Circulation: Heart Failure

ORIGINAL ARTICLE

Continuous Wearable Monitoring Analytics Predict Heart Failure Hospitalization

The LINK-HF Multicenter Study

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BACKGROUND: Implantable cardiac sensors have shown promise in reducing rehospitalization for heart failure (HF), but the efficacy of noninvasive approaches has not been determined. The objective of this study was to determine the accuracy of noninvasive remote monitoring in predicting HF rehospitalization.

METHODS: The LINK-HF study (Multisensor Non-invasive Remote Monitoring for Prediction of Heart Failure Exacerbation) examined the performance of a personalized analytical platform using continuous data streams to predict rehospitalization after HF admission. Study subjects were monitored for up to 3 months using a disposable multisensor patch placed on the chest that recorded physiological data. Data were uploaded continuously via smartphone to a cloud analytics platform. Machine learning was used to design a prognostic algorithm to detect HF exacerbation. Clinical events were formally adjudicated.

RESULTS: One hundred subjects aged 68.4±10.2 years (98% male) were enrolled. After discharge, the analytical platform derived a personalized baseline model of expected physiological values. Differences between baseline model estimated vital signs and actual monitored values were used to trigger a clinical alert. There were 35 unplanned nontrauma hospitalization events, including 24 worsening HF events. The platform was able to detect precursors of hospitalization for HF exacerbation with 76% to 88% sensitivity and 85% specificity. Median time between initial alert and readmission was 6.5 (4.2–13.7) days.

CONCLUSIONS: Multivariate physiological telemetry from a wearable sensor can provide accurate early detection of impending rehospitalization with a predictive accuracy comparable to implanted devices. The clinical efficacy and generalizability of this low-cost noninvasive approach to rehospitalization mitigation should be further tested.

REGISTRATION: URL: https://www.clinicaltrials.gov. Unique Identifier: NCT03037710.

Key Words: heart failure ■ hospitalization ■ machine learning ■ smartphone ■ telemetry

Heart failure (HF) is a major public health problem affecting >23 million patients worldwide.[1–3] Hospitalization costs for HF represent 80% of costs attributed to HF care.[4] Thus, accurate and timely detection of worsening HF could allow for interventions aimed at reducing the risk of HF admission.

Several such approaches have been tested. Tracking of daily weight, as recommended by current HF guidelines, did not lead to reduction of the risk of HF hospitalization,[5] most likely because the weight gain is a contemporaneous or lagging indicator rather than a leading event. Interventions based on intrathoracic impedance

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The Data Supplement is available at https://www.ahajournals.org/doi/suppl/10.1161/CIRCHEARTFAILURE.119.006513.

For Sources of Funding and Disclosures, see page 10.

Circulation: Heart Failure is available at www.ahajournals.org/journal/circheartfailure

WHAT IS NEW?

- We demonstrate that machine learning analytics using data from a wearable sensor can accurately predict hospitalization for heart failure exacerbation.
- We show that through this approach an alert indicating likely heart failure exacerbation can be generated at a median time of 6.5 days before the admission.

WHAT ARE THE CLINICAL IMPLICATIONS?

- The study shows that wearable sensors coupled with machine learning analytics have predictive accuracy comparable to implanted devices.
- The findings provide a basis for prospective testing of the clinical efficacy of this data-driven approach to improve clinical outcomes in heart failure.

Nonstandard Abbreviations and Acronyms

HF	heart failure
MCI	multivariate change index
MultiSENSE	Multisensor Chronic Evaluation in Ambulatory HF Patients
MUSIC	Multi-Sensor Monitoring in Congestive Heart Failure
ROC	receiver operating characteristic
SBM	similarity-based modeling

monitoring also did not result in reduction of readmission risk.[6,7] These results suggest that physiological parameters other than weight or intrathoracic impedance in isolation may be needed to detect HF decompensation in a timely manner. In fact, 28% reduction of rehospitalization rates has been shown with interventions based on pulmonary artery hemodynamic monitoring.[8,9] More recently, in the MultiSENSE study (Multisensor Chronic Evaluation in Ambulatory HF Patients), an algorithm based on physiological data from sensors in the implantable cardiac resynchronization therapy defibrillators, was shown to have 70% sensitivity in predicting the risk of HF hospitalization or outpatient visit with intravenous therapies for worsening of HF.[10]

Whether the risk of impending HF exacerbation could be accurately predicted using physiological parameters obtained by noninvasive means remains to be further investigated. Although proof of concept for this approach has been described in the MUSIC study (Multi-Sensor Monitoring in Congestive Heart Failure),[11] the investigation was limited by technical shortcomings of the monitoring device and data transmission capabilities at the time, which resulted in >40% subject drop-out. More recent technological advances, including sensor miniaturization, improved battery life, and ubiquitous use of handheld devices, provide opportunities for more reliable continuous telemonitoring. This is further amplified by advances in data science and artificial intelligence.[12] Hence, we hypothesized that a machine learning analytics algorithm using continuous remote monitoring data from a wearable sensor will predict HF rehospitalization with ≥70% sensitivity at a specificity level of 85%.

METHODS

The data and information of the analytical methods that support the findings of this study are available from the corresponding author upon reasonable request.

The LINK-HF study (Multisensor Non-invasive Remote Monitoring for Prediction of Heart Failure Exacerbation) was a multicenter, observational study with the primary aim of determining the accuracy of machine learning analytics of a remote patient monitoring system in predicting HF readmission to the hospital. Secondary aims included the assessment of subject compliance with the study procedures.

Inclusion Criteria

Adult subjects (≥18 years) with a history of HF and New York Heart Association functional class II-IV symptoms who were hospitalized for acute HF exacerbation were eligible for study participation. Inclusion criteria allowed enrollment of subjects with both HF with reduced ejection fraction (left ventricular ejection fraction <50%) and with HF with preserved ejection fraction (left ventricular ejection fraction ≥50%). Exclusion criteria were presence of skin damage preventing wearing of study device and visual or cognitive impairment that would preclude ability to comply with study procedures.

The study subjects were enrolled at Veterans Affairs medical centers in Salt Lake City, UT; Palo Alto, CA; Houston, TX; and Gainesville, FL. The study was approved by the Institutional review boards at all 4 institutions, and all subjects provided informed consent for study participation.

Remote Monitoring System

The study subjects were fitted with a wearable sensor (Vital Connect, San Jose CA) secured on their chest by an adhesive

Figure 1. Multisensor monitoring device consisting of a disposable sensor patch with a disposable battery and a reusable sensor electronics module.

surface. The sensor comprises of a disposable sensor patch with a disposable battery (7-day life) and a reusable sensor electronics module (Figure 1). The electronics module is activated by the battery when inserted into the disposable patch. The sensor has 2 electrodes facing the skin used for ECG detection and skin impedance measurement. A temperature sensor also faces the skin. A 3-axis accelerometer is located internally. The sensor collects continuous ECG waveform, continuous 3-axis accelerometry, skin impedance, skin temperature, and information on activity and posture. Data derived from the primary information include heart rate, heart rate variability, arrhythmia burden, respiratory rate, gross activity, walking, sleep, body tilt, and body posture.

The sensor patch was paired via bluetooth with an android phone equipped with a conventional cellular data plan, and data from the sensors were continuously streamed to the phone (Figure 2). The sensor has on-board storage of up to 10 hours in case the subject walks out of bluetooth range (≈20 feet). When back in range, stored data are offloaded to the phone assuring full data collection. Data collected on the phone were encrypted and uploaded through cellular connectivity at configurable intervals to a cloud analytics platform (PhysIQ, Chicago, IL; Figure 2).

Machine Learning Analytics

The cloud-based analytics platform used a general machine learning method of similarity-based modeling (SBM), to analyze collected data. SBM models the behavior of complex systems (eg, aircraft engines, computer networks, or human physiology) by learning tandem patterns among system variables as they are periodically sampled together.[13] Once patterns representative of system behavior are identified to create a dynamic baseline model, the platform switches over to surveillance mode, where interpolative estimates are calculated based on the learned patterns for comparison to ongoing monitored data.

Using data from a pilot study,[14] we configured SBM to handle data from the study sensor. We used a 1-minute trim-mean (10%) heart rate, respiratory rate, a cumulative gross activity, and posture as inputs to SBM. Atrial fibrillation, tachycardia, and bradycardia detection were used along with SBM. Based on the assumption that a subject is at a relatively stable point post-discharge, a personalized baseline model of dynamic patterns of monitored vital signs was established for each subject within 72 hours of discharge. After that, the personalized baseline model provided estimates of expected values to compare with the monitored physiological signals collected by the sensor. Vital sign measurements matching expected values indicated that the subject's physiology was behaving similar to baseline model training, regardless of the subject's activity (sedentary, walking, asleep, awake, etc). In this way, normal variation in the vital signs because of activities of daily living was effectively removed, leaving only differences between the learned dynamic behavior and actual monitored vital sign behavior.

The differences across vital signs were combined into a single index, the multivariate change index (MCI; range, −1 to 1; <0 implies improving health, >0 implies worsening health), to represent the likelihood that the subject's physiology was behaving differently than it did during baseline training. For unchanging vital sign behavior, the index is close to zero. The more a subject's physiology changes for the worse, the higher the index value, indicative of possible worsening of HF. MCI was determined on a 1-minute basis commensurate with vital sign data rates input to the model.

Study Procedures

The study subjects were enrolled at the time of discharge from an HF exacerbation hospitalization and trained on how to activate a disposable patch by inserting the reusable electronics module and on how to pair the electronics module with the phone. The subjects were instructed to put on a new patch once the previous patch battery was depleted or when the patch adhesive started to wear off. The study participants were also issued a printed patient manual with the corresponding instructions; these instructions were also present in an electronic format in the corresponding app on the phone.

All study subjects were asked to wear the sensor 24 hours a day, for a minimum of 30 days, and up to 90 days post-discharge. Subjects changed disposable patches on their own. The subjects were asked to continue routine care with their HF team. No constraints were placed on subjects' activities.

Clinical End Point Definition

The clinical event of interest was hospital readmission after the index discharge from the HF exacerbation hospitalization. We examined (1) hospitalizations due to worsening HF (HF hospitalization) and (2) all unplanned, nontrauma related hospitalizations (unplanned nontrauma hospitalization). Additional events of interest were emergency department visits and mortality.

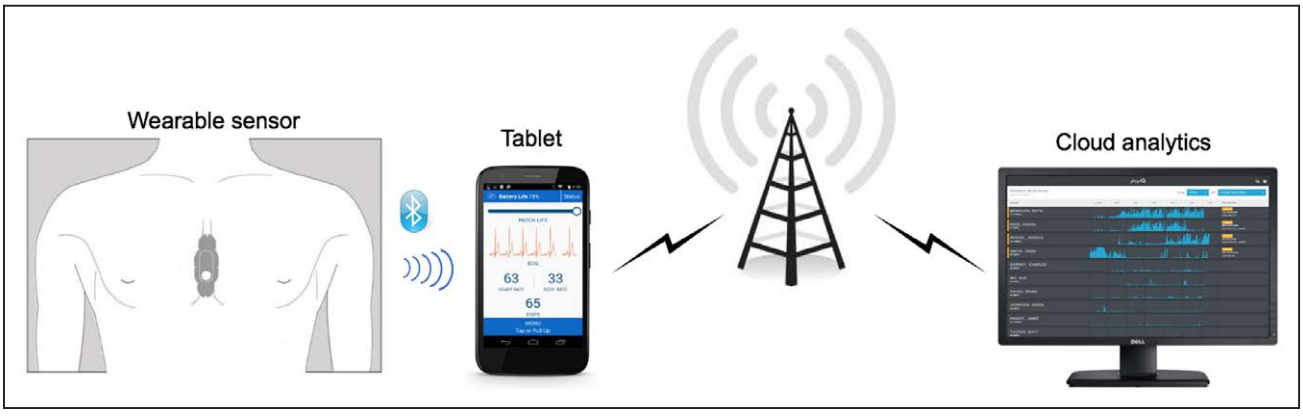

Figure 2. Data collected by the sensor are streamed to a phone and then encrypted and uploaded to a cloud analytics platform.

All clinical events were adjudicated by the study principal investigator and the corresponding site principal investigator. Source documents were the basis of adjudication decisions. At the time of adjudication, the investigators remained blinded to study remote monitoring data collected by the sensor. Admission for HF was defined as a hospitalization where the subject had signs and symptoms of HF on admission and was treated for HF during admission with medications including diuretic therapy (either intravenous diuretics or augmentation of oral diuretics) or vasodilators, inotropic support or ultrafiltration for treatment of HF.

Predictive Algorithm

The MCI reflects whether there is a significant difference in the observed remote monitoring data compared with the data expected based on the training period personalized baseline. The 1-minute MCIs are converted to a daily average MCI. If the daily average MCI crosses a prespecified threshold, the machine learning platform triggers a clinical alert. (In this observational study, providers were not made aware of clinical alerts.)

We constructed receiver operating characteristic (ROC) curves for the events of HF hospitalization and unplanned nontrauma hospitalization by applying a moving discrimination threshold to daily MCI values and scoring resulting alerts for accuracy as described below. The threshold set at 85% specificity was of particular interest to allow comparison with previous studies, and sensitivity for predicting HF hospitalization and unplanned nontrauma hospitalization at the 85% specificity is presented. Of note, in clinical use, the threshold applied to daily MCI for clinical alerting could be adjusted to allow a different sensitivity or specificity, as desired based on the clinical situation.

To score accuracy of the analytical platform as correct or incorrect, it was necessary to determine a plausible time window before each hospitalization in which a clinical alert could reasonably be associated with the hospitalization event (positive window). If an alert occurred in the positive window, it was assessed as correct; if an alert occurred outside of a positive window (in the negative window), it was assessed as incorrect.

Negative window decisions were assessed daily as correct or incorrect. In contrast, detection of positive events was scored on an event-basis, such that multiple clinical alerts in a positive event window counted as one detection. Such an approach mirrors clinical workflow, as generally each decision in a negative window represents false alert activity imposed on clinicians, while true positive detections would result in clinical triage that could intercept the evolving condition such that subsequent detections are redundant.

We used 2 alternative methods for defining the size of the positive window: (1) a fixed positive window of 10 days before hospitalization and (2) an event-specific positive window, an interval defined post hoc for each hospitalization event individually, based on contemporaneous evidence collected in the study, namely patient-reported symptoms, reported medication noncompliance, or self-evident data deviation from normal (eg, onset of rapid atrial fibrillation in the captured ECG). Event-specific windows were determined before any performance analysis, and in the absence of specific evidence in the record, defaulted to a 10-day window.

Statistical Analysis

For retrospective performance, a true positive occurs when an alert is generated on any one or more days of the positive window of an event; a false negative occurs if all days in the positive window lack alerts. Detection lead time is taken from the first alert in the positive window. A false negative occurs when an alert occurs on a day not in a positive window of an event. Data are presented as mean ± SD, median (interquartile range) or frequency (percent), as appropriate. Separate ROC curves were constructed to demonstrate the analytical algorithm accuracy in predicting HF hospitalizations and unplanned nontrauma hospitalizations using each of the 2 approaches to determining positive windows. Because a random alerting process would have multiple chances to detect an event, the random line in the ROC curves is higher than a simple diagonal; in our analysis, to be factually accurate, the random alerting process was given a number of chances equal to the number of days in the positive window up to and including the first day on which the predictive algorithm alerted.

To characterize prospective performance without reliance on any window definitions, we adapted a Kaplan-Meier analysis to explore time to HF hospitalization in 3 groups: (1) the entire study population, (2) an alert-free population—where time 0 was time of study entry and subjects were censored at the time of the first alert, and (3) a population with an alert—where time 0 was time of first alert. Log-rank test was used to compare time-to-hospitalization between those with and without an alert. Two-tailed tests were used in analyses. A $P<0.05$ was considered significant. Calculations were performed using SPSS 21 software (Chicago, IL).

RESULTS

Baseline Characteristics and Completeness of Data Capture

A total of 100 study subjects were enrolled in the study between August 2015 and December 2016. The mean age was 68.4±10.2 years and 98% of patients were male. There were 74 (74%) subjects with HF with reduced ejection fraction and 26 (26%) with HF with preserved ejection fraction. Baseline subject characteristics, including the comorbidity burden and medical therapy at discharge, are listed in Table 1. Table 1 also shows baseline characteristics of patients with and without HF admission in study follow-up.

Compliance with the use of the sensor patch was high. Of the 100 subjects enrolled, 87 completed 30 days of monitoring (the study's minimum monitoring period), 3 patients became ineligible for study continuation within the first 30 days (eg, died or were admitted to nursing facility after a rehospitalization), and 10 were noncompliant or dropped out of the study. Of the 87 subjects, 74 subjects completed 90 days of monitoring, and 13 subjects died or became ineligible for study participation between days 30 and 90.

Considering all time during study enrollment as a reference, data successfully uploaded from the study sensor covered 74.1% of the time subjects participated

Table 1. Baseline Subject Characteristics for the Entire Cohort, and for Patients With and Without HF Admission During the Study

	All, n=100	Without HF Hospitalization, n=75	With HF Hospitalization, n=25	*P* Value
Age, y	68.4±10.2	68.7±10.0	69.7±11.0	0.66
Sex (male), n (%)	98 (98)	74 (99)	24 (96)	0.44
Systolic BP, mm Hg	130±27	132±26	124±28	0.17
Diastolic BP, mm Hg	74±16	75±16	71±17	0.31
Heart rate, beats/min	82±16	83±16	78±16	0.25
Race, n (%)				0.95
White	79 (79)	59 (79)	20 (80)	
Black	15 (15)	11 (15)	4 (16)	
Asian	4 (4)	3 (4)	1 (4)	
Other	2 (2)	2 (3)	0 (0)	
BMI, kg/m^2	29.9 (25.6–37.3)	33.2±9.1	28.4±6.7	0.03
NYHA, n (%)				0.46
Class II	25 (25)	21 (28)	4 (16)	
Class III	55 (55)	39 (52)	16 (64)	
Class IV	20 (20)	15 (20)	5 (20)	
HF type, n (%)				0.07
HFrEF	74 (74)	52 (69)	22 (88)	
HFpEF	26 (26)	23 (31)	3 (12)	
Coronary artery disease, n (%)	74 (74)	52 (63)	22 (88)	0.07
Myocardial infarction	19 (19)	11 (15)	8 (31)	0.08
Coronary artery bypass	33 (33)	23 (31)	10 (40)	0.39
Percutaneous coronary intervention	35 (35)	22 (29)	13 (52)	0.04
Ejection fraction	37±14%	37.8±14.1%	34.5±14.6%	0.32
Diabetes mellitus, n (%)	57 (57)	41 (55)	16 (64)	0.41
Atrial fibrillation, n (%)	49 (49)	35 (47)	14 (56)	0.42
Anemia, n (%)	31 (31)	21 (28)	10 (40)	0.26
COPD, n (%)	28 (28)	18 (24)	10 (40)	0.12
Tobacco use, n (%)				
Current	12 (12)	9 (12)	3 (12)	0.77
Past	62 (62)	45 (61)	17 (68)	
Laboratory tests				
Na, mEq/L	137.6±4.2	137.6±4.0	137.5±4.6	0.86
K, mEq/L	4.2±0.5	4.2±0.5	4.2±0.5	0.74
BUN, mg/dL	28 (20–45)	27.5 (20–46.5)	30 (19.5–42)	0.74
Creatinine, mg/dL	1.33 (1.10–1.71)	1.33 (1.10–1.70)	1.33 (1.20–1.84)	0.65
BNP, pg/mL	754 (313–1409)	624 (288–1160)	941 (616–1971)	0.28
NT-proBNP	1539 (977–4542)	1343 (819–2394)	4542 (3589–7109)	0.023
Hematocrit, %	38.0±7.3	38.5±7.3	36.4±7.1	0.24
Hemoglobin, g/dL	12.4±2.2	12.7±2.1	11.7±2.4	0.05
Medication, n (%)				
β-blockers	80 (80)	62 (83)	18 (72)	0.26
ACE inhibitors/ARB/ARNi	59 (59)	44 (59)	15 (60)	0.91
Loop diuretics	92 (92)	67 (89)	25 (100)	0.09
Aldosterone antagonist	24 (24)	16 (21)	8 (32)	0.28
Anticoagulation	47 (47)	35 (47)	12 (48)	0.91
Nitrate	36 (36)	25 (33)	11 (44)	0.34

(*Continued*)

Table 1. Continued

	All, n=100	Without HF Hospitalization n=75	With HF Hospitalization n=25	*P* Value
Device therapy, n (%)				
Pacemaker	15 (15)	11 (15)	4 (16)	0.99
CRT	8 (8)	6 (8)	2 (8)	0.99
ICD	25 (25)	15 (20)	10 (40)	0.05

ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor neprilysin inhibitor; BMI, body mass index; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter-defibrillator; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and NYHA, New York Heart Association.

in the study. After imposing data quality requirements, 93.5% of uploaded data were analyzable (Figure I in the Data Supplement).

Clinical Events

There were 49 hospitalizations that took place during the 90 days of follow-up in 38 subjects at a median time from discharge to rehospitalization of 50.5 days. Of these, 27 were HF hospitalizations and 40 were unplanned nontrauma hospitalizations (Figure 3). Sensor use compliance failure by the subject led to 5 events with insufficient data. These 5 events were excluded from the ROC analysis but are included in the time-to-event analyses.

Fifty-two emergency department visits took place during the 90 days of follow-up, of which 28 resulted in hospitalization. Among the remaining 24 visits which did not result in hospitalization, only one was adjudicated to be for HF exacerbation, and therefore, no separate analysis was performed for emergency department visits.

Twelve subjects died during the study. Six deaths were adjudicated as sudden cardiac death, 2 were due to stroke, one due to HF, one due to sepsis, and in 2 subjects cause of death could not be determined. None of the sudden cardiac deaths were preceded by an alert in the 10-day positive window.

Predictive Algorithm Performance

Clinical alert-to-hospitalization times, calculated as a number of days before hospitalization on which a positive detection occurs in the positive window for each event detected, are shown in Table 2. Event-specific window size and first alert within each event-specific positive window is shown in Figure II in the Data Supplement. Depending on the positive window method used and the type of hospitalization, the median time between the clinical alert and hospital admission ranged between 6.5 (interquartile range, 4.2–13.7) and 8.5 (interquartile range, 3.8–13.0) days, an interval that should permit for introduction of an intervention aimed at reversing the worsening.

ROC curves for the predictive analytics platform were calculated using both definitions of the positive window. Using the fixed positive window of 10 days, the ROC area under the curve was 0.86 for HF hospitalizations and 0.80 for unplanned nontrauma hospitalizations (Figure 4). Using the event-specific positive window, the area under the curve was 0.89 for HF

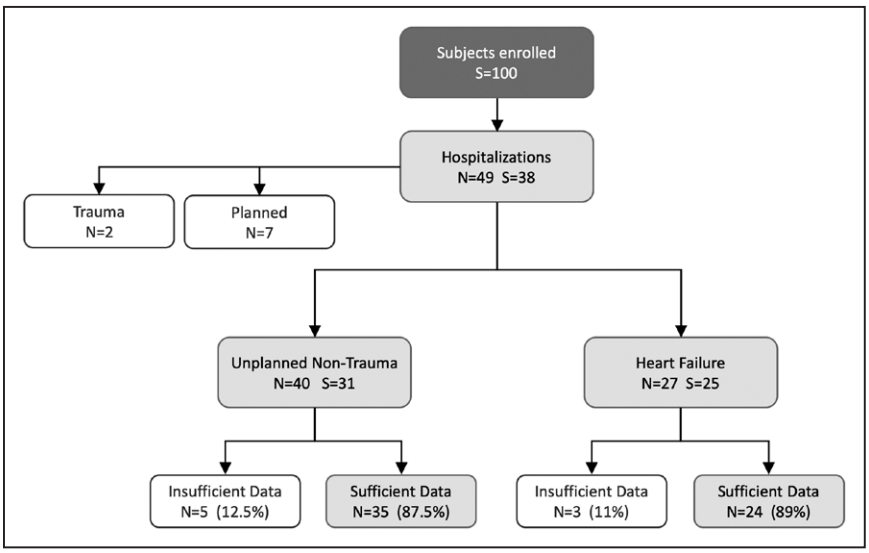

Figure 3. Study flowchart.
N indicates number of hospitalizations; and S, number of subjects.

Table 2. Clinical Alert-to-Hospitalization Time by Positive Window Type and Hospitalization Type

Positive Window Methodology	Mean SD, d	Median (IQR), d
Ten-day positive window		
HF hospitalization	6.8±2.7	6.5 (4.5/9.5)
Unplanned nontrauma hospitalization	7.2±2.6	8.5 (5.0/9.5)
Event-specific window		
HF hospitalization	10.4±8.7	6.5 (4.2/13.7)
Unplanned nontrauma hospitalization	11.3±12.1	8.5 (3.8/13.0)

HF indicates heart failure; and IQR, interquartile range.

hospitalizations and 0.84 for unplanned nontrauma hospitalizations (Figure 5).

In Table 3, we show the analytical platform sensitivity at a specificity of ≈85% achieved at the discrimination threshold of 0.03. The specificity of 85% was selected as an example of where the clinical alert could be anchored for clinical use. This specificity would seem practical for clinical decision making and is also similar to the specificity reported by the MultiSENSE algorithm which is currently marketed for clinical use.[10]

A prospective examination of the predictive algorithm performance was done using the time-to-event Kaplan-Meier analysis, which evaluates the change in hospitalization rate once an alert has been generated regardless of positive or negative windows. Figure 6 shows time-to-HF admission (Figure 6A) and time-to-unplanned nontrauma admission (Figure 6B) for the whole study population and for subjects with and without a clinical alert. There is a significant divergence in time-to-HF and time-to unplanned nontrauma hospitalization between those with and without an alert (P=0.001 and P=0.008, respectively).

DISCUSSION

The LINK-HF study demonstrates that a personalized machine learning analytical platform supplied with noninvasively captured remote patient monitoring data is able to accurately predict rehospitalization for HF. Depending on the approach to adjudicating pre-event positive windows, the platform was able to detect the risk of hospitalization for worsening of HF with 76.0% to 87.5% sensitivity and 85% specificity.

Furthermore, the clinical alerts preceded the hospitalization by a median time between 6.5 and 8.5 days, an interval that should provide sufficient time for an intervention aimed at preventing hospitalization. A time-to-HF hospitalization analysis also demonstrated a significant divergence between the group of subjects with and without a clinical alert.

Implantable Devices to Detect HF Exacerbation

Several previous studies evaluated the efficacy of implantable devices to predict worsening of HF and reduce the risk of hospitalization. Studies that evaluated only intrathoracic impedance had variable predictive accuracy,

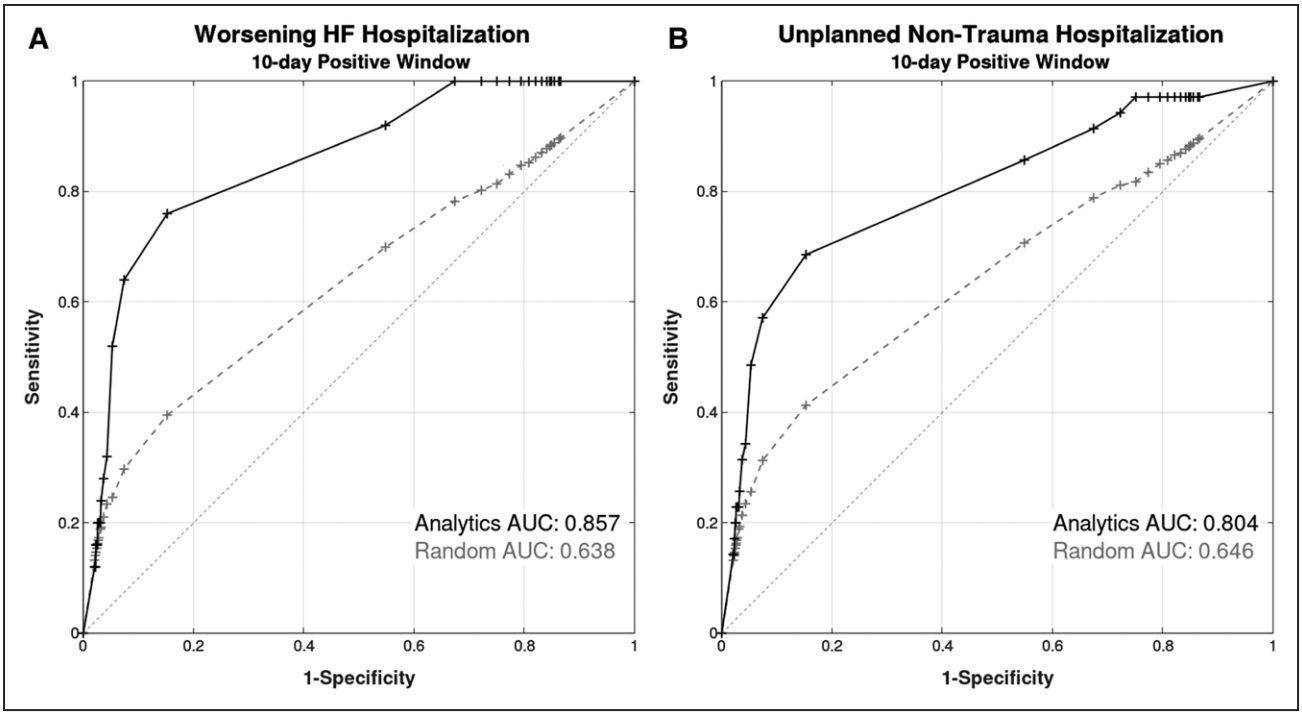

Figure 4. Receiver operating characteristic (ROC) curve for (A) heart failure (HF) hospitalizations and (B) unplanned nontrauma hospitalizations.
Fixed positive window of 10 days was used for calculation.

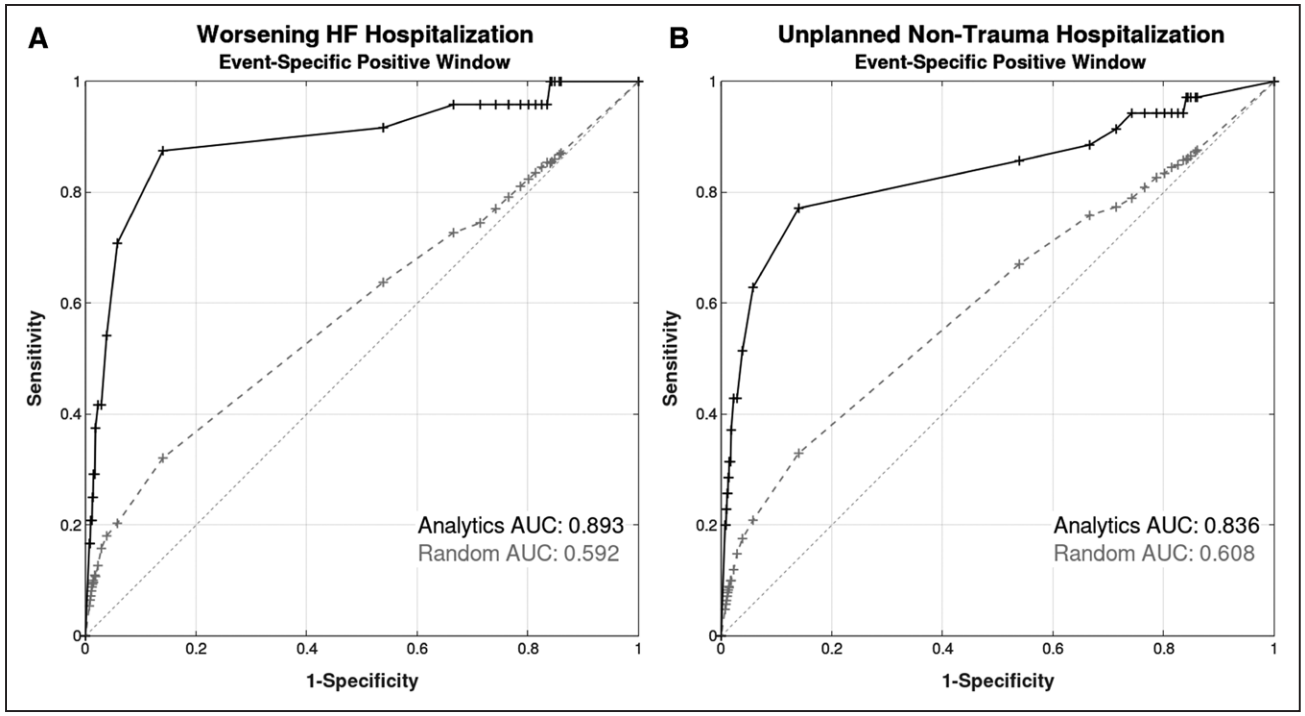

Figure 5. Receiver operating characteristic (ROC) curve for (A) heart failure (HF) hospitalizations and (B) unplanned nontrauma hospitalizations. Event-specific positive window approach was used for calculation.

ranging from 21% to 76%.[15–17] Higher expectations were set for studies using a multisensor approach, but a study that used minute ventilation and physical activity sensors had only 34% sensitivity.[18] More recently, in the MultiSENSE trial, the HeartLogic algorithm based on several variables collected from a cardiac resynchronization therapy defibrillator had 70% sensitivity for detection of subsequent hospitalization or outpatient visit with IV therapies for worsening of HF.[10] However, the long times between an alert and the hospitalization (median 34 days [19.0–66.3 days]) called into question whether the HeartLogic algorithm is just risk-stratifying the population for long-term acute event, rather than detecting an imminent event. The CardioMEMS device examined the utility of invasive pulmonary artery hemodynamic monitoring and resulted in a decrease of HF hospitalizations.[8,9] This device requires invasive implantation of a sensor in the pulmonary artery, and measurements need to be obtained by the patient.

Table 3. Analytical Platform Sensitivity and Specificity by Positive Window Type and Hospitalization Type

Positive Window Methodology	Sensitivity	Specificity
Ten-day positive window		
HF hospitalization	76.0%	84.8%
Unplanned nontrauma hospitalization	68.6%	84.7%
Event-specific window		
HF hospitalization	87.5%	86.0%
Unplanned nontrauma hospitalization	77.1%	86.0%

HF indicates heart failure.

Wearable Devices to Detect HF Exacerbation

Because not all HF patients have an indication for a pacemaker or a defibrillator, and because implantation of a dedicated device presents procedural risks, noninvasive methods of monitoring may be more useful and cost-effective in patients temporarily at increased risk of HF-related hospitalization. The risk of hospitalization is significantly elevated in the first 90 days after hospital discharge, with the readmission rate being ≈30%. This time of increased risk, therefore, appears to be an opportune period for noninvasive monitoring aimed at identifying patients with incipient HF decompensation.

One previous study examined the utility of a wearable monitoring device in a similar approach to ours. In the MUSIC study, physiological data recorded from a multisensor noninvasive skin-adherent monitoring system had 63% sensitivity for detection of HF events.[11] However, compliance with the device use was negatively influenced by the device size. Advances in electronics in recent years have led to the development of smaller sensors, which were used in the current remote monitoring system. The smaller sensor, which takes the form of an adhesive patch, minimizes interference with the patient's daily activities. The use of a bluetooth enabled transfer of the data to a tablet and further data upload via a cellular service was also more intuitive to the study subjects than previous approaches to data transfer. This may explain why the current study achieved data capture for 74% of all monitorable hours across all patients (Figure I in the Data Supplement).

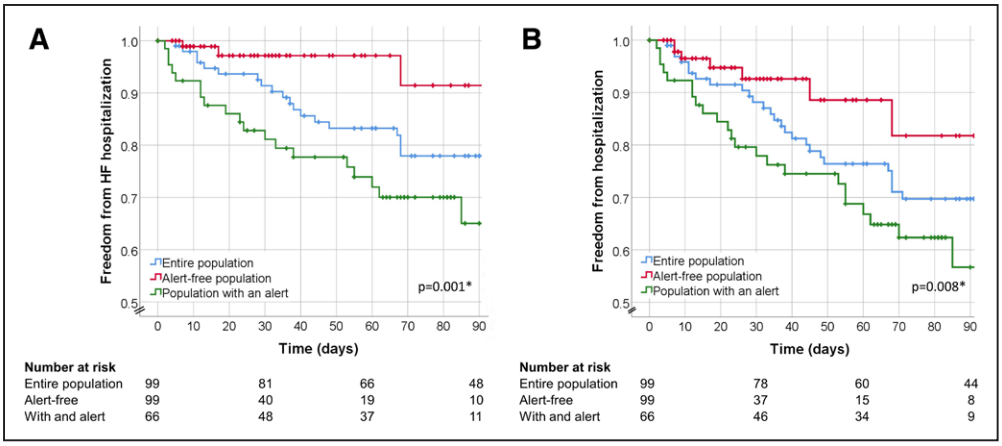

Figure 6. Time to (A) heart failure hospitalization and (B) unplanned nontrauma hospitalization.
Alert-free population: T_0 is the time of study enrollment and subjects are censored at the time of first clinical alert. Population with an alert: T_0 is the time of first alert. *Log-rank *P* for the comparison of population with alert vs alert-free population

Novelty of the LINK-HF Approach

A significant novelty of our approach is the use of personalized machine learning to combine multiple physiological data streams into a model specific to each individual. This has 2 advantages. First, combined analysis of several physiological parameters that reflect the complex pathophysiology associated with HF may explain superior sensitivity as compared to devices based on one parameter. Second, the analysis was facilitated by learning and comparing longitudinal continuous data streams to the normal dynamics of the individual's vital signs, rather than to population-based norms, thus controlling for intersubject variability and identifying true anomalies. Furthermore, as illustrated by the ROC curves (Figures 4 and 5), the MCI analytical discrimination threshold can be adjusted based on the specific clinical need, trading sensitivity and specificity. We also feel the key advantage of the adhesive patch device is that it does not require invasive implantation, which decreases the risk of procedure-related complications.

Study Limitations

The results of this study should be understood in the context of its limitations. First, we excluded from our analysis 5 events which were not preceded by sufficient data transfer from the study subjects. If these data were not missing at random, this could have introduced a bias. If these 5 events were to be included and considered failed detections due to the lack of a preceding alert, the resulting predictive platform sensitivity would be 72.4% for HF hospitalization and 67.5% for unplanned nontrauma hospitalization, at the selected specificity of 85%. We think compliance with the use of the sensor patch may further increase once patients may benefit from the monitoring, which was not the case in this study. We also think that data completeness and compliance will be further improved with the next-generation version of the patch currently available—a true band-aid-like disposable system with integrated battery and electronics. Second, we did not have formal testing and validation sets. Although we used a predictive algorithm developed using data from previous pilot investigations,[14] the length of the training period was configurable. A longer training period improves characterization of baseline but can potentially reduce available test days and testable events. We anticipated using between 2 and 3 days of training, but left this configurable parameter open to determination until we had substantial experience with data yield from enrolled subjects. In the end, we used a 3-day training period. Third, because of the study's observational nature, we do not know whether the alerts generated by the monitoring system with its machine learning analytics are clinically actionable to decrease the risk of hospitalization. Fourth, because the study was done in mostly male population with HF with reduced ejection fraction, it is unclear whether similar results apply also to female population and patients with HF with preserved ejection fraction.

These results provide a rationale for the next step, a prospective study, currently in planning, which will randomize patients to an active arm—remote monitoring with alerts communicated to the clinical team and clinicians following a standardized response algorithm, versus control—remote monitoring without alerts being generated. This study should provide important insights into the clinical efficacy of wearable analytics in improving HF outcomes. A critical step will be implementation into clinical workflow and development of an algorithmic treatment response to system clinical alerts.[19] In some previous studies, inadequate response to clinical alerts may explain good predictive performance with no significant effect on the risk of rehospitalization. Importantly, not all HF-rehospitalizations can or should be prevented. Indeed, as

recently recognized, the Hospital Readmissions Reduction Program based on financial penalization of hospitals with higher rates of readmissions was associated with reduction of readmissions but increased mortality.[20] We, therefore, estimate that up to one-half of the predicted HF hospitalizations can be prevented by a timely treatment intervention. Considering the platform's sensitivity, this provides an opportunity to reduce HF rehospitalization by approximately one-third.

Conclusions

In this study, multivariate physiological telemetry from a wearable sensor provided accurate early detection of impending HF rehospitalization with a predictive accuracy comparable to implanted devices. The clinical efficacy and generalizability of this low-cost noninvasive approach to rehospitalization mitigation should be tested.

ARTICLE INFORMATION

Received August 22, 2019; accepted December 20, 2019.

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Sources of Funding

This study was funded by the Department of Veterans Affairs Office of Information & Technology—the Veterans Affairs Industry Innovations (Vai2) Competition (VA118-11-P-0031) and by the Veterans Affairs Center for Innovation, Washington, DC.

Disclosures

M. Pipke, S. Wegerich, K. Rose, Dr Sekaric, Dr Anand, and D. Richards are employees of PhysIQ, the provider of the platform. Dr Stehlik is a consultant to Medtronic and Abbott. The other authors report no conflicts.

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