Predicting Heart Failure patient events by exploiting saliva and breath biomarkers information

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Abstract—The aim of this work is to present a machine learning based method for the prediction of adverse events (mortality and relapses) in patients with heart failure (HF) by exploiting, for the first time, measurements of breath and saliva biomarkers (Tumor Necrosis Factor Alpha, Cortisol and Acetone). Data from 27 patients are used in the study and the prediction of adverse events is achieved with high accuracy (77%) using the Rotation Forest algorithm. As in the near future, biomarkers can be measured at home, together with other physiological data, the accurate prediction of adverse events on the basis of home based measurements can revolutionize HF management.

Keywords-heart failure; event prediction; saliva biomarkers; breath biomarkers; data mining

I. INTRODUCTION

Heart failure (HF) is a chronic life-threatening condition characterized by high rates of mortality and re-hospitalizations. The European Society of Cardiology reports that 26 million people worldwide suffer from HF and 74% of them present at least one comorbidity [1]. HF is characterized by frequent re-admissions to hospital. HF accounts for 1-3% of all hospital admissions, while almost the 24% of hospitalized patients are re-hospitalized within a 30-day and the 46% within a 60-day, post discharge period.

Across the world, the 2-17% of patients admitted to hospital with HF die while in hospital and the 17-25% die within one year of admission [2]. The cost of HF management is driven by hospitalizations, corresponding to 1-2% of total healthcare expenditure.

The ability to accurately predict the aforementioned undesirable events enables the effective risk stratification of patients and allows the clinical decision making. This valuable prognostic information can guide the clinical experts in the adaptation of patient management and in the selection of the best treatment plan that should be followed. In turn, this is expected to improve the quality of care provided to the patients, while in parallel result in better health outcomes. Towards this direction, different factors have been studied for their predictive ability in HF morbidity and mortality, destabilizations and re-hospitalizations. In addition, several studies have been conducted focusing on the simultaneous examination of multiple factors using statistical methods (e.g. multi-variable Cox regression models). Such studies resulted in the creation of acknowledged in the clinical practice scores: (i) for the estimation of risk for mortality, the Heart Failure Survival Score [3], the Get With the guidelines score [4], the Seattle Heart Failure Model [5], the EFFECT [6], (ii) for re-hospitalizations [7], and (iii) for morbidity [8].

The prediction of re-hospitalizations [9-15] and mortality [11], [16-23] has gained the interest of researchers who developed prediction models exploiting different categories

of information (*e.g.* sociodemographic, clinical examination, medical condition, lab tests, medication intake, phenotypic data, sensor data) along with machine learning techniques. A description of the methods reported in the literature and a comparison of them are presented in [24].

Recent research has identified certain biomarkers which strongly correlate with the HF severity, progression and mortality [25-42]. Moreover, progress in analytical chemistry and biosensor development allows some of them to be detected in saliva and breath [43-46]. Uric Acid, Tumor Necrosis Factor Alpha (TNF-a), a-Amylase, Lactate, Cortisol and 8-iso-prostaglandin F2a, are among the most important saliva biomarkers, while Acetone (2-Propanon) and 2-methy-1,3-butadiene (isoprene) are indicative examples of breath biomarkers that play a key role in the patient diagnosis and prognosis.

The goal of this study is to introduce such biomarkers in the adverse event prediction process. Obtaining saliva and breath biomarkers is non – invasive and in a future setting can be performed at home [47], becoming on this way a significant tool for HF patient management. In our study, we employ these breath and saliva biomarkers in a machine learning approach which combines heterogeneous patient data (i.e. sociodemographic, clinical, sensor data and biomarkers) for the prediction of adverse events.

II. MATERIALS AND METHODS

A. Dataset

The proposed method is evaluated using a dataset of 27 patients collected by the clinical center of the Universita Di Pisa (UNIPI), Italy within the framework of the HEARTEN project [47]. The criteria for patient selection are reported in Table I.

TABLE I.   CRITERIA FOR PATIENT ENROLLMENT.

Criteria	Patients
I	diagnosed with HF (Framingham criteria) who have continuous symptoms with frequent recurrence
II	belonging to the functional NYHA I-IV class followed by an optimal treatment
III	recently hospitalized, (at least one in the last six months)
IV	undergone one electrocardiogram (in the last 12 months) and have HF symptoms
V	underage, with very severe HF, patients with obesity and advanced chronic kidney failure are not included

The features recorded for each patient can be grouped to the following categories (Table II).

TABLE II.   FEATURES RECORED FOR EACH PATIENT.

Category	Description
General information	Age, gender, existence/relation with caregiver, education level, ethnicity etc..
Allergies	Features expressing the presence or not of allergies
	and a feature indicating the presence or not of drug side effects.
Medical Condition	Experts annotation in terms of the NYHA class, smoking habit, alcoholism habit of the patient, as well as, the presence or not of comorbidities.
Drugs	Active substance, dose and frequency of intake.
Biological data	Height, Temperature, Systolic pressure, Diastolic pressure, Heart Rate, LDLc, HDLc, Glucose , triglycerides, Calcium, Sodium, Potassium, Natriuretic peptides, Hemoglobin A1c, Hemoglobin, International normalized ratio, Hematocrit, White Blood Cells, SGOT/SGPT, Oxygen saturation in Capillary blood by Oximetry, Partial pressure of oxygen, Partial pressure of carbonic, Cardiac troponin I, Cardiac troponin T, Creatinine, Microalbumin [Mass/volume] in Urine, C-reactive protein (CRP), Creatine kinase [Enzymatic activity/volume] in Serum or Plasma, Blood Urea Nitrogen, Urea, GFR/eGFR, Uric Acid , Iron binding capacity [Mass/volume] in Serum or Plasma, Iron [Mass/volume] in Serum or Plasma, Thyrotropin (TSH), Thyroxine (free T4), Thyroxine (free T3)
Clinical Examinations	Left bundle branch block or intraventricular delay, left ventricular ejection fraction, etc.
Adherence	Experts estimation regarding adherence of patients in terms of medication, activity, and nutrition and the prediction of the medication adherence risk of the patient which is extracted by the Adherence risk module of the HEARTEN project.
Score	Five scores are computed; European Heart Failure Self-care Behavior Scale 12-item scale for evaluating HF self-care [48], [49], Heart Failure Knowledge score that is related to HF knowledge in general, knowledge on HF treatment, symptoms recognition and occurrence [50], Get with the guidelines for estimating the in-hospital mortality [51], Seattle Heart Failure Model for predicting the 1-, 2-, and 3-year survival of HF patients [5], Minnesota Living with Heart Failure for providing feedback regarding the physical and emotional status of the HF patient [52].
Sensor data	Time and frequency domain Heart Rate Variability features extracted from the electrocardiogram (ECG), as well as respiration rate, weight and activity related data.
Biomarkers	Concentration of Tumor Necrosis Factor Alpha (TNF-a), Cortisol and Acetone (2-Propanon).

Based on clinical studies on biomarker behavior and influence, performed during the HEARTEN project, the following biomarkers are selected as most prominent marker compounds for monitoring HF conditions: (i) acetone in breath, (ii) cortisol and TNF-a in saliva. More specifically, acetone mirrors metabolism, as well as metabolic stress and the concentrations of acetone are elevated in HF patients compared to healthy subjects. A very significant increase in salivary cortisol levels is observed in peculiar cases when a sudden worsening of patients happened during hospitalization. In HEARTEN studies, after therapy adjustment, the cortisol decreased by a factor of about 2. As a consequence, cortisol was considered a good candidate for monitoring the HF patients. Additionally, chronic HF
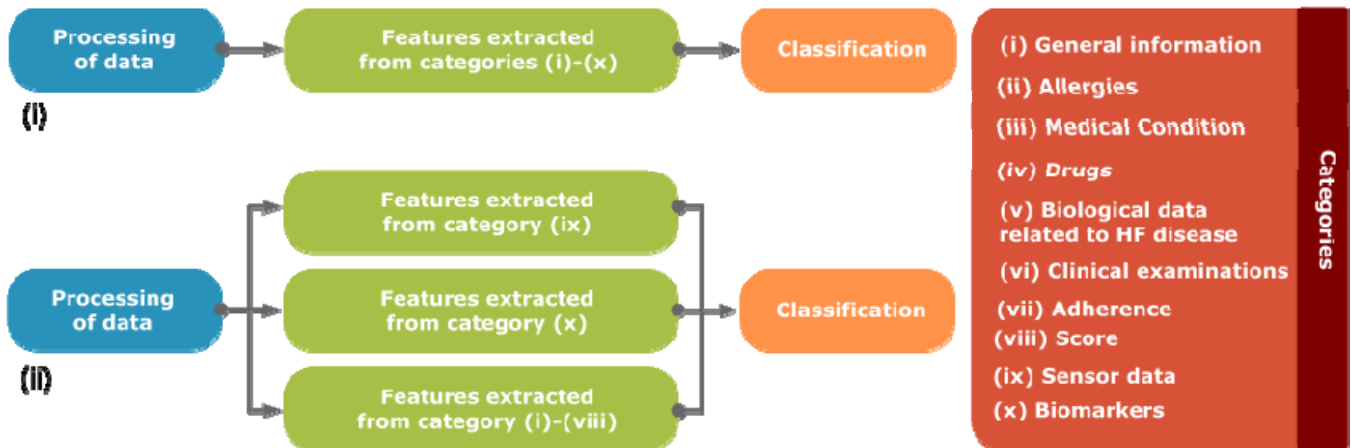
Figure 1.   Schematic representation of the proposed method.

patients have shown high circulating levels of TNF-a, which correlate with the severity of their disease, since TNF-a levels show a linear relation with HF prognosis. Moreover, several studies have demonstrated that concentrations of TNF-a in saliva may reflect those in serum, making the TNF-a an ideal HF-related salivary biomarker.

In total, 263 features are recorded for each patient (3 features corresponding to biomarkers, 151 features extracted from sensor data and 109 features corresponding to the other categories).

These features are recorded from the first time of patient's hospitalization until discharge, every second day. Thus, 141 instances are collected from all patients. It must be mentioned that the number of the hospitalizations days is not the same for all patients. On average, each stay lasts approximately 4 days. The dataset given as input to the proposed method is created with the assumption that the discharge instance of each patient is considered as event free ("no event" class), while the instance of the patient when the event was presented and/or the first hospitalization took place is considered as event ("event" class). This results to a set of 54 instances, with 25 corresponding to an event and 29 to a no event.

B.   The proposed method

The proposed method consists of three steps: (i) preprocessing, (ii) feature selection, (iii) classification. A schematic representation of the proposed method is shown in Fig. 1 and a detailed description of each stage is provided below.

In the first step, missing values are addressed. Features with more than 60% of missing values are removed, since imputation of missing values cannot be performed due to the nature of the data. Furthermore, features where the distribution between the values is greater than 80% are not retained. In the second step, the identification of features that can act as discriminators between the two expected situations (presence of an event or not) are selected following a wrapper approach [53], in combination with the classifiers employed in step 3. Two different approaches are tested. The first one (Fig. 1i) takes as input all the features,

while in the second (Fig. 1ii), the method is applied separately to features extracted from sensor data and to features corresponding to categories (i)-(vii). Finally, in the third step, nine classifiers are employed and tested [54]: (i) Random Forests (RF), (ii) Logistic Model Trees (LMT), (iii) J48, (iv) Rotation Forest (ROT), (v) SVM, (vi) Radial Basis Function Network (RBF Network), (vii) Bayesian Network (BN), (viii) Naïve Bayes (NB), (ix) Simple Classification and Regression Tree (Simple CART).

III.   RESULTS

The proposed method is evaluated on a dataset of 54 instances, while the number of features is differentiated depending on the outcome of the feature selection step. The obtained results in terms of accuracy (Acc), sensitivity (Sens), specificity (Spec) and area under curve (AUC) are presented in Table III. Both approaches produce rather similar results (accuracy 76% and 77%, respectively), with 12 features to be finally selected in the first apporach and 23 features in the second approach. Rotation Forests (ROT) seem to be the best performing classification algorithm (see Table IV).

In order to evaluate the contribution of biomarkers in the prediction of adverse events, the following experiments are made: (i) all available features are given as input, (ii) features only from sensors are employed, (iii) features only from biosensors are utilized as predictors, and (iv) features from sensors and biosensors are met. The results without feature selection are presented in Table V. The results

TABLE III.   RESULTS OF THE PROPOSED METHOD.

Classifiers	Evaluation measures			
	Acc	*Sens*	*Spec*	*AUC*
1st approach of feature selection approach				
NB	**76%**	76%	76%	76%

Classifiers	Evaluation measures			
	Acc	*Sens*	*Spec*	*AUC*
2ⁿᵈ approach of feature selection approach				
ROT	**77%**	77%	77%	74%

TABLE IV. EVENT PREDICTION RESULTS PER CLASSIFIER FOLLOWING THE SECOND APPROACH

Classifiers								
BN	**NB**	**RBF**	**SVM**	**ROT**	**J48**	**LMT**	**RF**	**CART**
37%	58%	60%	56%	**77%**	53%	58%	60%	58%

TABLE V. EVENT PREDICTION TESULTS ON DIFFERENT COMBINATIONS OF FEATURES (WITHOUT FEATURE SELECTION).

Case	Model	*Acc*
(i) All features without feature selection	ROT	57%
(ii) Features only from sensors without feature selection	RF	60%
(iii) Features only from biosensors without feature selection	CART	66%
(iv) Features from sensors and biosensors without feature selection	ROT	59%

TABLE VI. EVENT PREDICTION RESULTS ON DIFFERENT COMBINATION OF FEATURES (USING FEATURE SELECTION).

Case	Model	*Acc*
(i) All features with feature selection	NB	76%
(ii) Features only from sensors with feature selection	RF	71%
(iii) Features only from biosensors with feature selection	CART	66%
(iv) Features from sensors and biosensors with feature selection	RF	72%
The proposed method	ROT	77%

presented in Table VI are extracted from the same experiments, as those presented in Table V, but this time following feature selection.

It should be noted that in case (iii) where only biomarkers are utilized, the feature selection approach is not applied due to the already small number of biomarkers used (*i.e.* three).

As shown in Tables V and VI, our approach yields superior results. The positive effect of feature selection is also clear (accuracy improvement from 66% to 77%).

A comparison of the proposed method with those reported in the literature (Table VII) cannot be directly performed since the studies reported in the literature: (i) predict the presence or not of one specific adverse event only (destabilizations, re-hospitalizations, mortality) and not the presence or not of HF adverse event in general like the proposed method, and (ii) do not utilize biomarkers. Focusing on specific adverse events, of course it has advantages for clinical practice; still it requires a much larger dataset. In this sense, this can be considered as a limitation of the proposed method. This will be addressed in the future through the data that will be collected during the pilot phase of the HEARTEN project. The utilization of breath and saliva biomarkers is the innovative feature of the proposed method.

TABLE VII. COMPARISON WITH THE LITERATURE.

Study*	Evaluation measures	
Destabilizations		
Candelieri *et al.* 2008	Acc	92.03%
Candelieri *et al.* 2009	Acc	82.06%
Candelieri *et al.* 2010	Acc	87.35%
Guidi *et al.* 2014	Acc	87.60%
Guidi *et al.* 2015	Acc	71.90%
Re-hospitalizations		
Zolfaghar *et al.* 2013	Acc	87.12%
Vedomske *et al.* 2013	AUC	84.00%
Koulaouzidis *et al.* 2016	AUC	82.00%
Kang *et al.* 2016	AUC (c-statistic)	59.00%
Tugerman *et al.* 2016	AUC	84.20%
Mortality		
Shah *et al.* 2015	AUC	71.80%
Fonarrow *et al.* 2005	odds ratio for mortality	12.9
Bohacik *et al.* 2013	Acc	77.66%
Panahiazar *et al.* 2015	1-year AUC	68.00% (baseline set) 81.00% (extended set)
	2-years AUC:	70.00% (baseline set) 74.00% (extended set)
	5-years AUC	61.00% (baseline set) 73.00% (extended set)
Taslimitehrani *et al.* 2016	1-year Acc	91.40%
	2-years Acc	83.00%
	5-years Acc	80.90%
Austin *et al.* 2012	AUC	79.00%
Bochacik *et al.* 2015	Sens	63.27%
	Spec	65.54%
Ramirez *et al.* 2015	Sudden Cardiac Death	
	Sens	18.00%
	Spec	79.00%
	Pump Failure Death	
	Sens	14.00%
	Spec	81.00%
Subramanian *et al.* 2011	AUC(c-statistic)	84.00%
Prediction of adverse events		
Proposed method with biomarkers	Acc	77.00%
	AUC	74.00%

* Studies references are presented in reference [24] of the current study.

IV. CONCLUSIONS

An automated method for the prediction of adverse events related to HF, utilizing information from saliva and breath biomarkers, is presented. Different experiments are

conducted in order the proposed method to be evaluated and the contribution of biomarkers to the prediction problem to be estimated. The results confirm the prediction ability of biomarkers either if they are employed as the only input (Acc: 66%) or in combination with other categories of features (Acc: 77%). Among the biomarkers, TNF-a is the one that presents the largest correlation with the prediction of an adverse event. However, the small number of instances does not allow the extraction of "safe" conclusions. The collection of biomarkers measurements from a larger number of patients will lead to a more in-depth evaluation.

As in the near future biomarkers can be measured at home, together with biosensor data, the accurate prediction of adverse events on the basis of home based measurements will revolutionize HF patient management. Such an approach can become the core of a chronic care model, allowing for early action by both, patients and physicians.

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