

A Continuous Real-Time Analytic for Predicting Instability in Acute Care Rapid Response Team Activations

Ashwin Belle, Bryce Benson, Mark Salamango, Fadi Islim, Rodney Daniels, Kevin Ward

Abstract—A reliable, real-time, and non-invasive system that can identify patients at risk for hemodynamic instability is needed to aid clinicians in their efforts to anticipate patient deterioration and initiate early interventions. The purpose of this pilot study was to explore the clinical capabilities of a real-time analytic from a single lead of an electrocardiograph to correctly distinguish between rapid response team (RRT) activations due to hemodynamic (H-RRT) and non-hemodynamic (NH-RRT) causes, as well as predict H-RRT cases with actionable lead times. The study consisted of a single center, retrospective cohort of 21 patients with RRT activations from step-down and telemetry units. Through electronic health record review and blinded to the analytic's output, each patient was categorized by clinicians into H-RRT and NH-RRT cases. The analytic output and the categorization were compared. The prediction lead time prior to the RRT call was calculated. The analytic correctly distinguished between H-RRT and NH-RRT cases with 100% accuracy, demonstrating 100% positive and negative predictive values, and 100% sensitivity and specificity. In H-RRT cases, the analytic detected hemodynamic deterioration with a median lead time of 9.5 hours prior to the RRT call (range 14 minutes to 52 hours). The study demonstrates that an electrocardiogram (ECG) based analytic has the potential for providing clinical decision and monitoring support for caregivers to identify at risk patients within a clinically relevant timeframe allowing for increased vigilance and early interventional support to reduce the chances of continued patient deterioration.

Keywords—Critical care, early warning systems, emergency medicine, heart rate variability, hemodynamic instability, rapid response team.

I. BACKGROUND

UNRECOGNIZED or delayed identification of patient deterioration remains a persistent issue across all echelons of in-hospital care [1], [2]. The failure to recognize, communicate, or act on early signs of patient deterioration can lead to delays in patient care, adverse events, unplanned intensive care unit (ICU) admissions, and unexpected deaths [3]. Such delayed or absent clinical care responses to patient hemodynamic deterioration has been demonstrated to result in otherwise preventable adverse events, also known as 'failure

to rescue' [4], [5]. Even with immediately available bedside clinicians, patients hospitalized for major medical events with deteriorating conditions have poor outcomes. The result is unexpected transfers to a higher level of care and increased lengths of stay [6].

Studies have shown that in most cases, there are shifts in vital signs prior to adverse events [1], [7], [8]. Moreover, close monitoring of vital signs when done deliberately and consistently has been shown to improve early detection and clinical action with the potential to reduce adverse events, such as cardiopulmonary arrest [9], [10]. However, despite this, measuring, recording, and reporting of vital signs remain inconsistent and error prone in practice [11], [12].

Several compounding factors have been increasingly contributing towards the problem of failure to recognize patient deterioration, including growing clinical workload, data limitations to recognize emerging critical trends, complex patient co-morbidities, and resource constraints forcing increasingly sick patients into lower echelons of care [11], [13], [14]. Hence in an effort to detect and respond to the early onset of patient's hemodynamic decline, hospitals in many countries and across the United States are implementing systems called RRT [5], [9], also sometimes referred to as a medical emergency response team (MERT) or a high acuity response team (HART). An RRT is typically comprised of a multi-disciplinary team of clinicians focused on supporting deteriorating patients to prevent avoidable patient progression to cardiopulmonary arrest or other severe adverse events [15]. However, despite widespread adoption of such teams, RRT effectiveness and its patient safety implications continue to be under evaluation and debate [15]-[18].

A significant challenge facing RRT activation is the determination of when to trigger an RRT in the first place. Primary activation of an RRT is usually implemented by nursing staff caring for the patient. Therefore, the effectiveness of any RRT team depends heavily on the nurse's ability to identify the onset of patient deterioration and their decision to activate the RRT team in a timely manner [19]-[21]. Nurses continue to rely on clinical markers for hemodynamic instability, such as heart rate (HR), capillary refill, mental status, respiratory rate, and blood pressure as indicators for intervention [22]-[24]. However, many of these markers can either be confounded by multiple etiologies, such as fever, pain, anxiety, or are late signs of hemodynamic instability, making them poor markers or predictors of early hemodynamic instability [25], [26]. Apart from these simple

A. Belle, B. Benson, and M. Salamango are with Fifth Eye Inc, 110 Miller Avenue, Suite 300, Ann Arbor, MI, 48104, USA (e-mail: abelle@fiftheye.com).

F. Islim is with Nursing Informatics, Michigan Medicine, University of Michigan, 400 N. Ingalls, Suite 1160, Ann Arbor MI 48109, USA.

R. Daniels and K. Ward are with the Department of Michigan Center for Integrative Research in Critical Care, Michigan Medicine, Building 10-103A, North Campus Research Complex, 2800 Plymouth Road, Ann Arbor, MI 48109, USA.

physiological measures, traditional bedside tools like the Shock Index, Modified Early Warning System, National Early Warning Score 2 (NEWS2), and others have been developed that rely on chart-based measures that are largely 'static' (i.e., assessed once-a-day) but have failed widespread acceptance and adoption [27]-[29]. However, the unmet need and potential advantages of such scores have resulted in several variants of such early warning scores customized to meet specific needs of individual hospitals or systems.

Given the sheer number of early warning scores being developed and investigated, it is evident that there is a need for a clinical decision support system that can aid in continuous monitoring and identification of at-risk patients prior to transition into overt stages of hemodynamic instability [13], [30]. Favorable characteristics of such a system could include easy automation, continuous output, simple interpretation and no significant change to clinical workflow. To meet this need, a Software as a Medical Device (SaMD) product called the Analytic for Hemodynamic Instability (AHI) was developed. AHI utilizes data from a single lead of a non-invasive electrocardiograph (ECG) signal for analysis and identification of at-risk patients. AHI is a novel application of real-time nonlinear analysis of heart rate variability (HRV) that can detect significant perturbations in the autonomic nervous system that precede apparent hemodynamic instability prior to overt changes in traditional vital signs. Loss of HRV has been demonstrated to reflect autonomic nervous system function impacted by a diverse array of diseases including heart failure, respiratory distress, sepsis, hemorrhage, and others [31]-[35].

AHI was developed using machine learning and nonlinear HRV-complexity ECG morphology feature analysis from a variety of clinical models including human lower body negative pressure (as a surrogate of central hypovolemia) and hospitalized control patients with normal and abnormal physiology [36]. In this pilot study, AHI was retrospectively applied to continuous ECG signals obtained from hospitalized patients requiring an RRT activation in order to examine its ability to detect the need for RRT prior to activation. By comparing AHI's assessment of risk to that of the case review and real-time patient data, we sought to determine if AHI could provide additional insight, or act as an early warning of unrecognized patient changes that could have influenced clinical decision-making had it been available to the treating clinical teams. We also sought to explore if the AHI analytic could predict the event prior to it occurring, and if so, how long before the event AHI could begin signaling a problem.

II. METHODS

A. Study Setting

Data for this study were drawn from the ICUs, step-down and telemetry units in the University of Michigan Medical Center located in Ann Arbor, Michigan. The system is a quaternary health care system with 990 beds, 66 operating rooms, and over 47,000 admissions per year. It serves a six-county area with a catchment of over 700,000 residents. The

system provides care for a diverse patient population, with patients representing a wide variety of ethnic, racial, and socioeconomic backgrounds. The study was conducted under an approved Institutional Review Board (IRB) protocol by the University of Michigan. A waiver of patient consent was granted by the IRB since the study utilized retrospective de-identified data in its analysis. A data sharing agreement also exists between the company Fifth Eye, Inc. and the University of Michigan under a licensing agreement which is known to the IRB. All data exchanged are HIPPA (Health Insurance Portability and Accountability Act) compliant and were used by the company without patient identifiers. The University of Michigan's Center for Integrative Research in Critical Care (MCIRCC) served as the research partner for this study. It has a one-of-a-kind technical infrastructure that allows real-time capture of a variety of high-fidelity data from a subset of the monitored beds including waveforms (e.g., ECG, arterial blood pressure) and structured data (e.g., vitals, labs, medications, and other info in the electronic health record). The criteria for RRT activation in adult patients for this institution have been provided in Table I.

TABLE I
INSTITUTION SPECIFIC CRITERIA FOR RRT ACTIVATION FOR ADULT PATIENTS

Category	Criteria
Airway /Breathing	<ul style="list-style-type: none"> Respiratory rate < 8 or > 36 New onset of difficulty breathing or complaint of shortness of breath New SpO₂ < 90%
Circulation	<ul style="list-style-type: none"> HR < 40 or > 140 with new symptoms or any HR > 160 Blood pressure systolic < 80 or > 220 mmHg Blood pressure diastolic > 110 mmHg with symptoms (neuro changes, chest pain, dyspnea) Chest pain with symptomatic shortness of breath and/or another activation criteria or color change Uncontrolled bleeding (any site)
Disability	<ul style="list-style-type: none"> Any bleeding into airway Acute change in level of consciousness New onset lethargy or difficulty waking Sudden collapse Seizure (outside of "seizure monitoring unit") Sudden loss of movement (weakness) of face or limb Sudden slurring of speech
Other	<ul style="list-style-type: none"> More than one stat page to single service or >1 service stat paged Unexplained agitation for more than 10 minutes Suicide attempt Naloxone use without appropriate response Worried - patient just "looks bad"

B. Data Description

The patient cases selected for this study were identified through ongoing validation work using data collected from a subset of beds in the acute care units at the University of Michigan between 2016 and 2017. During this period, all available cases were evaluated and only 21 patient cases were identified to have had continuous ECG data captured and stored for retrospective use prior to the time of the RRT activation.

Each patient case analysis is based on retrospective file review by experienced clinicians with the intent of determining the nature of the RRT call and how early the AHI analytic began signaling a problem. The clinical review team

comprised of an emergency medicine physician, a critical care intensivist and an RRT nurse. While blinded to AHI's output, these clinicians reviewed each case to determine whether hemodynamic or other serious compromise occurred and to evaluate for any apparent change in traditional laboratory or vital sign changes that could indicate deterioration prior to the event. Concurrently, the AHI analytic would determine whether the patient was "stable" or "at risk" throughout the time period where ECG data was available prior to this event. Once clinicians reviewed each case in minute by minute detail, the AHI Analytic results were compared with the actual stored patient data, including patient streaming vital signs, labs, medication changes, and care provider notes, which included those related to the RRT call, as well as the clinical review team's assessment of patient status prior to and after the event, as available. This was done to understand if AHI was providing indications that could have influenced clinical decision-making, such as the ability to activate the RRT sooner, had it been available during patient care.

Blinded to AHI, reviewing clinicians created the ground truth dichotomization of 21 RRT cases into two groups: Hemodynamic related (H-RRT) or Non-hemodynamic related (NH-RRT) RRT activation.

Hemodynamic or other serious compromise RRT (H-RRT) cases are those in which the RRT was activated by the care providers due to the onset of hemodynamic related patient deterioration. Such RRT activation typically results in the RRT providing significant interventions and escalation of care to support to the patient's hemodynamic and/or respiratory system including transferring them to higher acuity care. These include but are not limited to cases such as:

1. Acute respiratory failure (6 cases)
2. Hemodynamic changes such as hypotension (3 cases) requiring fluid resuscitation and/or vasopressor therapy
3. Undetected hemorrhage (2 cases) requiring transfusion and/or surgery
4. Sepsis (1 case) requiring transfer to ICU and institution of vasopressor therapy

Non-Hemodynamic RRT (NH-RRT) cases are those in which an RRT was called but in which no acute interventions or escalated level of care occurred that could have been predicted. These included:

1. Cases where RRT activation did not result in any major actions by the RRT team beyond some routine adjustments to clinical care such as minor changes to the ventilator settings. (Patient with prolonged agitation undergoing mechanical or noninvasive ventilation) (4 cases),
2. Patient self-extubates (2 cases),
3. Agitated patient pulls off the oxygen mask (2 cases), and
4. Sudden wound opening during post-surgical inspection (1 case).

Table II provides the basic demographic information of the patient cases considered in this study.

TABLE II
COHORT DEMOGRAPHY

	All	H-RRT	NH-RRT
# MALE	14	8	6
# FEMALE	7	4	3
AGE (YEARS)			
AVERAGE	59.5	55.7	64.5
MEDIAN	66	59	67
MAXIMUM	83	82	83
MINIMUM	23	23	39

C.AHI Overview

The input to the AHI system is a continuous waveform produced from Lead-II of a standard U.S. Food and Drug Administration (FDA) approved ECG monitor, with a sampling rate of 120 Hz or greater. Since the system is designed for application in real-time continuous monitoring settings, rolling buffered windows are created with a fixed array size and a fixed frequency of delivery. Each window is 5 minutes of ECG waveform and consecutive windows are produced every 2 minutes. AHI analyzes each consecutive window to produce an output. The analysis consists of four major steps. The first step is a preprocessing step that normalizes and standardizes each window of ECG irrespective of its source or sampling frequency and recognizes any obvious issues with data quality such as missing data. The next step is a signal quality index (SQI) which automatically recognizes noise/artefacts in real-time that is inherent within the window of data and determines if it is acceptable or unacceptable to continued processing. The third step is pattern analysis where a combination of HRV and ECG morphology-based features is extracted using custom designed signal processing methodologies. In the final step, the extracted features are run through a clinically supervised, trained classification model which produces one of four outputs (Fig. 1):

- 'AHI Stable' (Top Short Bar): Indicating that the patient is hemodynamically stable,
- 'AHI Unstable' (Top Tall Bar): Indicating that the patient is undergoing or is at risk of hemodynamic instability,
- 'Missing data' (Bottom Black Bar): No ECG data available; where half or more of the 5-minute window is missing data,
- 'Noisy Data' (Bottom Gray Bar): Data identified to be too noisy for AHI analysis.

Additional details regarding creation of the AHI algorithm can be found in a previous publication [36].

D.Data Analysis Overview

For each patient in this study, all available high-resolution ECG Lead-II waveform data prior to the RRT activation were retrospectively processed using AHI. To visualize and compare values and trends between the H-RRT and NH-RRT cases, a region of 48 hours prior to the RRT call was considered for a comparative analysis in the primary evaluation. Statistical significance between the data from H-RRT and NH-RRT cases, leading up to the RRT activation was computed using the non-parametric Mann-Whitney U

Test. This test was chosen because the H-RRT and NH-RRT cohorts contained independent patient groups with variables being measured at a continuous level or ordinal level with unknown distribution for each hour of available data.

E. Computing Lead Time to RRT

In order to quantify AHI's performance as an early warning system, the duration of time where AHI was indicating hemodynamic instability (red bars) prior to the RRT activation for each patient case was computed. Here lead time is defined as the duration of time prior to an observed adverse RRT activation event where at least 80% or greater of the AHI output are 'Red Bars' indicating that the patient is 'at risk of hemodynamic instability'. An 80% red bar threshold was chosen as a conservative visually compelling threshold to ascertain a trend (Fig. 2). For the lead time computation,

windows identified as noisy or missing are not included as they do not contribute towards clinical assessment of the patient's hemodynamic status.

Clinicians on the review team also manually reviewed and adjudicated each of these cases in a two-step process. First blinded to AHI's outputs, clinicians reviewed each case using nursing and RRT team notes from the electronic health record (EHR) to assess the type of RRT call, either H-RRT or NH-RRT. Next the clinicians reviewed AHI's output for each case along with all available clinical information such as recorded vital signs, medications, labs, and interventions to adjudicate if AHI appropriately identified patients 'at risk' for an event requiring RRT activation and if so, how long prior to the RRT that AHI consistently labeled the patient as 'at risk' (lead time).



Fig. 1 AHI's single patient view showing the four possible outputs

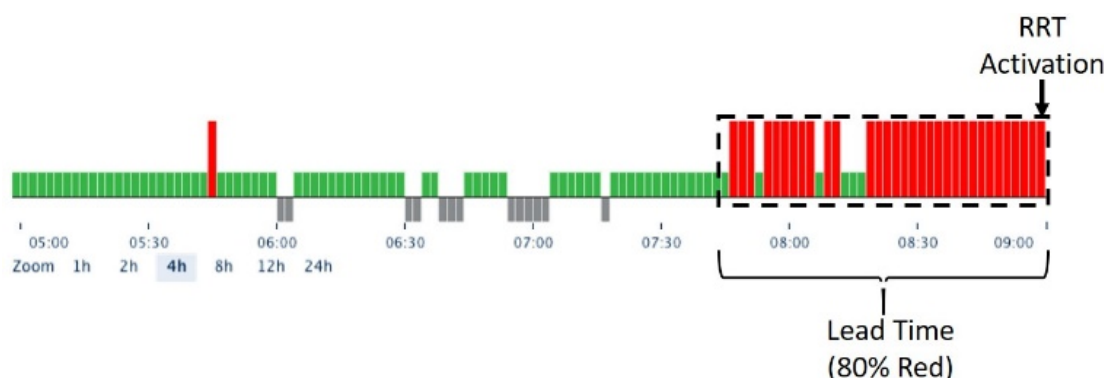


Fig. 2 Lead time analysis

III. RESULTS

A. Frequency of Recorded Vital Signs

During in-hospital care, common vital signs used for hemodynamic assessment are measured and recorded in the EHR intermittently. The frequency of these records varies depending on a variety of factors including the acuity of care, severity of the patient's condition, and nurse to patient ratio. Fig. 3 visualizes the number of times vital signs are recorded per hour in the 48-hour timeframe leading up the each RRT event. The right most corner of each graph in Fig. 3 at 'Hour 0' represents the time of the RRT activation.

Traditional vital signs are often infrequently measured and recorded by the bed-side nurses or other care-providers. Even vital signs collected electronically by monitors are usually

verified manually before they persist in the EHR. In the data used in this study, it can be seen that the patient's vital signs were recorded approximately one to two times per hour (Fig. 3). AHI on the other hand produces up-to 30 outputs per hour. Any windows of data that were assessed as noisy or missing by the AHI algorithm have been omitted in the analysis, since they do not contribute toward the hemodynamic assessment of the patient. In this study the average number of AHI outputs per hour ranged between 21 to 30 outputs (Fig. 3). Hence AHI may provide a more continuous reflection of the patient's hemodynamic status while not requiring any manual effort to gather the data.

B. Average Measurements Prior to RRT Activation

For the two groups, the average value per hour for each of

the available vital signs recorded in the EHR was plotted around a window of 48 hours prior to the RRT activation (Fig. 4). In addition, the percentages of 'Red AHI' bars, indicating at risk of hemodynamic instability per hour were averaged and plotted. Using Mann-Whitney U Test, statistical significance between the two groups per hour was determined with a p -Value < 0.05 . Blood pressure mean and systolic values were obtained from the EHR, as available.

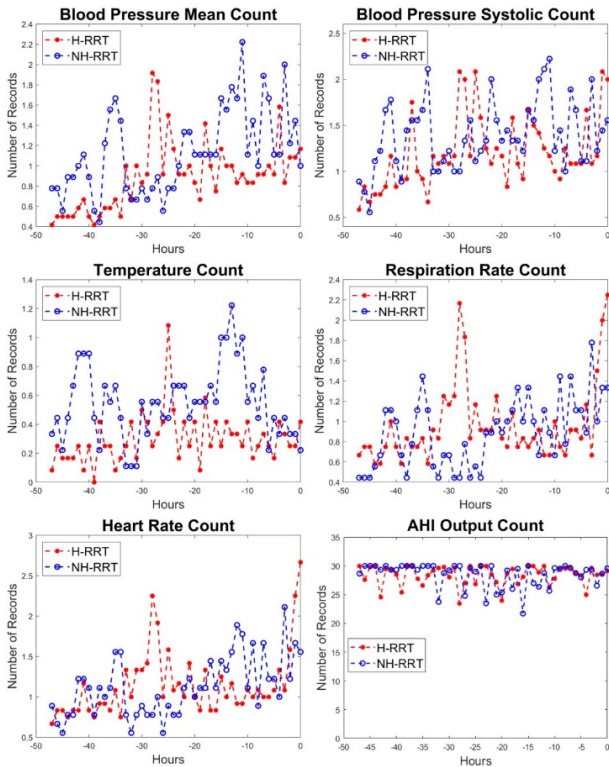


Fig. 3 Across all H-RRT and NH-RRT cases, the average number of times a vital sign is measured and recorded in the EHR per hour leading up to an RRT event at 'hour 0' (right corner of x-axis in each figure) compared with average number of hemodynamically stable or at-risk outputs produced by AHI per hour leading up to an RRT event at 'hour 0' as shown in the bottom-right graph. Note that the Y-axis range varies by graph

In Fig. 4, it can be seen that mean and systolic blood pressure values, which are commonly utilized in assessing a patient's hemodynamic status, were very similar between the H-RRT and the NH-RRT cases. None of the average values in the 48 hours leading up the RRT were differentiable in a statistically significant manner. Similarly, temperature measures also show no statistically significant ability to discern between H-RRT and NH-RRT cases. With respiration, it can be observed that there is some separation in the values closer to the RRT activation. However, there is minimal separation between the standard deviation of the respiration values.

The average HR values in Fig. 4 exhibit separation in trends between the H-RRT and NH-RRT cases, with the gaps in the

separation increasing closer the RRT activation. Even though there is a statistically significant separation in the average HR between the two groups, the difference especially in the upper and lower bounds of the deviation makes it difficult to understand if differences are clinically significant.

Fig. 4 displays a clear and consistent separation in AHI's output differentiating between the H-RRT and the NH-RRT cases with the average percentage of 'red bars' per hour plotted along time. This indicates that when AHI consistently starts showing red bars, the likelihood of an adverse event is high. In comparison against all other graphed vital signs in this data, AHI's ability to differentiate between the H-RRT and NH-RRT groups is statistically significant ($p < 0.05$).

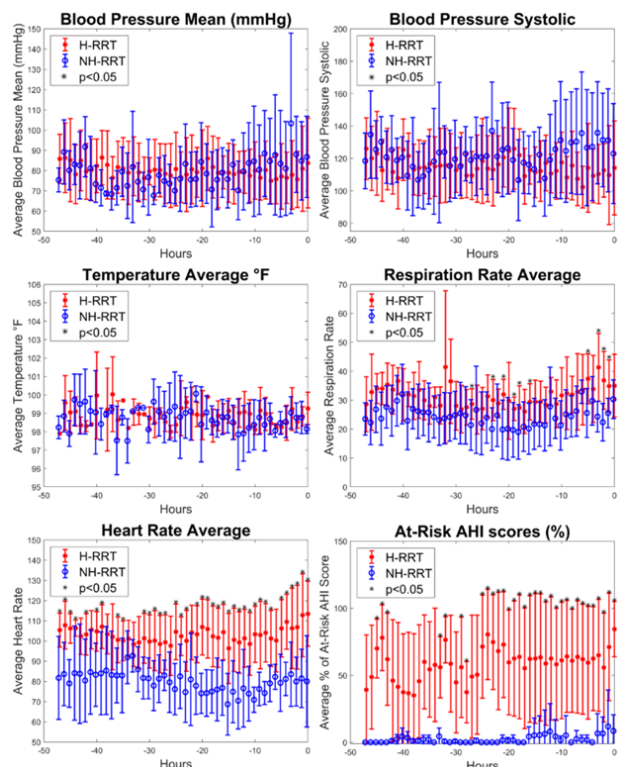


Fig. 4 Across all H-RRT and NH-RRT grouped cases, the average values of all available vital signs as recorded in the EHR per hour leading up to an RRT event at 'hour 0' (right corner of x-axis in each figure). The error bars show the mean and standard deviation of the values for each hour. The bottom-right graph plots the percentage of hemodynamically at-risk outputs produced by AHI per hour leading up to an RRT event at 'hour 0'. Statistical significance between values in H-RRT & NH-RRT in any given hour has been shown with '*' at the top of the H-RRT bar

C. Time to Event

Lead time for both H-RRT and NH-RRT groups were calculated. As defined in Section II E, lead time is the continuous duration of time wherein 80% of all AHI outputs were 'Red' indicating at risk of hemodynamic instability prior to the RRT event. Table III shows the lead times computed for each of the cases in the two groups. The table also lists the total duration of available ECG data leading up to the RRT

call. Based on the clinical review team, it was determined that all the H-RRT cases had clinically actionable timeframes whereas none of the NH-RRT cases did. With the H-RRT cases, the lead times of AHI recognizing patient's hemodynamic deterioration ranged from 14 minutes to 52 hours. This may be clinically significant since providing such advance warning of potential hemodynamic compromise in patients allows for care providers to intervene earlier and thereby improve potential for a positive outcome.

Table IV provides a statistical summarization of AHI's lead time and length of ECG available between the H-RRT and NH-RRT groups.

TABLE III
AHI LEAD TIME PER GROUP AND PATIENT CASE

	H-RRT Case	Lead Time AHI (hh:mm)	Total Hours of ECG (hh:mm)
Hemodynamic related RRT (H-RRT)	1	2:14	20:02
	2	1:44	1:44
	3	46:33	46:33
	4	11:44	11:44
	5	0:14	6:50
	6	35:22	63:00
	7	27:21	27:21
	8	52:00	124:27
	9	7:26	1330:32
	10	48:40	151:15
	11	0:14	39:11
	12	0:36	4:00
Non-Hemodynamic related RRT (NH-RRT)	NH-RRT	Lead Time AHI (hh:mm)	Total Hours of ECG (hh:mm)
	1	0:04	14:20
	2	0:00	100:02
	3	0:00	89:24
	4	0:00	23:27
	5	0:00	93:40
	6	0:00	27:29
	7	0:00	18:10
	8	0:00	32:06
	9	0:00	165:02

TABLE IV
SUMMARY STATISTICS OF AHI LEAD-TIME BETWEEN H-RRT AND NH-RRT CASES

Metric	H-RRT (hh:mm)	NH-RRT (hh:mm)
Average AHI lead time	19:30	0:00
Median AHI lead time	9:35	0:00
Range of AHI lead time	Min = 00:14, Max = 52:00	Min = 00:00, Max = 00:04
Average length of ECG data	152:13	62:38
Median length of ECG data	33:16	32:06
Range of ECG data	Min = 1:44, Max = 1330:32	Min = 14:20, Max = 165:02

D. Subject Level Performance Measures

To discern if AHI could differentiate between patients with H-RRT and NH-RRT events, the computed lead times for each patient case were used to identify those with clinically actionable timeframes and those without. Reviewing clinicians

then determined if the computed AHI lead time for each case was sufficient for a clinical intervention (predicted). The clinicians concluded that one NH-RRT case with a non-zero lead time and were insufficient to be predictive of hemodynamic instability, hence were not considered to be a false positive. All H-RRT cases provided sufficient lead times to be clinically actionable.

Using the reviewing clinicians' original validated grouping between H-RRT and NH-RRT as the 'ground truth', and AHI's dichotomization based on 'predicted' lead times, a confusion matrix was developed as shown in Table V.

TABLE V
CONFUSION MATRIX OF GROUND TRUTH AND PREDICTED H-RRT AND NH-RRT CASES

Predicted (AHI's Output)		Ground Truth (Clinician Adjudicated)	
		H-RRT	NH-RRT
	H-RRT	12 (True Positive - TP)	0 (False Positive - FP)
	NH-RRT	0 (False Negative - FN)	9 (True Negative - TN)

As stated before, of the 21 total RRT cases in this cohort, the clinical review team adjudicated that 12 of these cases were due to hemodynamic-respiratory related RRT activations requiring a range of life-saving interventions, and the remaining nine RRT cases were for reasons not associated with hemodynamic-respiratory deterioration of the patient requiring life-saving interventions. The analytic correctly distinguished between H-RRT and NH-RRT cases with 100% accuracy thus demonstrating 100% positive and negative predictive values as well as a 100% sensitivity and specificity. In the H-RRT cases, the analytic detected hemodynamic deterioration of these patients with a median lead time of 9.5 hours prior to the RRT call with a range of 14 minutes to 52 hours prior to the RRT call.

IV. DISCUSSION

Predicting the development of acute hemodynamic or respiratory episodes that require significant interventions is an important but challenging clinical problem. As a result, various systems and indices have been developed and variably adopted into clinical practice, which attempt to identify levels of severity or instability for early detection. These include scores such as the Modified Early Warning System (MEWS), Shock Index (SI), Acute Physiology and Chronic Health Evaluation (APACHE) score, Simplified Acute Physiology Scores (SAPS), Mortality Probability Model (MPM), and others [1], [37]. Most of these other scores are computed once during initial periods of admission and typically require access to additional patient data which may not be available in all cases. Due to the non-continuous nature of these measurements and their reliance on certain subjective parameters for computation such as mental status, these scores are not always effective and cannot be relied upon for a continuous assessment and prediction of patient deterioration. A major disadvantage of these scoring approaches to predict and quantify instability is the fact that these methods do not

consider continuous, or nearly continuous physiological measurements. Other related experimental works in this field include utilizing high-fidelity continuous physiological data sources such as pulse oximeter, arterial line waveform, etc. to monitor variety of clinical endpoints [38]-[40].

This study attempts to investigate the possibility of utilizing the continuous monitoring of a non-invasive physiological signal (ECG) to enhance the clinician's ability to early detect onset of a hemodynamic deterioration. While the analytic we developed was originally based on HRV changes produced by simulated hypovolemia and intended to scale to clinical subjects who developed hemodynamic instability, it is not surprising that the analytic was able to capture patients with significant respiratory compromise that resulted in life saving interventions and care escalation since changes in HRV associated with respiratory distress are well known [34], [35], [41]. It is also likely that this respiratory distress if left untreated would lead to hemodynamic compromise as well. It is also known that changes in respiratory rate are an important variable in other early warning systems such as MEWS and NEWS. Identifying high-risk patients prior to clinical recognition of overt hemodynamic or respiratory instability by traditional tools would have enormous clinical implications, as it would allow for better triaging of patients and earlier interventions by medical teams. The approach described here may serve to fill this need through the application of novel computer algorithms, coupled with machine learning techniques. These resulting AHI lead times in the H-RRT cases presents a potential for positive clinical impact by accurately recognizing patient deterioration, well before an event occurs or a care provider recognizes the need for intervention/RRT support. This could enable timely interventions that could avert an emergency situation. Earlier predictions of the onset and progression of hemodynamic decompensation would allow a longer period of time in which to take clinical action and may reduce the need for transfers to higher levels of care.

One of the key limitations of this study was the limited cohort size restricted by the availability of data. Since the data for this study were not collected prospectively, the next iteration of this study will be planned to include a prospective data collection process with a much larger cohort size and, if feasible, include data from more than one institution. Moreover, for this study, a case control design was adopted with an RRT activation as a clinical endpoint which limits the observation of AHI's clinical efficacy to a specific patient population or condition. Since AHI was designed to monitor any patient requiring hemodynamic monitoring, the direction of another study being considered is a cohort control study wherein all patients from a given set of units will be observed for a duration of time, to assess AHI's ability to provide patient monitoring support for a variety of hemodynamic related interventions and outcomes.

As an indicator of autonomic nervous system dysfunction associated with hemodynamic instability, AHI is not capable of determining the cause of hemodynamic or respiratory instability or the exact time that the patient will experience

overt decompensation. AHI is intended to provide care teams an opportunity to reassess their patients in a timely manner in the context of such things as the patient's admitting diagnosis, recent procedures performed, current therapies, etc. that may be a cause of their pending instability. Thus, a post-operative patient whose AHI score is abnormal may be at risk for post-operative hemorrhage or sepsis. Additional technologies or clinical decision support tools would need to be developed to assist in determining how proximal a patient is to overt deterioration.

V. CONCLUSION

Earlier clinical interventions may be possible by earlier detection of patients at risk for hemodynamic instability. A new clinical tool is needed that is reliable, real-time, and non-invasive. This pilot study examines the feasibility of AHI, a continuous analytic that uses a single lead of ECG waveform, to predict episodes of hemodynamic-respiratory instability in patients receiving RRT support. The results from this retrospective study demonstrate that AHI has the potential for identifying a subset of these patients within a clinically relevant timeframe. A future version of a validated AHI product which can be prospectively applied could potentially provide increased vigilance and early interventional support to reduce delayed identification of patient deterioration. The results suggest further studies are warranted examining a larger group of subjects.

VI. LIMITATIONS

The material discussed is pending United States FDA review and not for sale in the United States.

ACKNOWLEDGMENT

The authors would like to thank the clinicians who volunteered their time in support of this project. We also are grateful to the Michigan Center for Integrative Research in Critical Care at the University of Michigan, Ann Arbor in bringing the team together and facilitating the research.

REFERENCES

- [1] Kause J, Smith G, Prytherch D, Parr M, Flabouris A, Hillman K. A comparison of antecedents to cardiac arrests, deaths and emergency intensive care admissions in Australia and New Zealand, and the United Kingdom—the ACADEMIA study. *Resuscitation*. 2004;62(3):275–82.
- [2] Johnston MJ, Arora S, King D, Bouras G, Almoudaris AM, Davis R, et al. A systematic review to identify the factors that affect failure to rescue and escalation of care in surgery. *Surgery*. 2015;157(4):752–63.
- [3] Mitchell IA, McKay H, Van Leuvan C, Berry R, McCutcheon C, Avard B, et al. A prospective controlled trial of the effect of a multi-faceted intervention on early recognition and intervention in deteriorating hospital patients. *Resuscitation*. 2010;81(6):658–66.
- [4] Silber JH, Williams SV, Krakauer H, Schwartz JS. Hospital and patient characteristics associated with death after surgery: a study of adverse occurrence and failure to rescue. *Med Care*. 1992;615–29.
- [5] Brennan TA, Localio AR, Leape LL, Laird NM, Peterson L, Hiatt HH, et al. Identification of adverse events occurring during hospitalization: a cross-sectional study of litigation, quality assurance, and medical records at two teaching hospitals. *Ann Intern Med*. 1990;112(3):221–6.
- [6] Harvey EM, Echols SR, Clark R, Lee E. Comparison of two TeamSTEPPS® Training Methods on nurse failure-to-rescue performance. *Clin Simul Nurs*. 2014;10(2):e57–64.

- [7] Schein RM, Hazday N, Pena M, Ruben BH, Sprung CL. Clinical antecedents to in-hospital cardiopulmonary arrest. *Chest*. 1990;98(6):1388–92.
- [8] Fagan K, Sabel A, Mehler PS, MacKenzie TD. Vital sign abnormalities, rapid response, and adverse outcomes in hospitalized patients. *Am J Med Qual*. 2012;27(6):480–6.
- [9] Jones DA, DeVita MA, Bellomo R. Rapid-response teams. *N Engl J Med*. 2011;365(2):139–46.
- [10] Smith GB, Prytherch DR, Schmidt P, Featherstone PI, Knight D, Clements G, et al. Hospital-wide physiological surveillance—a new approach to the early identification and management of the sick patient. *Resuscitation*. 2006;71(1):19–28.
- [11] Chua WL, Mackey S, Ng EKC, Liaw SY. Front line nurses' experiences with deteriorating ward patients: a qualitative study. *Int Nurs Rev*. 2013;60(4):501–9.
- [12] Mok W, Wang W, Cooper S, Ang ENK, Liaw SY. Attitudes towards vital signs monitoring in the detection of clinical deterioration: scale development and survey of ward nurses. *Int J Qual Health Care*. 2015;27(3):207–13.
- [13] Sankey CB, McAvay G, Siner JM, Barsky CL, Chaudhry SI. "Deterioration to Door Time": An Exploratory Analysis of Delays in Escalation of Care for Hospitalized Patients. *J Gen Intern Med*. 2016;31(8):895–900.
- [14] Bates DW, Zimlichman E. Finding patients before they crash: the next major opportunity to improve patient safety. *BMJ Publishing Group Ltd*; 2015.
- [15] Spaulding A, Ohsfeldt R. Rapid response teams and team composition: a cost-effectiveness analysis. *Nurs Econ*. 2014;32(4):194–204.
- [16] Chan PS, Jain R, Nallmothu BK, Berg RA, Sasson C. Rapid response teams: a systematic review and meta-analysis. *Arch Intern Med*. 2010;170(1):18–26.
- [17] Sulistio M, Franco M, Vo A, Poon P, William L. Hospital rapid response team and patients with life-limiting illness: a multicentre retrospective cohort study. *Palliat Med*. 2015;29(4):302–9.
- [18] Barwise A, Thongprayoon C, Gajic O, Jensen J, Herasevich V, Pickering BW. Delayed rapid response team activation is associated with increased hospital mortality, morbidity, and length of stay in a tertiary care institution. *Crit Care Med*. 2016;44(1):54–63.
- [19] Considine J, Jones D, Pilcher D, Currey J. Physiological status during emergency department care: relationship with in-hospital death after clinical deterioration. *Crit Care Resusc*. 2015;17(4):257–62.
- [20] Fasolino T, Verdin T. Nursing surveillance and physiological signs of deterioration. *MedSurg Nurs*. 2015;24(6):397–403.
- [21] Bingham G, Fossum M, Barratt M, Bucknall T. Clinical review criteria and medical emergency teams: evaluating a two-tier rapid response system. *Crit Care Resusc*. 2015;17(3):167.
- [22] Asensio JA, McDuffie L, Petrone P, Roldán G, Forno W, Gambaro E, et al. Reliable variables in the exsanguinated patient which indicate damage control and predict outcome. *Am J Surg*. 2001;182(6):743–51.
- [23] Shoemaker WC, Wo CC, Chan L, Ramicone E, Kamel ES, Velmahos GC, et al. Outcome prediction of emergency patients by noninvasive hemodynamic monitoring. *Chest*. 2001;120(2):528–37.
- [24] McManus J, Yershov AL, Ludwig D, Holcomb JB, Salinas J, Dubick MA, et al. Radial pulse character relationships to systolic blood pressure and trauma outcomes. *Prehosp Emerg Care*. 2005;9(4):423–8.
- [25] Wo CC, Shoemaker WC, Appel PL, Bishop MH, Kram HB, Hardin E. Unreliability of blood pressure and heart rate to evaluate cardiac output in emergency resuscitation and critical illness. *Crit Care Med*. 1993;21(2):218–23.
- [26] Edmonds ZV, Mower WR, Lovato LM, Lomeli R. The reliability of vital sign measurements. *Ann Emerg Med*. 2002;39(3):233–7.
- [27] Grant S, Crimmons K. Limitations of track and trigger systems and the National Early Warning Score. Part 2: sensitivity versus specificity. *Br J Nurs*. 2018;27(12):705–10.
- [28] Downey CL, Tahir W, Randell R, Brown JM, Jayne DG. Strengths and limitations of early warning scores: a systematic review and narrative synthesis. *Int J Nurs Stud*. 2017;76:106–19.
- [29] Koch E, Lovett S, Nghiem T, Riggs RA, Rech MA. Shock index in the emergency department: utility and limitations. *Open Access Emerg Med Oaem*. 2019;11:179.
- [30] Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA*. 2016 Feb 23;315(8):762–74.
- [31] Stein PK, Bosner MS, Kleiger RE, Conger BM. Heart rate variability: A measure of cardiac autonomic tone. *Am Heart J*. 1994 May 1;127(5):1376–81.
- [32] Kleiger RE, Miller JP, Bigger Jr JT, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol*. 1987;59(4):256–62.
- [33] Sztajzel J. Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system. *Swiss Med Wkly*. 2004;134(35–36):514–22.
- [34] Chen I-C, Kor C-T, Lin C-H, Kuo J, Tsai J-Z, Ko W-J, et al. High-frequency power of heart rate variability can predict the outcome of thoracic surgical patients with acute respiratory distress syndrome on admission to the intensive care unit: a prospective, single-centric, case-controlled study. *BMC Anesthesiol*. 2018;18(1):34.
- [35] Gañán-Calvo AM, Fajardo-López J. Universal structures of normal and pathological heart rate variability. *Sci Rep*. 2016;6:21749.
- [36] Belle A, Ansari S, Spadafore M, Convertino VA, Ward KR, Derksen H, et al. A signal processing approach for detection of hemodynamic instability before decompensation. *PloS One*. 2016;11(2):e0148544.
- [37] Rao MH, Marella P, Kath B. Assessment of severity and outcome of critical illness. *Indian J Anaesth*. 2008;52:652–62.
- [38] Mukkamala R, Reisner AT, Hojman HM, Mark RG, Cohen RJ. Continuous cardiac output monitoring by peripheral blood pressure waveform analysis. *IEEE Trans Biomed Eng*. 2006;53(3):459–67.
- [39] Moulton SL, Mulligan J, Santoro MA, Bui K, Grudic GZ, MacLeod D. Validation of a noninvasive monitor to continuously trend individual responses to hypovolemia. *J Trauma Acute Care Surg*. 2017;83(1):S104–11.
- [40] Pirracchio R, Cohen MJ, Malenica I, Cohen J, Chambaz A, Cannesson M, et al. Big data and targeted machine learning in action to assist medical decision in the ICU. *Anaesth Crit Care Pain Med*. 2019;38(4):377–84.
- [41] Huang C-T, Tsai Y-J, Lin J-W, Ruan S-Y, Wu H-D, Yu C-J. Application of heart-rate variability in patients undergoing weaning from mechanical ventilation. *Crit Care*. 2014;18(1):R21.