# A Simple Prognostic Index in Acute Heart Failure

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Abstract

Background
Rapid effective triage is integral to emergency care in patients hospitalized for heart failure, to guide the type and intensity of therapy.
Several indexes and scores have been proposed to predict outcome; most of the them are complex and unfit to use at the bedside.

Methods
We propose a new prognostic index for in hospital mortality in acute heart failure.
The index was built according to the formula; 220 – age – heart rate + systolic blood pressure – ( creatinine X 10). The index was tested in 1628 patients admitted for acute heart failure and enrolled, from November 2007 to December 2009, in the Italian Registry on Heart Failure Outcome ( IN-HF); a prospective, multicentre, observational study.

Results
The prognostic index was an independent predictor for in hospital mortality risk ( c statistic= 0.74) ($p<0.0001$), together with left ventricular ejection fraction ($p= 0.001$), Glycemia ( $p= 0.019$) and hemoglobin concentration ($p = 0.002$).

Conclusion
A simple prognostic index based on variables easily assessed can be useful to predict mortality in acute heart failure at the first arrival in hospital.

Key words; Acute Heart Failure- Emergency care- Prognostic index.

## Introduction

Heart Failure (HF) is one of the prevalent and increasingly common reason for hospitalization in the west countries and this multifactorial condition has a substantial public health and economic impact.
Actually a wide range of therapies exists and the possibility to predict the outcome could guide appropriate applications.
Several prediction models have been proposed (1)(2) (3)(4) in patients admitted for HF.
These models are not widely used in clinical practice, despite their validation in several studies.
The reason could be the number of the variables involved and the complexity of the algorithms for obtaining a synthetic risk value.
The objective of this study is to propose a new, user friendly and accessible Prognostic Index (PI) to predict in-hospital mortality for Acute Heart Failure (AHF).

The PI was tested using the database of the Italian Registry on Heart Failure Outcome from patients with Acute Heart Failure hospitalized on 61 Italian Cardiology Centres (5).

**Methodogy**

The Italian Registry on Heart Failure Outcome ( IN-HF) is a national, prospective, multicentre, observational study.
The goal of the study was to improve knowledge of demographic, clinical and biological characteristics, to assess the diagnostic and therapeutic approach, the outcome and the prognostic predictors in patients with HF, in the " real word ".
Patients were enrolled in the study from November 2007 to December 2009 and followed for 1 year.
Exclusion criteria were age below 18 years and a patient's unwillingness to participate.
The participating centres were a mix of academic and community hospitals, well distributed over the whole country.
All variables were collected at admission in cardiology centres and registered in a central database using a web connection.
A total number of 5610 patients were included in the original study.
We considered, for our analysis, only subjects classified as Acute Heart Failure (1855 patients), new HF ( 797 pts.) (43%) or worsening HF ( 1058 pts.) (57%).
From the total cohort of 1855 patients, 227(13%) were excluded, lacking of the all considered variables.
AHF was defined according to the European Society of Cardiology (ESC) Guidelines during the enrolment period (6).
A total number of 1628 patients (87%) were submitted to our analysis.
General characteristics of the study population and the considered variables are shown in Table 1.
The mean age was 72.4±11.6 (range 21-98) years.
Women were 650 ( 40%) of the cohort.
An Implantable Cardioverter Defibrillator (ICD) and/or a Cardiac Resynchronization Therapy (CRT) were present in 203 subjects (12.4%); 168 patients (10.3%) had an implanted Pacemaker; thus a number of 371 pts (22.8%) had an electrical device and possibly a paced rhythm.
The Atrial Fibrillation documented by ECG at admission or anamnestic was present in 44.5% of the patients.
Diabetes was present in 41.2% of pts, Previous Acute Myocardial Infarction (AMI) in 34.6%, Chronic Obstructive Pulmonary Disease (COPD) in 31.8%, 25.4% has had a previous myocardial revascularization therapy, 1073 (65%) had a story of hypertension.
The mean value of the LVEF was 37.7±13.9 %.
The pharmacological therapeutic interventions during the acute phase were with Furosimide in 99,4%, other intra venous Diuretics 15.7%, i.v. Nitrates 29.9%, Dopamine 13.9%, Dobutamine 7.7%, Levosimendan 3.9%.
The variables collected and considered possible predictors of in-hospital mortality have been divided in our as in the original study(5) in; demographic (age and sex); anamnestic (history of atrial fibrillation, chronic obstructive pulmonary disease, diabetes, peripheral vascular disease, previous myocardial infarction, previous stroke or TIA, previous and treated hypertension, Implantable Pace Maker, Implantable Cardioverter Defibrillator, Cardiac Resynchronization Therapy) ; laboratory (serum sodium, serum hemoglobin, glycemia, serum creatinine); clinical ( systolic blood pressure, diastolic blood pressure, heart rate, PI ) and instrumental by 2D-echo (left ventricular ejection fraction ).
The PI was built considering the predictors for mortality evaluated in our previous studies (7) (8), in large studies (9) (10) (11) and in IN-HF and according to the formula;
220- age – heart rate + systolic blood pressure – (creatinine X 10).
The PI was calculated in all patients (1628) and the statistical power was evaluated in predicting

hospital mortality for any cause.

**Statistical methods**

In the preliminary univariate analysis, means ± SD and percentage frequencies were used as descriptive summaries, respectively, for the continuous and categorical variables. Group differences were assessed with the unpaired Student's t-test for continuous variables and with $X^2$ or Fisher's exact test for categorical variables and the corresponding results were employed as a preparatory tool to explore the association with the event from a more accurate multivariate perspective.
The multivariate analysis was based on the logistic regression model, in order to identify independent predictors and to estimate the adjusted effect of the PI on the binary outcome of interest.
Subsequently, the ROC curve of the PI was built and the optimal cut-off value was determined with the resulting accuracy measures (sensitivity and specificity) and predictive values.
All tests performed in the analysis were two-sided and a p-value $< 0.05$ was considered statistically significant.
Analyses were performed with SAS system software.

**Results.**

The in-hospital death rate, for any cause, was 5.7% ( 92 deaths), almost 90% of deaths were cardiac.
In Table 2 is reported the univariate analysis of the all variables.
As shown, none of the categorical variables was statistically significant.
At the contrary all the continuous variables, except the BMI ( p = 0.95) and Heart Rate ( p= 0.45), were significant.
The Results of the logistic regression model are shown in Table 3.
The independent variables were; LVEF, p = 0.001, OR 0.96, 95% CI ( 0.94 - 0.98 );
Glycemia, p = 0.019, OR 1.003, 95% (1.00-1.005); Hb, p = 0.002, OR 0.84, 95% (CI 0.75-0.93);
PI, p = < 0.0001, OR 0.98, 95% CI 0.97-0.99.
ROC curve (Fig 1) of PI showed the best AUC value 0.74 with a sensitivity 72.8% and specificity 62.3%.
The PI Positive Predictive Value (PPV) was 10.4%, Negative Predictive Value (NPV) was 97.5%.

**Discussion**

Our analysis was made on the basis of a Registry which recruited patients admitted consecutively in hospital for acute and chronic heart failure.
The choice of a registry was done to adhere to a real representative patients spectrum.
Analysis of the Italian Registry was conducted to test a new, practical, friendly user risk-prediction tool that could be proposed for larger disposable databases and in clinical practice.
The majority of the studies that obtained mortality risk predictors have considered single variables, but in the same patient multiple risk factors contemporary exist, thus the analysis should consider the combination and interaction of these factors.
This goal is respected in our analysis and PI is a combination-interaction of predictors.
Usually the proposed clinical models to stratify the risk in pathological conditions are scores that put patients into a category risk and not in an individual position.
Moreover, significant disadvantages of the risk schemes are the complexity of calculations and the need to convert point scores in nomograms.
The simplicity and the parsimony of the variables of the PI makes it fit to evaluate a patient rapidly and at bedside.

Our PI evaluates patient's risk, it does not require to convert the value in nomograms.
Considering the four variables in the formula, age, heart rate, systolic blood pressure, and creatinine concentrations, we can say that these variables have been found independent predictors for mortality in most of the large studies concerning HF (9) (10) (11) (12).
Moreover, PI is not an artificial tool, because the formula has a precise biological and physiological meaning.
In fact, there is no doubt that age is a powerful risk factor for mortality.
" Senectus ipsa est morbus ", as Terentius said (13).
Subtracting the numbers of the years to 220, we obtain the theoretical maximal frequency, it means the maximal $O^2$ consumption for that patient; in other words the maximal aerobic power.
Considering the formula, it is evident that increasing heart rate decreases the interval to the anaerobic threshold.
Heart Rate (HR), the second variable of PI is a well known independent predictor of cardiovascular death, particularly in ischemic heart disease.
Elevated HR may be a marker of haemodynamic instability and/or may represent an unfavourable increase of the sympathetic activity.
An elevation on HR increases the myocardial oxygen consumption and, at the same time, reduces the availability of the diastolic time for coronary flow.
In fact the shortening of the cardiac cycle reduces the duration of the single intervals.
Despite these considerations HR in the Italian Registry analysis is the only variable of the formula which did not show to be an independent predictor for death.
The reason is in the fact that a lot of patients (22.8%) enrolled in the Registry had an implanted Pacemaker (10.3%) or ICD-CRT ( 12.5%) and 44.5% had an atrial fibrillation at admission or anamnestic; nevertheless we have maintained HR in the formula, thinking it adds something to PI value.
Systolic blood pressure is a predictor of mortality for its low values.
Low systolic blood pressure, in fact, should be regarded with suspicion in HF (14), as a marker of a poor stroke volume and cardiac function reflecting inadequate response to stress.
Additional lowering of the systolic pressure in patients with baseline hypotension may result in organ hypoperfusion, causing worsening renal function, cardiac ischemia and reducing cardiac out-put.
According to our study, the well known sentence; " the lower the better ", for blood pressure (15), true in primary prevention could be wrong in secondary prevention, particularly in patients with HF.
In the OPTIMAZE-HF (11) a large registry for patients hospitalized with HF in 259 United States hospitals (48612 patients enrolled) , admission low systolic blood pressure was found to be one of the most strongly predictive variables for in-hospital mortality, whereas the increased SBP up to the threshold of approximately 160 mm Hg was associated with a lower risk (16).
Why do subjects admitted for heart failure with low systolic pressure are at higher risk of death?
Low systolic blood pressure can be a consequence of left ventricular dysfunction, frequently associated with right ventricular involvement; moreover, low systolic pressure can be expression of a damaged neurohormonal pathway, resulting in an unfit response to usual and unusual stressors (17).
The second question is; which is the meaning of an important systolic reduction by drugs as ACE inhibitors, angiotensin receptors blocker and β -blockers in HF.
These drugs should increase stroke volume reducing heart rate and the peripheral resistances; thus a reduction of systolic pressure can indicate that lower peripheral resistances and lower heart rate are not followed by an increasing stroke volume, unmasking a severe systolic dysfunction.
" Last but not least" in the formula is the creatinine blood concentration.
Creatinine is considered to provide only a rough estimate of the renal function, despite the glomerular filtration rate (GFR) which is regarded as the best clinical index of the kidney function.
In our formula we maintained, as a variable, the creatinine concentration, because the formulas calculating GFR contains the patient's age which is just considered in our model, independently.

Several studies have demonstrated that low kidney function is a significant risk factor for mortality in HF.
The ADHERE Registry (10) studied hospitalized patients with a primary diagnosis of Acure Decompensated Heart Failure and revealed that blood urea nitrogen (BUN) level of 43 mg/dl or higher was the best single predictor of mortality.
The second best predictor was admission systolic blood pressure (SBP) < 115 mm Hg.
Serum creatinine levels of 2.75 mg/dl or higher provided additional prognostic value in patients with BUN level ≥ 43 mg/dl and SBP ≤ 115 mm Hg.
The authors employed a Classification and Regression Tree method (CART) to derive the risk of mortality, identifying acutely decompensated heart failure patients at several levels of risk in the validation cohort.
Heart rate and age did not improve the risk stratification and this surprising result, especially for age, can be due to the CART method and to the very strong power of the predictors.
These findings underscore the importance of the renal function in HF, confirming the established link between heart and kidney and thus the association between clinical outcomes and markers of renal function (18) (19) (20).
How does the kidney insufficiency work, in worsening heart failure?
First of all, kidney impairment causes sodium and fluid retention, determining a ventricular overload thus a progressive ventricular dilation and remodeling.
Furthermore, renal insufficiency is associated with multiple changes in vascular biology, including abnormalities in coagulation/fibrinolytic system, endothelial dysfunction, insulin resistance, hyperactivation of the sympathetic nervous and rennin-angiotensin systems; all of them associated with adverse outcome (21).
Thus the synergistic action increases the predictive power of the single variables, in a multiplicative manner.
Finally some considerations about the predictive values of PI.
The low positive predictive value (10.4) can depend on the low percentage of in-hospital mortality (5.7% ); at the contrary PI has a very high negative predictive value, 97.5%.
This high negative predictive value can be a good tool for beginning the screening of the subjects admitted in hospital for acute HF, meaning that subjects who have a PI higher than 168 have a low risk (only a 2.5 % in our study) to die.

**The study limitations**

The first limitation of the study is the small size of the cohort .
The second is that PI has been tested in a retrospective way, in a derivation test.
A desirable validation should be obtained in larger populations and in a prospective way.
The third consideration to do is that the four variables in the formula are equally weighted, all as 1, but it is probably that it's not true in the real world; in fact it is possible that age or creatinine concentrations can have a stronger impact in outcome than systolic pressure and heart rate.
Validation with prospective studies should be done to confirm the efficiency of this simple formula that is based on physiological considerations.

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Table 1. General characteristics of study population: percentage frequency (%) for categorical variables, mean and standard deviation (Sd) for continuous variables.

| **Categorical variables** | **%** | **Continuous variables** | **Mean±Sd** |
|---|---|---|---|
| With events | 5.7 | Age (years) | 72.4 ± 11.6 |
| Males | 60.0 | BMI (kg/m$^2$) | 27.7 ± 5.1 |
| Diabetes | 41.2 | DBP (mmHg) | 78.8 ± 17.5 |
| Previous Hypertension | 65.9 | SBP (mmHg) | 135.6 ± 32.5 |
| Treated Hypertension | 60.8 | Heart Rate (bpm) | 93.1 ± 25.4 |
| Previous AMI | 34.6 | LVEF (%) | 37.7 ± 13.9 |
| Previous Revascularization | 25.2 | Creatinine (mg/dl) | 1.4 ± 1.0 |
| PVD | 19.7 | Glycemia (mg/dl) | 162.5 ± 79.7 |
| COPD | 31.8 | Hb (g/dl) | 12.6 ± 2.1 |
| Previous Ictus-TIA | 8.6 | Sodium (mEq/L) | 138.9 ± 4.7 |
| ICD-CRT | 12.5 | PI | 175.9 ± 40.6 |
| PCMK | 10.3 | | |
| AF ECG-Previous AF | 44.5 | | |

AF, Atrial Fibrillation, AMI, Acute Myocardial Infarction; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CRT, Cardiac Resynchronization Therapy; DBP, Diastolic Blood Pressure; Hb, Haemoglobin; ICD, Implantable Cardioverter Defibrillator; LVEF, Left Ventricular Ejection Fraction; PCMK, Pacemaker; PVD, Peripheral Vascular Disease; PI, Prognostic Index; SBP, Systolic Blood Pressure; TIA, Transient Ischaemic Attack.

Table 2. Univariate analysis by outcome status: percentage frequency for categorical variables (upper panel), mean and standard deviation (Sd) for continuous variables (lower panel).

| **Explanatory variables** | **Without events** | **With events** | **p-value** |
|---|---|---|---|
| Males | 60.3 | 55.4 | 0.356 |
| Diabetes | 41.0 | 45.7 | 0.374 |
| Previous Hypertension | 66.0 | 64.1 | 0.711 |
| Treated Hypertension | 61.2 | 53.3 | 0.130 |
| Previous AMI | 34.6 | 33.7 | 0.854 |
| Previous Revascularization | 25.3 | 23.9 | 0.772 |
| PVD | 19.7 | 19.6 | 0.982 |
| COPD | 31.5 | 37.0 | 0.270 |
| Previous Ictus-TIA | 8.3 | 13.0 | 0.118 |
| ICD-CRT | 12.4 | 14.1 | 0.620 |
| PCMK | 10.4 | 8.7 | 0.598 |
| AF ECG-Previous AF | 45.3 | 40.6 | 0.385 |
| Age (years) | 72.0 ± 11.5 | 78.3 ± 10.9 | <0.0001 |
| BMI ($kg/m^2$) | 27.7 ± 5.2 | 27.6 ± 4.4 | 0.955 |
| DBP (mmHg) | 79.5 ± 17.2 | 67.5 ± 19.7 | <0.0001 |
| SBP (mmHg) | 136.9 ± 32.2 | 114.5 ± 30.9 | <0.0001 |
| Heart Rate (bpm) | 93.0 ± 25.4 | 94.7 ± 26.3 | 0.459 |
| LVEF (%) | 38.1 ± 13.9 | 31.5 ± 11.2 | <0.0001 |

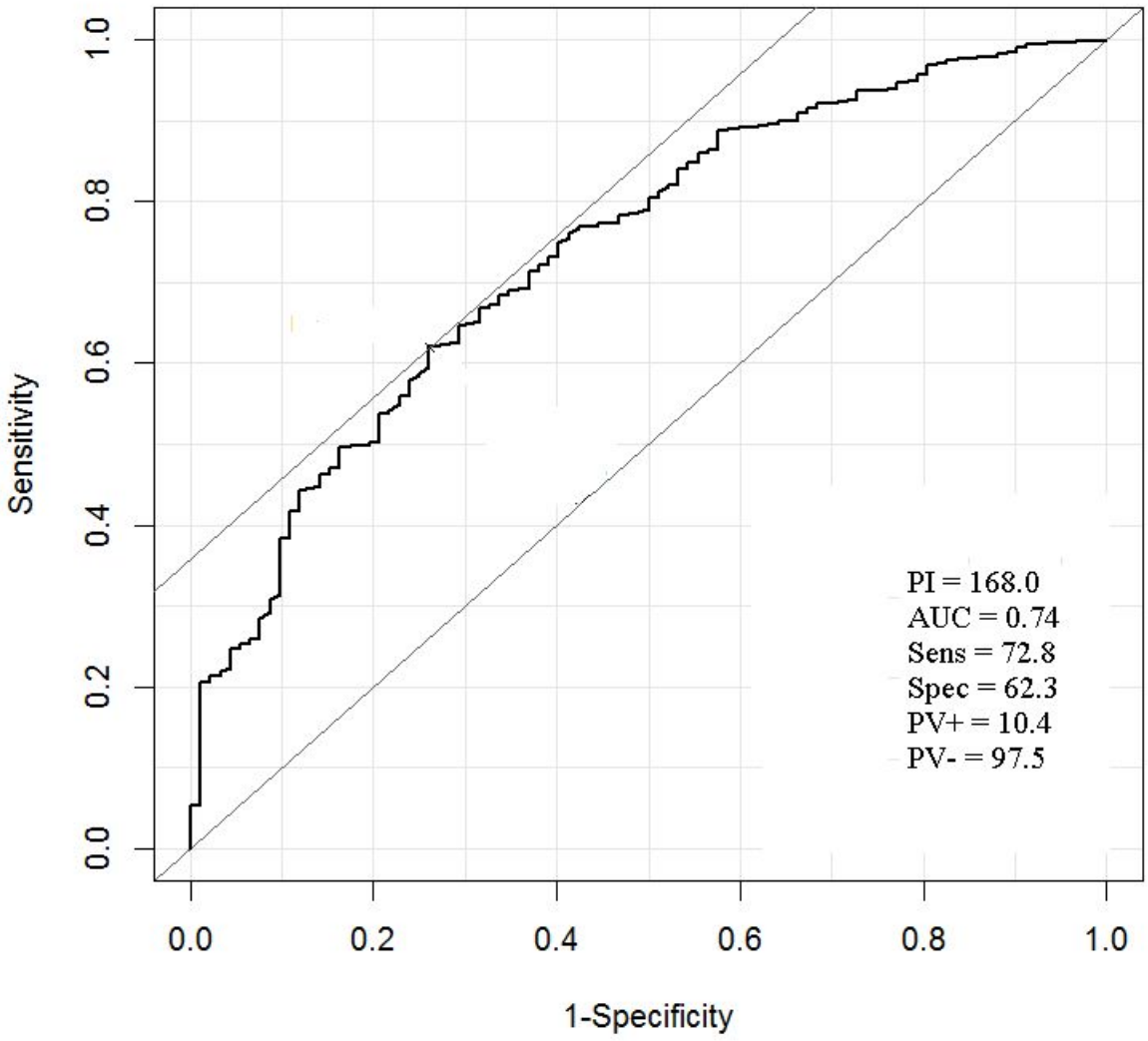
| | | | |
|---|---|---|---|
| Creatinine (mg/dl) | 1.4 ± 0.9 | 2.1 ± 1.5 | <0.0001 |
| Glycemia (mg/dl) | 161.3 ± 79.1 | 182.3 ± 85.7 | 0.005 |
| Hb (g/dl) | 12.6 ± 2.1 | 11.7 ± 2.1 | <0.0001 |
| Sodium (mEq/L) | 139.0 ± 4.6 | 137.0 ± 6.4 | 0.003 |
| PI | 178.0 ± 39.6 | 141.0 ± 42.1 | <0.0001 |

AF, Atrial Fibrillation, AMI, Acute Myocardial Infarction; BMI, Body Mass Index; COPD, Chronic Obstructive Pulmonary Disease; CRT, Cardiac Resynchronization Therapy; DBP, Diastolic Blood Pressure; Hb, Haemoglobin; ICD, Implantable Cardioverter Defibrillator; LVEF, Left Ventricular Ejection Fraction; PCMK, Pacemaker; PVD, Peripheral Vascular Disease; PI, Prognostic Index; SBP, Systolic Blood Pressure; TIA, Transient Ischaemic Attack.

Table 3. Results of the logistic regression model.

| **Explanatory variables** | **OR** | **95% CI** | **p-value** |
|---|---|---|---|
| DBP | 0.984 | 0.967 - 1.001 | 0.063 |
| LVEF | 0.968 | 0.949 - 0.987 | 0.001 |
| Glycemia | 1.003 | 1.000 - 1.005 | 0.019 |
| Hb | 0.840 | 0.752 - 0.939 | 0.002 |
| Sodium | 0.971 | 0.932 - 1.011 | 0.157 |
| PI | 0.985 | 0.978 - 0.991 | <0.0001 |

OR, Odds Ratio; CI, Confidence Interval.




Prognostic Index. ROC Curve.

PI= Prognostic Index
AUC= Area Under Curve
Sens= Sensitivity
Spec= Specificity
PV+= Positive Predictive Value
PV- = Negative Predictive Value
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