Risk Prediction for Heart Failure Incidence within 1-year Using Clinical and Laboratory Factors

Fen Miao, Yun-Peng Cai, and Yuan-Ting Zhang, *IEEE Fellow*

Abstract— **Validated risk scores for heart failure incidence are still lacking, especially for short-term prediction. In this paper we aim at developing a 1-year risk prediction model for heart failure (HF) incidence using both clinical risk factors and laboratory variables. The public MIMIC II clinical database is studied. Two multivariable Cox models are built to assess the 1-year risk of HF, one with conventional clinical risk factors only, another combined with laboratory parameters, including serum creatinine (SCR), blood urea nitrogen (BUN), glucose, prothrombin time (PT), activated partial thromboplstin time (APTT) and total bilirubin (TBIL). The discrimination performances of the different models are internally validated at last with bootstrapping. In addition to known risk factors, more clinical and laboratory indices, including pulmonary circulation diseases, peripheral vascular disease, chronic pulmonary disease, hypothyroidism, electrolyte and fluid disorders, BUN and APTT are identified to be independent predictors of heart failure incidence. Moreover, we found that the long-term risk factor, hypertension, has opposite effect on short-term risk. The C-statistics of 0.712 with internal validation has demonstrated the effectiveness of the prediction model combined clinical and laboratory factors.**

I. Introduction

Heart failure (HF) occurs when the heart is unable to provide sufficient pump action to maintain blood flow to meet the needs of the body. It can cause a number of symptoms including shortness of breath, leg swelling, and exercise intolerance. It is investigated that in developed countries, around 2% of adults suffer from heart failure, and the rate increases to 6–10% for elderly people aged over 65 [1]. Therefore, heart failure has become a major health threat worldwide and investigation on HF prediction is becoming a hot topic in medical science.

Recent researchers have identified dozens of risk factors concerning HF onset. It has been demonstrated that conventional predictors of heart failure included age, sex, obesity, myocardial infarction and other forms of ischemic heart disease, hypertension, atrial fibrillation, valvular heart disease, and cardiomyopathy in [2-6]. Other kinds of variables such as some features in 12-lead ECG, biomarkers and genetic risk factors were also found to be predictors for HF incidence [2,5,7,8] with high hazard ratios. A few researchers also attempted to create a prediction model or score to quantitatively access the risk of HF incidence [9-10]. Nevertheless, previous studies mainly focus on long-term HF prediction (10-year) with conventional risk factors. In fact, short-term prediction is necessary for hospital patients to facilitate the triage and management of different patients, during whom emergency situation are common. On the other hand, some laboratory results, such as serum creatinine (SCR), blood urea nitrogen (BUN), Glucose, prothrombin time (PT), activated partial thromboplstin time (APTT), total bilirubin (TBIL) may be potential predictors for HF and will improve the quality of prediction when added to the model. Therefore, the topic of finding new laboratory predictors and developing prediction models for short-term HF is not yet well established in previous literature and still demands investigation.

This paper aims to establish a short-term 1-year HF prediction model based on conventional clinical risk factors and laboratory indices for ICU patients, using a variety of newer statistical measures designed specifically to evaluate the models. We assessed laboratory indices including SCR, BUN, PTT, TBIL, APTT, glucose individually and in combination to predict HF, compared with the basic model comprising of conventional clinical risk factors. More clinical and laboratory indices, including pulmonary circulation diseases, peripheral vascular disease, chronic pulmonary disease, hypothyroidism, electrolyte and fluid disorders, BUN and APTT were found to be independent predictors of heart failure incidence in our paper. Moreover, the long-term risk factor, hypertension, was identified with opposite effect on short-term risk. The C-statistics of 0.712 with internal validation has demonstrated the effectiveness of the proposed prediction model built upon clinical and laboratory factors.

II. Materials and Methods

A. Data preparation

Our study is based on the public MIMIC II (Multi-parameter Intelligent Monitoring in Intensive Care) clinical database [11][12], which contain comprehensive clinical data including results of laboratory tests, medications, ICD9 diagnoses, admitting notes, discharge summaries, and more obtained from hospital medical information systems, for 32,536 ICU patients. The data were collected over a seven year period, beginning in 2001, from a variety of ICUs (medical, surgical, coronary care, and neonatal), in Boston's Beth Israel Deaconess Medical Center (BIDMC). We defined the patients with HF according to ninth revision of the international classification of diseases (ICD9) adopted in the

Fen Miao is with Key Laboratory for Health Informatics of the Chinese Academy of Sciences (HICAS), Shenzhen Institutes of advanced technology. Shenzhen, China.

Yun-peng Cai is with Key Laboratory for Health Informatics of the Chinese Academy of Sciences (HICAS), Shenzhen Institutes of advanced technology. Shenzhen, China.

Yuan-Ting Zhang is with Key Laboratory for Health Informatics of the Chinese Academy of Sciences (HICAS) and Joint Research Centre for Biomedical Engineering, The Chinese University of Hong Kong. (corresponding author. email: yt.zhang@ee.cuhk.edu.hk)

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database. The subjects with multiple records are extracted in our study to establish the survival model for HF incidence. In the data 3,048 individuals are with multiple stays and during which 555 subjects developed HF over 1-year follow-up period. The following 28 potential conventional clinical predictors are studied to predict HF, including age, sex, cardiac arrhythmias, valvular disease, peripheral vascular disease, hypertension, paralysis, other neurological diseases, chronic pulmonary disease, diabetes, hypothyroidism, renal failure, liver disease, peptic ulcer disease, aids, lymphoma, metastatic cancer, solid tumor, rheumatoid arthritis, obesity, weight loss, electrolyte and fluid disorders, deficiency anemia, alcohol abuse, drug abuse, psychoses, depression. In addition, laboratory indices are considered in the proposed risk model. After removing variables with many missing values, examination indices with more than 80% effective values, including SCR, BUN, Glucose, PT, APTT, TBIL are kept and analyzed to assess their influence on HF incidence. We deal with missing data by mean imputation technique. The status at endpoint is denoted as 0/1 for censored, transplant.

B. Statistical Analysis

Continuous age and laboratory data (age, SCR, BUN, Glucose, PT, APTT, TBIL) were log-transformed before analysis. Cox proportional hazards models were used to assess association of potential conventional predictors and laboratory indexes with HF using bootstrapping with 1000 replications of individuals sampled with replacement [13], with Wald tests for significance testing. Firstly, the conventional models were determined using multi-variable Cox regression analysis with backward elimination including age, sex and other conventional risks. Secondly, each laboratory index was individually tested in models for HF incidence with adjustment for conventional predictors. All laboratory indices associated with disease ($p<0.05$) were then included in a backward elimination model with adjustment for conventional risk factors to examine the joint and comprehensive effect for predicting HF events.

We evaluated the ability of laboratory indices to reclassify risk, following methods suggested by [14][15]. Clinical covariates were firstly entered into the model. Patients were then allowed to be reclassified into different categories with the addition of the laboratory data. We assessed the number of participants reclassified and calculated the Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) [16].

We internally validated the performance of the model by bootstrapping method presented in [17]. It has been demonstrated that this approach provides the least biased and most stable estimates of optimism corrected performance among the various proposed methods for internal validation [18], with "optimism" referring to the inherent bias toward an overestimated performance in the derivation dataset. The goodness-of-fit of the final model was evaluated both formally by the Hosmer-Lemeshow statistic and visually by plotting the cumulative expected versus observed events across the cluster of risk scores [19]. All analyses were performed with R (R version 3.0.0). Tests were considered significant if the two-sided P-value was <0.05.

I. RESULTS

During a median follow-up of 1 year, 555 individuals were diagnosed with new onset heart failure while 2493 were censored. The mean age for patients suffering HF within one year was 66.33±16.46 while for patients without HF it was 56.6±21. From the 2-sample t-test, conventional clinical risk factors including age, cardiac arrhythmias, hypertension, pulmonary circulation diseases, chronic pulmonary disease, uncomplicated diabetes, hypothyroidism, renal failure, liver disease, obesity and electrolyte and fluid disorders are significantly different in HF and non-HF cases. All laboratory indices are significantly different in HF and non-HF cases.

A. Conventional clinical predictors for HF

Clinical risk factors with significance level 0.05 were selected for multivariable Cox proportional regression and conferred a substantial risk for incident HF within one year (Table 1). From the table we can see, 11 of 14 predictors are statistical significant and presented to be independent predictors for incidence of HF. In addition to previously discovered predictors such as age (HR=2.78, 95% CI=1.993-3.753, p<0.001), diabetes (HR=1.335, 95% CI=1.095-1.628, p=0.004), renal failure (HR=1.621, 95% CI=1.277-2.058, p<0.001) and obesity (HR=2.191, 95% CI=1.194-4.022, p=0.011), a list of new factors, including cardiac arrhythmias (HR=1.337, 95% CI=1.055-1.694, p=0.016), pulmonary circulation (HR=2.417, 95% CI =1.262-4.628, p=0.008), peripheral vascular (HR=1.342, 95% CI=1.032-1.745, p=0.028),chronic pulmonary (HR=1.255, 95 % CI=1.025-1.538, p=0.028), hypothyroidism (HR=1.486, 95% CI=1.142-1.932, p=0.003) and fluid electrolyte (HR=1.289, 95% CI=1.077-1.543, p=0.006) are also found to independently predict short-term incidence of HF. Moreover, the traditional long-term risk factor, hypertension, was also found to be a predictor for short-term incidence of HF, but in an opposite direction (HR=0.706, 95% CI=0.569-0.875, p=0.002). The reason will be demonstrated in the DISCUSSION part.

Table 1 Cox proportional Hazard Model with conventional clinical risk factors

Predictor	BC HR	95% CI		P –value
Age	2.780	1.993	3.753	.000
Cardiac arrhythmias	1.337	1.055	1.694	.016
Pulmonary circulation diseases	2.417	1.262	4.628	.008
Peripheral vascular disease	1.342	1.032	1.745	.028
Hypertension	.706	.569	.875	.002
Chronic pulmonary disease	1.255	1.025	1.538	.028
Diabetes	1.335	1.095	1.628	.004
Hypothyroidism	1.486	1.142	1.932	.003
Renal failure	1.621	1.277	2.058	.000
Liver disease	.738	.499	1.093	.130
Aids	1.767	.989	3.157	.054
Obesity	2.191	1.194	4.022	.011
Weight loss	1.421	.933	2.162	.102
electrolyte and fluid disorders	1.289	1.077	1.543	.006

BC indicates bias-corrected after bootstrapping (1000 samples, random seed); HR, hazard ratio; CI, confidence level

Table 2 Laboratory indices for incident HF (Model 1: model with individual laboratory index; Model 2: model with multiple laboratory indices)

Predictor		BC HR	95% CI		P value	NRI (p-value)	IDI (p-value)	ΔC(p-value)
Model 1	SCR	1.461	1.231	1.734	.000	0.052(0.086)	0.001(0.186)	0.003(0.04)
	BUN	2.262	1.807	2.832	.000	0.115(<0.001)	0.009(0.007)	0.01(0.008)
	GLU	1.611	1.184	2.192	.02	0.035(0.352)	0.002(0.140)	0.001(0.02)
	PT	1.270	1.140	1.449	.000	0.031(0.924)	0.000(0.319)	-0.0003(0.12)
	APTT	1.562	1.312	1.858	.000	0.121(<0.001)	0.007(<0.001)	0.006(0.005)
	TBIL	.910	.758	1.093	.312	0.011(0.385)	0.000(0.605)	-0.0002(0.18)
Model 2	BUN	2.079	1.654	2.613	.000	0.131(<0.001)	0.016(<0.001)	0.016 (0.005)
	GLU	1.300	.952	1.776	.06			
	APTT	1.420	1.192	1.693	.000			

B. Laboratory risk factors for HF events

When considered individually, the following laboratory indexes including SCR, BUN, Glucose, PT, APTT were significantly associated with heart failure after adjustment for conventional predictors as shown in Table 2 (model 1). Several metrics were used to summarize the prognostic utility of adding individual laboratory index to conventional risk factors (Table 2). Except from BUN (changes=0.01, p=0.008), the addition of individual laboratory index resulted in small increases in the c-statistics (all changes less than 0.005). The NRI and IDI were both significant for indexes including BUN and APTT. In backward elimination models, 2 predictors were retained for prediction of HF (BUN, APTT), as shown in Table 2 (model 2). Incorporation of the set of significant indexes into prediction models for HF led to significant increments (approximately 0.016, p=0.005) in the C-statistics. In addition, the NRI and IDI were both significant increased (p<0.001) while combined with all independent predictors (Table 2, model 2).

C. HF prediction model

The short-term HF incidence model for incident HF had acceptable discrimination (c-statistic 0.712 by internal validation with bootstrap-derived samples and correction for optimism). Fig. 1 depicts the cumulative survival curve of HF according to different groups. Kaplan-Meier survival curves stratified according to the survival data of different risk groups further confirmed the classification performance of the predictive model. In addition, hazard ratio (HR=3.602) and log-rank test p-values (<0.0001) for the two groups are given to demonstrate that the multivariable predictive model is with better discrimination performance by a stratified Cox-regression model.

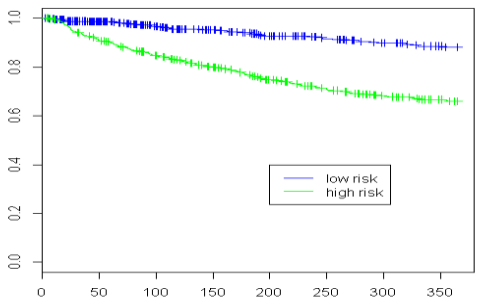

Fig.1 Kaplan-Meier plot based on the combination of conventional predictors and laboratory indices

I. DISCUSSION

In ICU patients' cohort, we found that conventional risk factors predicted heart failure within one year with reasonable accuracy and that the addition of laboratory indices to conventional risk factors modestly improved discrimination and thus substantially improved risk classification performance for heart failure.

A. Conventional predictors for HF

Our results confirmed prior researches regarding individual risk factors for long-term incident HF such as age, obesity and diabetes in short-term prediction. Hypertension, which was demonstrated as a risk factor in long-term prediction for HF, is presented to with opposite effect in short-term study. In addition, we have found a series of new predictors which are not demonstrated in long-term studies, including pulmonary circulation, peripheral vascular, chronic pulmonary, hypothyroidism and fluid electrolyte disorders, all of which shown a high hazard ratio in the final Cox proportional model.

Hypertension, as a traditional risk factor for a poor long term clinical outcome and mortality in general CVD population, shows an opposite effect in 1-year HF incidence in ICU patients in our study. It is likely that this correlation is a consequence of the fact that more severe cardiac dysfunction causes a decline in systemic blood pressure, making low blood pressure a marker for more advanced HF. As for our study, patients with high risk of HF within short-term may have cardiac dysfunction in a certain degree. It was also demonstrated in [20] that high blood value is associated with greater survival among HF patients. That's why hypertension is presented to be a protective predictor in short-term prediction model of HF.

Pulmonary circulation is the portion of the cardiovascular system which carries deoxygenated blood away from the heart, to the lungs, and returns oxygenated (oxygen-rich) blood back to the heart. The diseases in pulmonary circulation make it harder for the heart to pump blood through the lungs. Over time, the affected blood vessels become both stiffer and thicker, in a process known as fibrosis. In addition, the increased workload of the heart causes hypertrophy of the right ventricle, making the heart less able to pump blood through the lungs, ultimately causing right heart failure. That's why pulmonary circulation and chronic pulmonary diseases are presented to be predictors for HF.

Peripheral vascular disease is a condition that develops when the arteries that supply blood to the internal organs, arms, and legs become completely or partially blocked as a

result of atherosclerosis. As a result, the internal organs will be lacking blood supply. Insufficiency in blood supply developed in carotid will cause ischemia, including stroke, CHF or renal failure.

Hypothyroidism is a state in which the thyroid gland does not make enough thyroid hormone. It is characteristics of increased neuromuscular excitability, hypocalcemia, hyperphosphatemia, and decrease in serum PTH. Not timely detection and treatment of chronic hypothyroidism may influence the cardiovascular system due to long-term hypocalcemia and hypomagnesemia, expressed as decreased myocardial tension, cardiac dilation, arrhythmia, and thus cause congestive heart failure.

Fluid electrolyte disorders such as acidosis and hyperkalemia can directly or indirectly affect myocardial function, also cause arrhythmias, and thus induces heart failure

B. Laboratory predictors

Some laboratory indices including SCR, BUN, Glucose and APTT were found to be valuable predictors for HF. During the four predictors, SCR and BUN are the indicators of renal function while glucose is the indicator of diabetes and thus may be the predictors of HF from the analysis on conventional predictors. Also, elevated SCR or BUN means chronic and acute nephritis, renal function disease or heart failure. PTT or APTT is a performance indicator measuring the efficacy of both the "intrinsic" (now referred to as the contact activation pathway) and the common coagulation pathways. On the one hand, prolonged APTT is an indicator of Von Willebrand disease or Hemophilia. On the other hand, it is confirmed in [21] that the plasma levels of Von Willebrand disease might be important predicators of the severity of coronary heart disease in association with HF. That's why PTT and APTT were confirmed to be a predictor for HF.

C. Conclusions

In conclusion, our study identified a set of clinical factors, including cardiac arrhythmias, pulmonary circulation diseases, peripheral vascular disease, chronic pulmonary disease, hypothyroidism and fluid electrolyte disorders, as independent predictors for incidence of heart failure in ICU patients. Moreover, we also discovered that some laboratory indices such as BUN and APTT, also predicts the onset of heart failure in one-year scope. We further illustrated that combining both clinical and laboratory indices lead to better accuracy in HF risk prediction.

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