In all panels, dots represent the mean observed value. In panel A and B, solid lines represent fit lines and dotted lines represent 95% confidence intervals of the fit lines.

DISCUSSION

We performed this study to evaluate whether continuous HRV measurement during the first 48 hours of hospitalization could provide an early warning signal for patient deterioration. In this preliminary analysis, we found that deteriorating patients had less variability in the time and non-linear domains from an outcome-oriented perspective. In the frequency domain, deteriorating patients had higher normalized HF (HF_{norm}) components and lower normalized LF (LF_{norm}) components. The group-based trajectory modeling (GBTM) from the data-driven perspective confirmed that trajectories with less variability were associated with higher risk of patient deterioration. The GBTM models in the frequency domain suggested an optimum for both the HF_{norm} and LF_{norm} parameters with higher risks of deterioration on the edges of the spectrum. Overall, the HF_{norm} model was the best predictor of patient deterioration.

Our preliminary results confirmed that a lower HRV is associated with patient deterioration in patients presenting to the ED with infection or sepsis, suggesting that HRV could be useful to detect patient deterioration in this population. This would supplement the successful application of HRV in neonates and its scare use in the adult ICU[5,11,13].

Few studies have been performed on HRV in relation with deterioration in sepsis, especially related to the change of HRV features over time. Garrard *et al* found an increase in LF_{norm} in adult ICU patients during recovery from sepsis. McNames *et al* described an increase in LF_{norm} and LF/HF ratio and a decrease in HF_{norm} in pediatric patients recovering from septic shock in the pediatric ICU[37,39]. Chen *et al* found significantly lower LF_{norm}, LF/HF ratio, VLF and SDNN, and a significantly higher HF_{norm} at admission to the ED in septic patients that died in the hospital[40]. Those patterns are similar to the pattern we observed in non-deteriorating patients (Figure 5A, D and G). Barnaby *et al* previously found a threshold for deterioration in LF_{norm} and the LF/HF ratio in their 15-patient convenience sample study in the ED using a 5-min ECG from the ED[12]. The GBTM models in our results suggested that there is an optimum in these parameters instead of a threshold (Figure 5F and I). The frequency domain HRV features appear to have been most studied in previous studies and were also the best predictors of patient deterioration in our preliminary results.

The HRV features calculated in our study are a selection of the available HRV features. There are countless HRV features that could be calculated, some simple, others very complex[5,29,41]. No single feature offers a one-size-fits-all solution and new HRV features are still being discovered[7,42]. This poses one of the challenges in clinically applying HRV features, since there is no standardized methodology for performing HRV analysis and many features are highly related. Therefore, there is a need to merge clinically relevant information and eliminate redundancy. Furthermore, the physiology related to the HRV features (Table 1) and the influence of different comorbidities or medication on HRV are incompletely understood, especially in the heterogeneous ED population of patients with sepsis[5]. These factors make analysis of HRV features in a clinical setting very complex, especially since we are dealing with time series data. Furthermore, most (basic) statistical models compare only single measurements, require variables that are not highly correlated, or assume linear relations in the data. Therefore, we chose to use GBTM models, since they do not assume independence of the variables, can cope with time series data, do not assume linear relationships, and the outcomes at the same time still are comprehensible for the clinician[33]. However, we were not able to model the trajectory changes directly preceding the deterioration using this technique.

Determining the exact time of deterioration is in itself not straightforward. We used laboratory results and routinely performed measurements of vital signs as the gold standard to detect signs of organ failure. However, laboratory measurements were generally performed at most once a day on the wards, meaning that the deterioration could have occurred hours before it was clinically detected. The same holds for routine vital sign measurements that are performed only a few times a day on the wards. Modeling the exact time of deterioration would require even more complex analysis techniques, which we were unable to perform in this study. When complex analysis techniques are used, it is important to condense and compose the results of the model and present them to the clinician in a comprehensible manner.

To the best of our knowledge, the SepsiVit study is the first study to explorer and model trajectories in continuously measured HRV features in relation to patient deterioration in ED patients with infection or sepsis. Liu *et al* retrospectively used machine learning to predict death versus survival based on HRV features calculated on segments of ECG recordings from the ED[43]. In contrast to our results, they concluded that the HRV features used in their model did not correlate well with short-term or long-term patient outcome. Samsudin *et al* recently retrospectively created a prediction model for in-hospital mortality using HRV features from ECG recordings at triage, vital signs and demographic patient data[44]. Their model included five components (age, respiratory rate, systolic blood pressure, mean N-N interval, and detrended fluctuation analysis alpha2) and had an AUROC of 0.78 for in-hospital mortality. Our HF_{norm} model had an AUROC in the same range (0.74), but predicted short-term outcomes like organ failure, that may be treatable, as well as in-hospital mortality, which may be preventable with early warning of deterioration. We previously performed a study using vital signs (heart rate, mean arterial pressure, respiratory rate and body temperature) measurements at 30-minute intervals during the patient's stay in the ED with the same outcome parameter as the current study[36]. Continuous HRV measurements improved the best AUROC from 0.68 to 0.74 compared to 30-minute interval discrete value heart rate measurements. Henry *et al* retrospectively created a machine learning model to detect the development of septic shock based on a continuous stream of information from a database of electronic patient records of patients admitted to the ICU[45]. This information stream did not include any HRV features, but their model was able to detect deterioration towards septic shock many hours before routine procedures did. This emphasizes the potential usefulness of models using continuous streams of information, like continuously measured HRV features, vital signs or information from electronic patient records over infrequent discrete measurements a couple of times per day.

In this study, we used bedside patient monitors connected to a laptop to record vital signs of the patients continuously. Although bedside monitors represent the gold standard of vital sign measurements, they are also responsible for the high early dropout of the study. The big monitor mounted together with the laptop on a computer-on-wheels cart and the many wires between the monitor and the patient for the ECG leads, blood pressure and peripheral oxygen saturation caused discomfort in the patients. The patients reported feeling restricted by the wires in their mobility and their ability to sleep and the fact that they had to be unplugged before bathroom visits or a walk around. The peak dropout was around 24 hours after admission. Especially patients that were recovering (i.e. not deteriorated) reported that they wanted to mobilize at that time and felt restricted by the study equipment (Figure 2). The early dropout caused an average loss of potential data in the 48-hour measurement period of 33-40%. Smaller equipment with less or no wires, like wearable devices, to measure the vital signs might have led to better patient compliance and less dropout. However, at the time of

the start of the study, we were unable to find a wearable device that was able to measure the required vital signs at a sufficiently high sample rate (>200 Hz for ECG) and have a battery-life of at least 48 hours. Despite the high dropout, its impact on the results may be limited, since if patients deteriorate, this mostly happens within 24 hours from admission as was previously shown by Glickmann *et al* and our recent study[2,36]. Therefore, we feel that our study generated valuable insights in the relation between HRV and patient deterioration in ED patients with sepsis.

STRENGTHS AND LIMITATIONS

The SepsiVit study is the largest study on HRV in ED patients with sepsis, with a 48-hour observation window it has the longest continuous observation period for patient deterioration. Furthermore, the study had a prospective design and we did not only predict mortality outcomes, but also modifiable factors like ICU admission and signs of organ failure. With regard to the decreasing sepsis-related mortality in the last decades, we consider the latter outcome much more interesting, since organ failure might be treatable or even preventable[36,46]. Furthermore, the ECG data was acquired at high sample rates (500Hz) and automatically processed to prevent a subjective bias and inter-observer variability.

Our study has several limitations. First, the main limitation of the presented results is that they are preliminary and should therefore be interpreted with caution. Especially some of the groups in the GBTM models were small, as described above, which limits their accuracy. Second, the dropout discussed above might have introduced an attrition bias, since non-deteriorating patients dropped out of the study earlier (Figure 2), probably because they felt better and wanted to mobilize. Furthermore, this may have resulted in the loss of valuable data on the recovery pattern in HRV from sepsis. Third, the study may suffer a selection bias for patients with septic shock, since these patients were often not able to provide informed consent because of their condition. However, the goal of the SepsiVit study was to detect patient deterioration early. Patients in septic shock in the ED were already recognized as critically ill by the ED physician with subsequent ICU admission. These patients are therefore not the primary group of interest for the early detection of deterioration in this study. Fourth, the composite outcome parameter including mortality, ICU admission and signs of organ failure is heterogeneous. A composite outcome parameter was chosen to keep the required number of patients for the study low and therewith the inclusion period of the study feasible. It could be that different types of organ failure present different types of trajectories in HRV features. However, to verify this assumption a larger sample size would be required.

CLINICAL IMPLICATIONS AND RECOMMENDATIONS

Our preliminary results show that trajectories in continuously measured HRV features can predict patient deterioration. However, before HRV can be clinically applied for the early warning of patient deterioration a number of issues need to be resolved. First, the information from the models about individual patients needs to be condensed further into a format comprehensible for the clinician. We recommend the exploration of models that combine multiple features and the use of more advanced analysis techniques, like machine learning technology. In addition, there is a need to identify the early signs of deterioration in the trajectories, which also requires a more advanced analysis technique. Information from the models could, for example, be visualized in the form of partial effect plots or (real-time)

predicted risks[45,47]. Second, the use of bedside patient monitors restricts the patients too much for a feasible clinical application of continuous HRV measurements. We recommend the exploration of the use of wearable devices. Third, pending the advanced modeling of deterioration and the analysis of the full cohort, the question how long and at which interval patients should be monitored for deterioration remains an open issue. Fourth, the use of individual endpoints instead of the current composite endpoint may result in different HRV trajectories, as described above. Therefore, we recommend further exploration of the relation between the various types of organ failure and the HRV features.

PRELIMINARY CONCLUSIONS

Patients presenting with infection or sepsis to the ED who deteriorated within 72 hours from admission exhibited different trajectories in HRV features compared to patients who did not deteriorate. In general, a lower variability was associated with an increased risk of patient deterioration. The association between lower variability and increased risk of deterioration is consistent with previous studies in the pediatric and ICU population with sepsis. The HRV features in the frequency domain were the best to distinguish between deterioration and non-deterioration, especially the normalized high frequency components. However, before continuous HRV analysis can be applied in clinical practice for the detection of deterioration, wearable monitors are required as well as a comprehensible representation of the risk of deterioration for individual patients. Once these issues are solved, continuous HRV could be an easily applicable method for the continuous detection / early warning of deterioration in vulnerable patients in the ED and on the nursing wards.

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