Heart Failure Risk models and their readiness for clinical practice

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***Abstract*—The aging population is putting an ever increasing burden on healthcare costs, of which care for Heart Failure patients constitutes a major portion. High readmission rates are observed for this large and increasing patient population, which contribute to a large extent to the costs involved in care for Heart Failure. Risk models, when applied in a Clinical Decision Support system, have the potential to help to optimize care based upon expected mortality or readmission. By tailoring care and optimizing care transitions, healthcare costs can be reduced and quality of life of patients may be improved.**
Although numerous risk models for hospitalized Heart Failure patients have been coined, the uptake of such models in clinical practice is currently very limited. In a quest to identify risk models with high potential and the conditions for successful adaptation, a literature review was performed, identifying 55 Heart Failure risk models, and opportunities explored to apply such models in clinical practice.

***Keywords*-Risk Models, Heart Failure, Clinical Application**

I. Introduction

Heart Failure is a chronic and progressive syndrome that is characterized by the inability of the heart to pump enough blood to accommodate the body's needs. Reduced blood flow to the kidneys causes fluid retention in ankles and lungs, the latter causing severe shortness of breath when exercising or (in more severe stages) at rest. One in five people will develop Heart Failure (HF), the majority at an age above 70 [1]. Increasing prevalence figures [2] will cause HF to be a growing phenomenon over the coming years. If the condition is left untreated or is not well managed, clinical deteriorations may require acute care, which inevitably worsens the condition of the patient and worsens the prognosis for subsequent survival.

HF is a syndrome with high rates of mortality, readmission and acute episodes of care. Approximately 25% of HF patients die within one year [3], 20-30% of HF patients are readmitted into hospital within 30 days following an episode of acute care [4], and up to 68% within one year [5]. Readmissions constitute the majority of costs related to the treatment of HF. It is estimated that expenditures on HF already now constitute 1 - 2% of the total health care budgets in developed countries [6]. There is no consensus on the estimated percentage of readmissions considered avoidable [7]. In a review study, Van Walraven and colleagues [7] find a median of 27.1%, while some estimates are as high as 76%. These estimates show that a significant portion of early readmissions can indeed be avoided. Gwardry-Sridhar and colleagues [8] demonstrate in a systematic review that interventions explicitly targeted to prevent readmissions significantly decrease readmission rates for HF patients. In [9] it is demonstrated that such interventions are also cost-effective.

Hence, to reduce healthcare costs, focus is on reducing such preventable readmissions. Clinical Decision Support (CDS) systems using risk models can guide in-hospital treatment and post-discharge care in order to prevent HF patients from early re-hospitalizations. The Patient Protection and Affordable Care Act, that has recently been put into action in the United States, has further motivated the research of readmission risks as it penalizes care providers for excessive readmissions. To compare readmission rates between hospitals, the Risk Standardized Readmission Rate (RSRR) [10] is calculated to compensate for differences in patient populations. The starting point of the RSRR is a risk model applied to all individual patients in a hospital's patient population to calculate expected readmissions, which are compared to actual readmissions. Although the risk models within RSRR are now widely used by US hospitals, they are by design no model to support clinical decision making.

For Acute Coronary Syndrome (ACS) there are guidelines that, based upon the outcome of a risk model [11] provide a structured and objective treatment protocol [12]. For HF there is no such guideline yet, however the need for it is becoming more and more eminent. At the basis of such guidelines should be the assessment of (a variety of) patient risks. Following from the guidelines should be proposed treatment options (e.g., interventions) as well as evidence-based suggestions for the discharge preparation (e.g., suitable moment of discharge). There is a clear need to use risk models in clinical practice, but what is apparent is that the models are sparsely used and underutilized. In this paper we provide a comprehensive overview of the risk

models, barriers to their use in clinical practice, and review the existing models and their applicability.

The structure of this paper is as follows: First, the requirements for HF risk models are described, then the literature analysis is presented and discussed. We finish with the conclusion and outlook.

II. Requirements for risk models

Many different flavors of risk models for hospitalized HF patients have been proposed in recent years, focussing on different outcomes, ranging from readmission to mortality. In this work, we focus on patient level risk models given the need for the objective assessment of risks at an individual level. Recently, two review studies have been published that list and compare such models [13], [14]. The work of Ross et al. [13] focusses on the analytic value of HF risk models for mortality, readmission or both. Kansagara et al. [14] review disease unspecific hospital readmission models and classify 26 unique models per intended usage: either for hospital comparison purposes (such as the models used in RSRR) or for clinical usage. The first, based on retrospective medical claim data (i.e., data that becomes available during a later stage of hospitalization and hence can be used for retrospective analysis only) is merely used to compare patient populations and outcomes, as data elements may not be available in the first phase after the admission. The second class of models can actually be used to steer and influence treatment of a patient, as they are based on real-time data (i.e., data that was captured from a patient close to admission). In their study, two models were identified that are applicable to be used for CDS purposes specifically for hospitalized HF patients. In contrast to the previous work, our analysis focusses at the ability to apply the risk models in clinical practice with the purpose of predicting future events for individual patients.

Uptake of such risk models in clinical practice is still very limited. Next to usability issues originating from troublesome integration in existing health IT systems, this might be due to lacking performance [14] of the models, and (un)availability of risk parameters [15], but also failure to see relevance and applicability [16], and resistance to change [17], [18]. Above all, a major reason for limited uptake of clinical risk models is that results have not been replicated. There are only limited attempts to replicate findings from literature, and those that do publish re-evaluation of predictive risk models [19], [20], only report modest performances. Hence, it is uncertain how reported performance will translate to hospitals with different patient characteristics. The recent announcement of errors in the RSRR model [21], has once more indicated the importance of open and complete publication of risk models such that their correctness can be verified by others.

In summary, we wanted to identify risk models for HF ready to be deployed in clinical practice. To this end, we composed the following minimal set of criteria:

- **Completeness of the description.** In order to create a technical implementation of a model from literature, its description should be complete. That is, an expert with sufficient technical knowledge should be able to implement the model from its description in the publication.
- **Availability of data.** The data included in the model should be available in routine clinical practice. Moreover, in order to be meaningful for treatment and discharge preparation, it should be possible to evaluate the model within 24 hours after the admission.
- **Performance.** To successfully introduce a predictive model in clinical practice, the model should be reliable (i.e., with a high C-statistic) and is preferably validated in multiple settings.

In order to quantify *completeness*, we used the following scale to indicate whether the model description...

$+++$	Is fully and explicitly specified
$++$	Requires more work to derive all information needed (e.g., interpretation of hazard ratios)
$+$	Reports all but a single constant (e.g., intercept, or baseline risk)
$-$	Does not provide all coefficients
$--$	Does not specify all parameters
$---$	Does not even specify the model structure/type

Note that the $+$ category does not allow direct application, but would require a (small sized) set of patients to estimate the missing constant from, which might be feasible for certain applications. Complete reporting is vital to the ability to implement, validate and reproduce the models. For validated use of risk models in clinical practice, the models need to have been published in detail and should not require a full study to determine missing values of coefficients, hence the model should be awarded at least $++$.

Availability of data we assessed for two key moments of hospitalizations: (within 24 hours of) admission, and discharge. These two classifications reflect whether the parameters are generally available in cardiology practice, as assessed by clinical specialists. Hence, this assessment reflects the distinction between 'administrative' and 'primary' data as used by Kansagara et al. [14], where 'primary' data is considered non-available as it consists of parameters specifically gathered for a clinical study rather than data generally available. The moment of availability reflects the distinction between 'real-time' (available at admission) and 'retrospective' (available at discharge) parameters [14], [20]. Models that use data that

are available at admission are most versatile in their use throughout hospitalization, but at least at discharge values for all parameters should be available.

Finally, for *performance*, we considered reported C-statistics of validated risk models. We require a C-statistic of at least 0.7, which is generally considered a lower boundary of acceptable performance [22].

In addition to the minimal set of requirements, we analyze the level to which risk models consider a complete set of aspects that describes a patient's status. For the best risk assessment, it is believed that a risk model should comprise a holistic view of the patient and their context [23].

III. HF RISK MODELS

The treatment of HF patients involves a precise analysis of the condition of the patient. The heart, the aetiology of the disease, and other bodily functions are examined as well as a psychosocial profile of the patient. The latter is especially important for chronic conditions such as HF as it affects the ability of self-care. Generic (disease unspecific) risk models do not incorporate those parameters that are specifically addressed in the clinical treatment of HF patients, while many of those parameters are associated with patients' risk [13], [14], [23] (e.g., past Myocardial Infarction (MI), heart disease related biomarkers such as BNP and a classification of the condition (NYHA)). Models that have not been developed specifically for HF patients do not incorporate these risk factors, and therefore incompletely represent the condition of the patient. Hence, we focus on HF specific risk models.

Hundreds of studies have been performed that investigated whether individual parameters correlate with mortality and/or early readmission for HF patients [13]. Compared to this, only a small number of studies investigated correlations with multiple parameters and parameter interactions by developing multi-parameter risk models (e.g., [13] identified only 5 studies). In recent years, more risk models have been developed using a variety of parameters and several techniques to compose them into a model.

A literature search including keywords "heart failure" and "risk model" identified 23 publications that disclose one or more HF risk models. The publications were analyzed for the three criteria listed earlier: completeness of the description, availability of data, and performance. From the researched body of literature, 55 risk models were identified, as listed in Table I. They vary in their predicted end-point: in-hospital mortality, post-discharge mortality, and readmission. Also the period during which the end-point is predicted varies, ranging from 4 days to 10 years, with periods of 30 days and 1 year being most common.

It can be observed that most models can be applied to data taken close to the moment of discharge, however, only a limited subset also validated such usage. Most popular techniques are Cox Proportional Hazards (PH) regression and logistic regression. Often regression models are turned into point scoring systems (labeled with 'handmade' in Table I) to ease manual computation of risk scores. Performances, in terms of C-statistic, range from 0.667 to 0.81 for mortality/survival models and 0.58 to 0.72 for readmission models. Models predicting a combined end-point have performance in between. Out of 55 models, 20 have been fully and openly specified such that they can directly be implemented, 27 model publications miss critical details that hinder implementation and revalidation.

Performance of mortality/survival models is generally higher than that of readmission models, as also found in [13], [14]. It follows from this that identifying the risk of readmission is a more difficult problem than that of mortality. This is further motivated by the inclusion of more (different) risk parameters in readmission models, obviously in an attempt to find better predictors. Overall, the performance of the risk models is not too impressive with C-statistics ≤ 0.8 (with one exception of 0.92 for the retrained Tabak 2007 model, although only limited information is given on the validation method). This might be due to the level of difficulty of this classification/regression task. However, the limited set of modeling techniques (e.g., logistic regression) with limited expressive capacity, that has currently been used to obtain risk models, suggests that better performances could be obtained by the application of more sophisticated methods, including machine learning techniques.

Many descriptions of risk models were found erroneous or incomplete. For example, omission of the intercept of a logistic regression model, not specifying the encoding schemes used, omitting the units used for certain parameters, or incorrect mathematical formulas printed. The amount of errors and incompleteness in the publications on HF risk models is striking, and seems to indicate that the risk models are created as statistical means to verify importance of single parameters rather than the correct application of the models to predict the outcome they have been developed for. This simplistic view towards the use of risk models could be another explanation for the difficulties of introducing risk models to the clinical practice.

Table I: Overview of HF risk models; Abbreviation used: Proportional Hazards (PH)

Name of model / first author	End-point[e]	Available at admission[f]	Available at discharge[g]	Type	Complete-ness[h]	Performance (C-statistic)
MORTALITY / SURVIVAL						
Axente [24]	$\leq$65month survival	Yes	Yes	Cox PH	$--$	-
Brophy long-term [25]	12month survival	No	Yes	PH	$++$	-
Brophy - very long-term [25]	36month survival	No	Yes	PH	$++$	-
CCI - Very long-term [26]	10year survival	No	No *	log-linear	$++$	-
CCI - Long-term [26]	1year mortality	No	No	unspecified	$---$	-
Chin 1997 - Mortality [27]	60day mortality	Yes	Yes	Cox PH	$+$	-
Felker / OPTIME-CHF - M. logistic [28]	60day mortality	Yes *	Yes	logistic	$-$	0.77
Felker / OPTIME-CHF - M. points [28]	60day mortality	Yes	Yes	log-linear, handmade	$++$	-
Fonarow / ADHERE - Logistic [29]	hospital mortality	Yes *	Yes	logistic	$+++$	0.757
Fonarow / ADHERE - CART model [29]	hospital mortality	Yes *	Yes	decision tree	$+++$	0.668
Hammill - Mortality, claims [30]	30day mortality	No	No	logistic	$-$	0.718
Hammill - Mortality, claims-clinical [30]	30day mortality	No	No	logistic	$-$	0.761
Krumholz 2006 - Medical [31]	30day mortality	No *	Yes	logistic	$+++$	0.78
Krumholz 2006 - Administrative [31]	30day mortality	No *	No	logistic	$+++$	0.71
Lee / Toronto / EFFECT - Short-term, logistic [32]	30day mortality	No *	No	logistic	$+$	0.79
Lee / Toronto / EFFECT - Short-term, points [32]	30day mortality	No	No	handmade	$+++$	-
Lee / Toronto / EFFECT - Long-term, logistic [32]	1year mortality	No *	No	logistic	$+$	0.76
Lee / Toronto / EFFECT - Long-term, points [32]	1year mortality	No	No	handmade	$+++$	-
Levy / SHFM	$\{1,\ldots,5\}$year survival [33]	No	No	Cox PH	$++$	0.729[a]
O'Connor / HF-ACTION - Mortality [34]	$\approx$ 2.5year mortality	No	Yes	Cox PH	$+$	0.7357
O'Connor / HF-ACTION - M. Simple [34]	$\approx$ 2.5year mortality	No	Yes	Cox PH	$+$	0.73
O'Connor / HF-ACTION - M. Points [34]	1year mortality	No	Yes	handmade	$+$	0.70
Pocock / CHARM - mortality [35]	2year mortality	No *	Yes	Cox PH	$++$	0.75
Tabak 2007 [36]	hospital mortality	No *	No	logistic	$+$	0.81
Tabak 2007 - Retrained [20]	mortality[b]	No *	Yes	logistic	$+$	0.92 / 0.84[b]
Tabak 2007 - Retrained - points [20]	mortality[b]	No	Yes	handmade	$+++$	-
Yamokoski / ESCAPE - Nurse M. [37]	6month mortality	No	Yes *	linear	$+++$	0.611
Yamokoski / ESCAPE - Physician M. [37]	6month mortality	Yes	Yes *	linear	$+++$	0.675
Wedel / CORONA - Simple [38]	Unspecified[c] mortality	No	No	Cox PH	$+$	0.667
Wedel / CORONA - Lab [38]	Unspecified[c] mortality	No	Yes	Cox PH	$+$	0.684
Wedel / CORONA - Lab-extended [38]	Unspecified[c] mortality	No	Yes	Cox PH	$+$	0.719
MORTALITY OR READMISSION						
Amarasingham [20]	30day (readmission or mortality)	No *	No	logistic	$+$	0.72
Chin 1997 - Readmission or mortality [27]	30day (readmission or mortality)	No	No	Cox PH	$+$	-
Chin 1997 - R. or M. - points [27]	30day (readmission or mortality)	No	No	handmade	$+++$	-
Felker / OPTIME-CHF - M. or R. [28]	60day (mortality or readmission)	Yes *	Yes	logistic	$--$	0.69
O'Connor / HF-ACTION - R. or M. [34]	$\approx$ 2.5year (mortality or readmission)	No	Yes	Cox PH	$+$	0.6437
O'Connor / HF-ACTION - R. or M. Simple [34]	$\approx$ 2.5year (mortality or readmission)	No	Yes	Cox PH	$+++$	0.63
O'Connor / HF-ACTION - R. or M. Points [34]	1year (mortality or readmission)	No	Yes	handmade	$+++$	0.63
O'Connor / PROTECT [39]	7day (mortality or HF readmission or WHF)	No *	Yes	Cox PH	$+$	0.67
Pocock / CHARM - R. or M. [35]	2year (CVmortality or HFreadmission)	No *	Yes	Cox PH	$++$	0.75
READMISSION						

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Table I – *Continued from previous page*

Name of model / first author	End-point[e]	Available at admission[f]	Available at discharge[g]	Type	Complete-ness[h]	Performance (C-statistic)
Hammill - Readmission, claims [30]	30day readmission	No	No	logistic	$-$	0.587
Hammill - Readmission, claims-clinical [30]	30day readmission	No	Yes	logistic	$-$	0.599
Krumholz 2000 [40]	6month readmission	Yes	Yes *	Cox PH	$++$	-
Krumholz 2008 / CMS - Medical [41]	30day readmission	No *	No	logistic	$+++$	0.58
Krumholz 2008 / CMS - Admin. [41]	30day readmission	No *	No	logistic	$+++$	0.61
Philbin - Logistic [42]	6month CHF readmission	No	No	logistic	$+$	0.62
Philbin - Simple risk score [42]	6month CHF readmission	No	No	handmade	$+++$	0.60[d]
Yamokoski / ESCAPE - Nurse R. [37]	6month readmission	No	Yes *	linear	$+++$	0.579
Yamokoski / ESCAPE - Physician R. [37]	6month readmission	Yes	Yes *	linear	$+++$	0.566
MISCELLANEOUS						
CCI [26]	generic co-morbidity	No	No	handmade	$+++$	-
CCI - Age-adjusted [26]	generic co-morbidity	No	No	handmade	$++$	-
Chin 1996 [43]	(hospital mortality or major complication)	Yes *	Yes	logistic	$+$	-
Kannel / Framingham - Extensive [15]	4year developing HF	No	Yes	logistic	$+++$	-
Kannel / Framingham - Reduced [15]	4year developing HF	No	Yes	logistic	$+$	-
Troughton / HFSS [44]	HF severity (HF diagnosis)	Yes	Yes	handmade	$+++$	-

[a] Evaluated only for the 1-year survival model.

[b] No specification is given on the time window for the end-point that was used to train the model, validation was performed both on in-hospital mortality and 30-day mortality.

[c] No further specification given than "total mortality".

[d] Obtained when the score was applied in logistic regression (with unspecified coefficients and intercept).

[e] Abbreviations used: d(ays), m(onths), y(ears).

[f] * indicates that validation has been performed using data available at admission.

[g] * indicates that validation has been performed using data available at discharge.

[h] Abbreviations used: $---$ model structure unknown; $--$ (some) parameters unknown; $-$ (most) coefficients unknown; $+$ constant unknown (intercept/baseline risk/...); $++$ fully specified (potentially obfuscated); $+++$ explicitly specified.

Following the three minimal criteria outlined earlier, we only find the logistic model of Fonarow et al. [29] to comply. When we ease the restriction on full data availability on admission, and allow for models with complete data only at discharge, also the models of Pocock et al. [35], and Krumholz et al. (2006, medical) [31] suffice. They all predict mortality (or survival), over a time period ranging from in-hospital to 2 years. For the parameters used in these models we refer to their respective publications.

It is interesting to observe only one dedicated classification method (decision tree [29]) next to a multitude of regression techniques, while the problem that is addressed with these models is a binary classification problem (e.g., dead or alive; readmitted or not). We argue that it would be much more natural to treat the classification problem as such by applying a binary classifier rather than regression analysis. This would result in systems that return a (binary) label indicating which of the outcomes is most likely to happen. If needed, a risk score in the interval $[0, 1]$ can be returned as well by using some measure of the level of certainty of the classifier as risk score. This certainty-measure can be, e.g., the probability outputted by Bayesian approaches, the distance to the separating hyperplane (the margin) in Support Vector Machines (SVMs), a ratio of the class-wise output of Artificial Neural Networks (ANNs), or the distance to closest correct and incorrect prototypes in Learning Vector Quantization (LVQ). A detailed description of these techniques goes beyond the scope of this paper; we refer the reader to, e.g., Duda et al. [45].

IV. Conclusion and Outlook

Whereas existing risk models seem to have been built more as statistical tools to investigate importance of single parameters, we assessed opportunities to apply risk models in clinical practice for the prediction of an individual patient's risks. These risk predictions can steer the in-hospital care plan as well as the discharge preparation and post-discharge care plan, tailored to individual patients' needs. Next to that, the results of these patient level risk models can be aggregated to derive population level statistics. In such applications they can be used for quality assessment purposes and form the basis for optimizing care at hospital level.

Only half of the published risk models have been disclosed to the extent that they can be implemented in clinical practice, lacking essential details. Reported performances are modest for mortality models, and worse for readmission risks. The techniques used to develop HF risk models are mostly simple statistical techniques and do not include more sophisticated machine learning techniques, indicating that there may be room for improvement in their performance. A boost in performance will be required in order to gain sufficient trust of care givers, especially clinical specialists, to improve uptake in clinical practice. Given that medicine is not an exact science, perfect performance cannot be expected and is not required either. What level of performance is sufficient to base medical decisions upon is hard to define and will probably require the application of risk models in daily practice to be specified. In line with this issue on performance, a major question that remains unanswered is to what extent the validated performance can be extrapolated to other patient populations as structured validation studies still have to be conducted and ultimately whether the application of these risk models really improves the outcomes of the patients by allowing further personalized care. Most ready for clinical application is the logistic model of Fonarow et al. [29] which uses data commonly available throughout the hospitalization; followed by the models of Pocock et al. [35], and Krumholz et al. (2006, medical) [31]. They predict mortality (or survival) over various time spans.

Critical to successful deployment of risk models in clinical practice is proper integration in existing health IT systems. In order to allow optimal integration, implementations of risk models should conform to the standards for medical data exchange, such as HL7[1] to allow automated read in of data from Electronic Health Records (EHRs) and other clinical data sources. For parameters that could not be retrieved automatically, there should be an easily accessible option to input their values and store them to avoid having to enter them again a next time the risk needs to be evaluated. To optimize usability evaluated risks should, preferably, be visible in patient dashboards, or at most one mouse click away.

Analogue to the guidelines for ACS, we expect guidelines for HF to integrate risk models in the decision making for the care of HF patients in the near future. Similar to the Global Registry of Acute Coronary Events (GRACE) model [11] being used in guidelines to steer the moment of discharge [12], we foresee HF risk models being used for discharge planning as well as the treatment plan.

Performance of current risk models requires improvement in general. With better predictive quality, however, they are considered a valuable addition to clinical practice, especially when used to prioritize patients at admission, as a basis for the in-hospital treatment plan, and post-discharge care plan through dedicated CDS applications. In order to address and improve upon the drawbacks of existing risk models we have started a data collection study with the primary aim to develop and validate HF risk models.

[1] http://www.hl7.org

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