Predictors of Post-Discharge Outcomes from Information Acquired Shortly After Admission for Acute Heart Failure: A Report from the PROTECT Study

Cleland et al: A Report from the PROTECT Study

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List of Abbreviations

ACE: angiotensin converting enzyme
AHF: acute heart failure
BNP: brain natriuretic peptide
BUN: blood urea nitrogen
COPD: chronic obstructive pulmonary disease
eGFR: estimated glomerular filtration rate
ESCAPE: Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness
NT-proBNP: amino-terminal pro-brain natriuretic peptide
NYHA: New York Heart Association
OPTIME-CHF: The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure
OPTIMIZE-HF: Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure
PROTECT: Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function
SURVIVE: Survival in Patients with Acute Heart Failure in Need of. Intravenous Inotropic Support
Abstract

Background—Acute heart failure (AHF) is a common reason for admission and outcome is often poor. Improved prognostic risk stratification may assist in the design of future trials and in patient management. Using data from a large randomized trial, we explored the prognostic value of clinical variables, measured at hospital admission for AHF, to determine whether a few selected variables were inferior to an extended data-set.

Methods and Results—The prognostic model included 37 clinical characteristics collected at baseline in PROTECT, a study comparing rolofylline and placebo in 2,033 patients admitted with AHF. Pre-specified outcomes at 30 days were death or re-hospitalization for any reason, death or re-hospitalization for cardiovascular or renal reasons and, at both 30 and 180 days, all-cause mortality. No variable had a c-index >0.70 and few had values >0.60; c-indices were lower for composite outcomes than for mortality. Blood urea was generally the strongest single predictor. Eighteen variables contributed independent prognostic information but a reduced model using only eight items (age, prior heart failure hospitalization, peripheral edema, systolic blood pressure, serum sodium, urea, creatinine and albumin) performed similarly. For all-cause mortality at 180-days, the model C-index using all variables was 0.72 and for the simplified model, also 0.72.

Conclusions—A few simple clinical variables measured on admission in patients with AHF predict a variety of adverse outcomes with similar accuracy to more complex models. However, predictive models were of only moderate accuracy, especially for outcomes that included non-fatal events. Better methods of risk-stratification are required.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00328692 and NCT00354458.

Key Words: acute heart failure, randomized controlled trial, prognostic model, mortality, rolofylline
Despite improvements in therapy, the risk of re-admission or death in the months following an episode of worsening heart failure remains substantial (1). Indeed, recent data suggest that most patients admitted with acute heart failure (AHF) will die or be re-hospitalized within 12-18 months (2). Risk-stratification tools could help target those at highest risk, in whom additional support and interventions might deliver the greatest benefits. Perhaps more importantly, prognostic models might identify factors that are modifiable and plausible targets for treatment.

Prognostic models and risk stratification tools have been developed from several large, epidemiologically-based observational studies of AHF (3-6) but few from large randomized trials of AHF (7-9). These models may differ and should be considered complimentary. Models based on epidemiological populations of AHF may be more relevant to overall clinical practice but may be less relevant to the sort of patients managed by cardiologists and those enrolled in clinical trials. Clinical trial populations are usually younger, more carefully characterized and may be better managed (10). Clinical trials usually collect more information on patient characteristics and laboratory variables and have more detailed follow up with greater accuracy on mode-specific cause of hospitalization. Also, protocols usually exclude patients where the risk is already clearly extremely high or very low. For these reasons, prognostic models based on clinical trials might be more relevant when planning future trials. Moreover, the prognostic models that have been developed have not reported on mortality over different time-frames or on other outcomes such as readmission. Predictive variables may differ depending on the time-frame and the event of interest. However, if key prognostic variables are similar for different outcomes and time-frames this provides powerful evidence of their importance and lends weight to the argument that they might be mechanistically important and potential therapeutic targets. We hypothesised that a model based on a small number of readily available clinical variables
would provide similar prognostic information as more complex statistical models and that the same variables would perform similarly well for different outcomes and time-periods, providing the analytical basis for a research programme on novel biomarkers in AHF using plasma stored during the trial.

Methods

Inclusion criteria and study design.

The design and main results of the Placebo-controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) have been published (11, 12). Patients with pre-existing heart failure, mild or moderate renal impairment (estimated creatinine clearance of 20-80 ml/min) and increases in brain natriuretic peptides (BNP), presenting with an acute worsening of breathlessness associated with symptoms and signs of volume overload requiring intravenous diuretic therapy were enrolled within 24 hours of admission were enrolled (13). The protocol was approved by the ethics committees at each participating center, and patients provided written informed consent.

At baseline, information on demographics, clinical presentation, medical history, physical examination and standard laboratory blood tests were recorded. Natriuretic peptides were not included in this analysis because measures were done locally using various assays. Glomerular filtration was estimated (eGFR) using the four-variable MDRD equation. Medications and device interventions were also excluded from models as these reflect many factors, including patient characteristics, quality of care and physician and patient choice, which may confound interpretation. For instance, use of aldosterone antagonists is often associated with adverse
outcomes in prognostic models and yet randomized trials consistently show improved outcomes. This may be because aldosterone antagonists are targeted at sicker patients with an intrinsically worse prognosis. Moreover, medications and device interventions change over time and are often discontinued intermittently or permanently during follow-up which is difficult to track.

Patients were reviewed at Day 14 and then contacted by telephone to identify deaths and readmissions up to Day 60 and to assess vital status alone at Day 180. The definitions of the primary and secondary end-points of PROTECT have been reported in detail (11). For the purposes of this analysis, four end-points were considered: all-cause mortality at 30 days, death or re-hospitalization for any reason by 30 days, death or re-hospitalization for cardiovascular or renal reasons by 30 days and all-cause mortality at 180 days. Endpoint assessment was conducted by a committee of cardiologists, nephrologists, and neurologists blinded to treatment allocation.

**Statistical Methods**

All randomized patients were included in the analysis. For the time-to-event analyses patients with incomplete follow-up were included assuming non-informative censoring. Event rates at the time-points of interest were presented using percentages and Kaplan-Meier estimates. Clinical investigators identified 37 baseline clinical characteristics as candidate predictor variables (Table 1). For the purpose of model development, twenty-five data sets were generated with multiple imputation of missing values (14). No adjustment for multiple comparisons across the endpoints was made. Regression analysis was performed using the Cox proportional hazards model. For each continuous predictor, the assumption of linearity was checked in one imputed data set. Logarithmic or linear spline transformations were applied to model non-linear relationships.
Groups of continuous predictors showing strong multi-collinearity were identified, and a single variable was chosen to represent each group. If a representative variable was selected for inclusion then other variables from the same group were added or substituted to check for possible improvements in prediction. The assumption of proportional hazards was checked for all candidate predictors. The univariable predictive power of each candidate predictor variable was quantified using the c-index. For a time-to-event analysis, the c-index measures the ability to correctly rank patients with respect to their predicted and actual event times with 0.50 indicating no ability and 1.0 indicating perfect ranking. A multivariable Cox proportional hazards model was selected using backward elimination of predictor variables in each imputed data set. The significance level to stay in the model was set to 0.10. Variables selected in at least 20 imputed data sets were retained for inclusion in the final model. Applying the forward selection method for variable selection produced a similar set of predictors. For each outcome, the final model, estimated by pooling results from the 25 imputed datasets, was used to produce hazard ratios (HR) along with their 95% confidence intervals (CI), chi-squared statistics and p-values. Estimates of the c-index for each of the 25 imputed datasets were averaged to produce the c-index for each selected model. Internal validation of each c-index estimate was performed using bootstrap re-sampling. The resulting optimism-corrected c-index corrects for fitting the model and evaluating its predictive power using the same data set. For each endpoint, patients were grouped according to quartiles of predicted risk averaged across the imputed data sets. Within each risk group the observed univariable distributions for variables included in the final model were summarized with frequencies and percentages for categorical variables, and with the medians and 25th and 75th percentiles for continuous variables. After reviewing the multivariable modeling results the clinical investigators picked the eight best predictor variables.
that are also readily available during routine patient care. A simplified model including only these eight variables was fitted, and discrimination ability quantified with a c-index. The predictive ability of the simplified model was compared graphically to that of the selected model using calibration curves (15). All statistical analyses were performed at Duke Clinical Research Institute (Durham, NC). SAS version 9.22 (SAS Institute, Cary, NC) and R version 2.12 (The R Foundation for Statistical Computing) were used for the analysis.

Results

Of 2,033 patients randomized (1,356 to rolofylline and 677 to placebo), vital status was assessed by telephone at approximately 180 days and was known beyond day 60 in all but fourteen patients. The number of patients reaching each end-point and the components of composite end-points is shown in Table 2. The overall mortality at 30 days was 5.2% and 17.6% at 180 days.

The patient characteristics have been published in detail (16, 17). Most patients had an acute exacerbation of chronic heart failure rather than new onset heart failure. The median time from presentation to randomization was 17 hours (quartiles 6-22 hours) with baseline clinical data being gathered shortly before randomization. The median age was 72 years, 33% were women and co-morbidities including diabetes mellitus, ischemic heart disease, stroke and respiratory disease were common. Most patients were already receiving an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker and a high proportion were receiving beta-blockers and aldosterone antagonists at the time of admission. There was evidence of rounding of some key clinical variables, particularly blood pressure and heart rate.

Few variables were strongly related to any of the specified outcomes (Figure 1). No variable had a c-index >0.70 and few had values exceeding 0.60. Markers of renal or metabolic
function, including blood urea nitrogen (BUN) (c-index: 0.68), eGFR (0.62), the urea/creatinine ratio (0.70) and serum albumin (0.68) were the strongest predictors of 30-day mortality. Variables were generally more strongly related to mortality than to composite outcomes.

Variables that predicted 30-day mortality also predicted other outcomes.

Altogether, 18 variables contributed some independent prognostic information to at least one of the multi-variable models (Tables 3-6; Figure 2) but only seven contributed to three or more models. Multi-variable models were also better at predicting mortality than composite outcomes. BUN was the strongest predictor of 180-day mortality followed by age, systolic blood pressure, serum albumin and sodium. These five variables were amongst the strongest predictors of each of the other three outcomes. Mean, pulse or diastolic blood pressure carried similar predictive power to systolic blood pressure but the latter was generally most strongly related to outcome. New York Heart Association class in the month prior to admission and the severity of lung rales provided additional prognostic information in all models except 30-day mortality. Patients with more severe peripheral edema had longer hospital stays, a higher in-patient mortality and a lower rate of recurrent hospitalization.

Serum urea and creatinine exhibited high collinearity, but urea/creatinine ratio was a slightly stronger predictor than serum urea alone for some outcomes. On univariate analysis, serum creatinine predicted an adverse outcome but when it was added to urea in the multi-variable analysis, a higher creatinine predicted a lower mortality. This reflects a particularly poor outcome in patients with a disproportionately high urea compared to creatinine. Excluding urea brought one or more alternative measures of renal function, eGFR, creatinine or uric acid, into each of the models. Thirty day mortality rose as respiratory rate dropped below 20 breaths per minute but did not increase with higher breathing rates. A nadir in 180-day mortality was
observed with a serum bicarbonate of 27mEq/L and of 30-day death or re-hospitalisation with a serum alanine transaminase of 35U/L; risk rose above or below these values. A history of recurrent heart failure hospitalization predicted outcomes except 30-day mortality.

Some variables were notable by their absence in the multi-variable models, including sex, hemoglobin, presence of COPD (20% of patients) and diabetes (45% of patients). Indeed, higher blood glucose was associated with a slightly better outcome in a multi-variable analysis of 180-day mortality. A greater body mass index was a weak predictor of an increased risk of composite outcomes at 30-days and did not predict mortality.

A different perspective of the data is derived from examining patient characteristics by quartile of risk (Tables 3-6). These demonstrate that for many variables, although there was a strong statistical relationship to risk, absolute and relative differences in values across risk groups were small. For instance, for 180 day mortality, although serum albumin was strongly related to risk, there was only a 10% difference (0.3g/dL) in values between the lowest and highest risk quartile and for serum sodium the difference was <4% (4mmol/L). In contrast, for urea there was more than a two-fold difference (26mg/dL or 9.3mmol/L) between lowest and highest quartile of risk.

We constructed further models for each of the four outcomes using only eight items that are readily and fairly reliably available during routine care including age, history of prior heart failure hospitalization, severity of peripheral edema, systolic blood pressure, serum sodium, urea, creatinine and albumin. We did not include the severity of lung rales as the inter-observer variability of this measure may be high. The c-indices using the eight-item model were not substantially different from those obtained from the full multi-variable models (Tables 3-6) and each approach provided similarly good calibration (Supplemental Figure). The overall model C-
index for 30-day mortality was moderately good at 0.79 (0.78 when corrected for optimism) and 0.77 using the simplified 8-item model, with similar results at 180-days (C-index of 0.74, 0.72 corrected for optimism and 0.72 using the simplified model). For death or hospitalization for any reason by 30 days, the overall model C-index was poorer at 0.66 (0.64 when corrected for optimism) and 0.64 using the simplified model with similar results for death or re-hospitalization for cardiovascular or renal reasons by 30 days (C-index of 0.66, 0.64 corrected for optimism and 0.65 using the simplified model.

**Discussion**

There is a bewildering array of prognostic markers and models in heart failure. Our analysis shows that a single set of just eight readily available variables chosen by clinicians performs similarly to separate multi-variable models constructed for each individual outcome. Measures of renal and metabolic function were the best predictors, although no single variable was strongly linked to outcome. This might reflect the greater precision and consistency of laboratory measurements compared to symptoms or physical examination. Many variables are strongly inter-related and which one is incorporated into a model will depend on the play of chance. Variables associated with the risk of death alone or with composite outcomes were broadly similar. Small differences amongst models should not be over-interpreted as such differences may be more apparent than real. In the highest quartile of risk, 15% of patients died within 30 days and 40% by 6 months while in the lowest quartile of risk, the mortalities for these time-frames were <1% and <5% respectively.

Three large epidemiological studies have investigated predictors of outcome after discharge in patients with AHF. OPTIMIZE-HF (4) enrolled 5,791 with AHF; by 60 to 90 days
29.6% had been re-hospitalized and 8.6% had died, compared to our 30-day event rates of 14.1% and 5.2%. Systolic blood pressure was the strongest predictor of death, followed by age, weight, chronic lung disease, depression, serum sodium and creatinine, liver disease and peripheral edema but data on serum albumin or urea were not collected. Interestingly, measurements made at admission rather than discharge were generally stronger predictors of outcome, except for natriuretic peptides, although they provided little improvement in prognostic discrimination (18). The EFFECT study (6) was a retrospective chart review of 4,031 patients with AHF admitted to a community hospital in Canada. Mortality at 30-days was 10.5%. The strongest predictors of prognosis were age, systolic blood pressure, respiratory rate (higher breathing rates had worse outcome), BUN and serum sodium and co-morbidities including dementia, cancer and chronic lung disease. Data on albumin were not collected. The EuroHeart Failure survey (3) collected data on 10,701 patients; by 12 weeks, 24% had been re-admitted and 14% had died. The strongest predictors were age, hemoglobin, creatinine, sodium, left ventricular systolic dysfunction and atrial fibrillation. Systolic blood pressure, serum urea and serum albumin were not recorded. In most respects the consistency of predictors across models and with our analysis is substantial. However, despite applying clinical and biochemical criteria to select patients at higher risk of events, mortality was lower in PROTECT than that in epidemiological studies. Either by protocol design, by patient choice or by investigator decision, clinical trials appear to have a bias against enrolling high risk patients.

Several trials of AHF have also reported prognostic models. OPTIME-HF (7), which included 977 patients, suggested that age, urea, systolic blood pressure, NYHA class and serum sodium predicted 60-day mortality, which was about 10%, with a c-index of 0.77. ESCAPE (8), included 423 patients and suggested that BNP, cardiac arrest or mechanical ventilation, BUN and
serum sodium predicted 180-day mortality, which was about 18.7%, with a c-index of 0.76. SURVIVE (9) included 1,036 patients and suggested that BNP, blood pressure, serum creatinine, and pre-existing heart failure predicted mortality at 31-days, which was about 13%, with a c-index of 0.79. The consistency in reported prognostic variables might have been greater if all studies had included the same variables and used similar outcomes and durations of follow-up.

Observational studies cannot distinguish between cause and effect, but these data suggest five potential targets for therapeutic intervention, including renal dysfunction, low arterial pressure, low serum albumin, low serum sodium and the severity of congestion. However, age itself could be a target. Perhaps the failure to alter outcome in this population reflects the inability of existing treatments to halt or reverse cardiovascular ageing effectively.

The main reason for treating congestion with diuretics and vasodilators is to improve symptoms but such treatment almost certainly also improves prognosis. Rapid relief of breathlessness is associated with better short-term outcomes (16) while patients with more severe peripheral edema have longer hospitals stays and a higher in-patient mortality. Hyponatremia often co-exists with congestion, reflecting water in excess of sodium overload, and indicates a poor prognosis (19-21). More effective means of dealing with congestion and hyponatremia are required but remain elusive (22, 23).

Renal dysfunction is common in patients hospitalized with CHF and predicts a poor outcome (24-28). It usually reflects a combination of pre-existing renal damage, impaired perfusion and congestion the contribution of each varying greatly amongst patients (28). Conventionally, creatinine is used as the marker of renal function both to inform management and prognosis but may under-estimate the severity of renal dysfunction in cachexia (29). In this and other studies, serum urea is a better prognostic marker than creatinine in patients with heart
failure (30-32). Up to 50% of urea is passively re-absorbed in the renal tubules. Serum urea may be more sensitive than creatinine to changes in diuretic dose, venous congestion, hydration status and increases in vasopressin (33). Serum urea also rises during periods of increased protein catabolism due either to worsening heart failure or concomitant problems such as infection and reduced dietary protein intake (34). Transient changes in serum urea, but not serum creatinine, carry some long-term prognostic significance (7, 35). This may be because urea is a better overall measure of complex changes in renal function associated with AHF. Renal dysfunction will affect treatment, leading to reductions in dose or cessation of ACE inhibitors and aldosterone antagonists and impeding attempts to control congestion with diuretics (25), contributing to an adverse outcome. In patients with heart failure, ACE inhibitors, aldosterone antagonists and beta-blockers all cause an initial decline in renal function, but each improves prognosis. Clearly, severe renal dysfunction is lethal but whether subtle changes in renal function are a target for therapy is unclear.

Systolic blood pressure is easy to measure and strongly and consistently related to prognosis in acute and chronic heart failure (36). This is remarkable because measurement of blood pressure is subject to rounding errors and to great variability in the accuracy of clinical measurement and equipment calibration. Blood pressure might be a much better predictor of outcome if it was measured precisely and accurately. Low arterial pressure probably reflects, in part, low cardiac output and is an important mediator of renal dysfunction in heart failure, but all pharmacological agents that are known to reduce mortality in heart failure also lower blood pressure (36). A low arterial pressure indicates that a patient is running out of therapeutic options. This group of patients should be considered for device therapy, either cardiac
resynchronization therapy which increases systolic blood pressure (37) and improves outcome or a left ventricular assist device or heart transplantation if appropriate.

The causes of low serum albumin are likely to be multi-factorial. Urinary losses are probably not substantial for most patients with heart failure (38). Hepatic dysfunction due to congestion or ischemia could impair albumin synthesis. Curiously, both low and elevated transaminases indicate an adverse prognosis in patients with heart failure (39, 40). A low albumin could also reflect the catabolic stress associated with AHF or even the effects of prolonged bed-rest (41-43). Whether albumin or hepatic function should be a target for therapy in heart failure is uncertain. Although body mass was not a strong predictor of outcome in this study, it has been in longer term studies (44). A catabolic state leading to cachexia is not only likely to be a bad prognostic sign but also a plausible target for therapy.

Tachypnea, a measure both of the patient’s anxiety and cardiovascular and metabolic stress, had only a weak association with adverse outcome. However, a respiratory rate <20 breaths per minute was associated with an adverse outcome. This might reflect a sicker group of patients given opiates leading to respiratory depression which might have contributed to an adverse outcome (45).

There are many limitations to this analysis. The trial protocol excluded many patients, investigators will have chosen not to include some eligible patients and some patients who were eligible will have refused to take part. Measurements were made some hours after initial presentation and it is likely that symptoms and signs will have changed from initial presentation. Echocardiographic measurements of cardiac function were not available for more than half the patients and therefore we have no useful measure of cardiac function that can be applied to the model. Natriuretic peptides were not measured in a standard way, although samples have been
retained for later analysis. Many other factors that may affect re-admission and longevity were not measured including general frailty, assessment of mood and cognitive function, socioeconomic status, and social support.

In conclusion, eight readily available clinical variables measured on admission in patients with AHF predict adverse outcomes with similar accuracy to more complex models. There is little evidence that specific variables are related to specific adverse outcomes. However, predictive models were of only moderate accuracy, especially for composite outcomes. Other variables that were not included in this data-set may improve predictive accuracy. The eight chosen variables provide the basis for a prospective research program to determine the incremental prognostic value of novel biomarkers in AHF.

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References


### Table 1. Univariable c-index values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median (IQR) or n (%)</th>
<th>N Missing</th>
<th>30-Day Mortality</th>
<th>30-day death or AC Hosp</th>
<th>30-day death or CV/Renal Hosp</th>
<th>180-day Mortality</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>72 (62 - 79)</td>
<td>0</td>
<td>0.591</td>
<td>0.555</td>
<td>0.542</td>
<td>0.580</td>
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<tr>
<td>Male sex</td>
<td>1364 (67.1)</td>
<td>0</td>
<td>0.504</td>
<td>0.510</td>
<td>0.515</td>
<td>0.517</td>
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<tr>
<td>Ischemic Heart Disease</td>
<td>1417 (69.8)</td>
<td>3</td>
<td>0.562</td>
<td>0.532</td>
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<td>History of Angina</td>
<td>447 (22.0)</td>
<td>4</td>
<td>0.511</td>
<td>0.514</td>
<td>0.512</td>
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<tr>
<td>Prior stroke or PVD</td>
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<td>5</td>
<td>0.527</td>
<td>0.521</td>
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<tr>
<td>Diabetes Mellitus</td>
<td>922 (45.4)</td>
<td>1</td>
<td>0.511</td>
<td>0.528</td>
<td>0.534</td>
<td>0.501</td>
</tr>
<tr>
<td>Respiratory Disease</td>
<td>402 (19.8)</td>
<td>4</td>
<td>0.504</td>
<td>0.506</td>
<td>0.505</td>
<td>0.519</td>
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<tr>
<td>Mitral Regurgitation</td>
<td>687 (33.8)</td>
<td>3</td>
<td>0.519</td>
<td>0.503</td>
<td>0.506</td>
<td>0.533</td>
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<tr>
<td>HF Hosp. in prior year</td>
<td>1002 (49.3)</td>
<td>0</td>
<td>0.537</td>
<td>0.539</td>
<td>0.546</td>
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<tr>
<td>NYHA in prior month (v. Class IV)</td>
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<td></td>
<td></td>
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<tr>
<td>none/I/II</td>
<td>450 (22.2)</td>
<td></td>
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<tr>
<td>III</td>
<td>982 (48.4)</td>
<td>2</td>
<td>0.515</td>
<td>0.547</td>
<td>0.540</td>
<td>0.528</td>
</tr>
<tr>
<td>IV</td>
<td>599 (29.5)</td>
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<td></td>
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<tr>
<td>Physical Exam</td>
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<tr>
<td>BMI kg/m²</td>
<td>27.8 (24.4 - 31.9)</td>
<td>30</td>
<td>0.516</td>
<td>0.506</td>
<td>0.514</td>
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<td>Heart rate</td>
<td>78 (70 - 90)</td>
<td>2</td>
<td>0.537</td>
<td>0.528</td>
<td>0.521</td>
<td>0.508</td>
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<td>1103 (54.6)</td>
<td>14</td>
<td>0.522</td>
<td>0.504</td>
<td>0.515</td>
<td>0.517</td>
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<td>124 (110 - 140)</td>
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<td>0.605</td>
<td>0.555</td>
<td>0.558</td>
<td>0.616</td>
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<td>DBP mmHg</td>
<td>72 (65 - 80)</td>
<td>1</td>
<td>0.557</td>
<td>0.568</td>
<td>0.556</td>
<td>0.585</td>
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<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
<td>Median (IQR)</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>----------------</td>
<td>-----------</td>
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<td>-----------</td>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td><strong>MBP</strong></td>
<td>90 (82 - 99)</td>
<td>1</td>
<td>0.584</td>
<td>0.570</td>
<td>0.564</td>
<td>0.609</td>
</tr>
<tr>
<td><strong>Pulse pressure mmHg</strong></td>
<td>50 (40 - 60)</td>
<td>1</td>
<td>0.580</td>
<td>0.513</td>
<td>0.525</td>
<td>0.575</td>
</tr>
<tr>
<td><strong>Edema (ref. 0)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>284 (14.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+</td>
<td>366 (18.1)</td>
<td>8</td>
<td>0.579</td>
<td>0.539</td>
<td>0.526</td>
<td>0.537</td>
</tr>
<tr>
<td>2+</td>
<td>815 (40.3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>560 (27.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>JVP (ref &lt;6 cm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 cm</td>
<td>217 (11.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 – 10cm</td>
<td>868 (47.5)</td>
<td>206</td>
<td>0.507</td>
<td>0.505</td>
<td>0.510</td>
<td>0.521</td>
</tr>
<tr>
<td>&gt; 10cm</td>
<td>742 (40.6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory Rate</strong></td>
<td>20 (18 - 24)</td>
<td>95</td>
<td>0.572</td>
<td>0.523</td>
<td>0.529</td>
<td>0.529</td>
</tr>
<tr>
<td><strong>Orthopnea (ref. none)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>80 (4.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One Pillow</td>
<td>244 (12.2)</td>
<td>26</td>
<td>0.570</td>
<td>0.508</td>
<td>0.516</td>
<td>0.539</td>
</tr>
<tr>
<td>Two Pillows</td>
<td>803 (40.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 30 degrees</td>
<td>880 (43.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>RALES (ref. none)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>0</td>
<td>197 (9.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1/3</td>
<td>593 (29.3)</td>
<td>11</td>
<td>0.545</td>
<td>0.524</td>
<td>0.529</td>
<td>0.543</td>
</tr>
<tr>
<td>1/3 – 2/3</td>
<td>1033 (51.1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 2/3</td>
<td>199 (9.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory Variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>12.6 (11.3 – 14.0)</td>
<td>267</td>
<td>0.545</td>
<td>0.557</td>
<td>0.553</td>
<td>0.539</td>
</tr>
<tr>
<td>WBC Count (x10^9/L)</td>
<td>7.5 (6.0 - 9.2)</td>
<td>267</td>
<td>0.582</td>
<td>0.530</td>
<td>0.536</td>
<td>0.531</td>
</tr>
<tr>
<td>Sodium (mEq/L)</td>
<td>140 (137 - 142)</td>
<td>73</td>
<td>0.609</td>
<td>0.573</td>
<td>0.590</td>
<td>0.602</td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>4.2 (3.9 - 4.6)</td>
<td>166</td>
<td>0.554</td>
<td>0.517</td>
<td>0.519</td>
<td>0.531</td>
</tr>
<tr>
<td>Test</td>
<td>Lower Range</td>
<td>Upper Range</td>
<td>Mean</td>
<td>SD 1</td>
<td>SD 2</td>
<td>SD 3</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------</td>
<td>------</td>
<td>------</td>
<td>------</td>
</tr>
<tr>
<td>Bicarbonate (mEq/L)</td>
<td>24 (21 - 26)</td>
<td>152</td>
<td>0.548</td>
<td>0.507</td>
<td>0.525</td>
<td>0.571</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>1.4 (1.1 - 1.8)</td>
<td>81</td>
<td>0.568</td>
<td>0.562</td>
<td>0.569</td>
<td>0.598</td>
</tr>
<tr>
<td>eGFR mL/min/1.73 m²</td>
<td>45.7 (34.0 - 59.9)</td>
<td>81</td>
<td>0.620</td>
<td>0.575</td>
<td>0.579</td>
<td>0.630</td>
</tr>
<tr>
<td>BUN mg/dL</td>
<td>29 (22 – 41)</td>
<td>70</td>
<td>0.678</td>
<td>0.601</td>
<td>0.607</td>
<td>0.672</td>
</tr>
<tr>
<td>BUN / creatinine ratio</td>
<td>21.1 (17.5 - 26.2)</td>
<td>81</td>
<td>0.698</td>
<td>0.516</td>
<td>0.519</td>
<td>0.646</td>
</tr>
<tr>
<td>Uric acid mg/dL</td>
<td>8.8 (7.2 - 10.6)</td>
<td>150</td>
<td>0.545</td>
<td>0.532</td>
<td>0.543</td>
<td>0.568</td>
</tr>
<tr>
<td>Albumin g/dL</td>
<td>3.9 (3.6 - 4.1)</td>
<td>78</td>
<td>0.675</td>
<td>0.541</td>
<td>0.54</td>
<td>0.589</td>
</tr>
<tr>
<td>ALT capped at 220 U/L</td>
<td>21 (15 - 32)</td>
<td>203</td>
<td>0.540</td>
<td>0.540</td>
<td>0.539</td>
<td>0.494</td>
</tr>
<tr>
<td>Glucose mg/dL</td>
<td>126 (103 - 162)</td>
<td>131</td>
<td>0.503</td>
<td>0.526</td>
<td>0.531</td>
<td>0.499</td>
</tr>
<tr>
<td>Cholesterol (mg/dL)</td>
<td>141 (116 - 172)</td>
<td>76</td>
<td>0.608</td>
<td>0.556</td>
<td>0.562</td>
<td>0.598</td>
</tr>
<tr>
<td>Triglycerides capped at 99th percentile (300) mg/dL</td>
<td>89 (65 - 124)</td>
<td>91</td>
<td>0.586</td>
<td>0.540</td>
<td>0.537</td>
<td>0.567</td>
</tr>
</tbody>
</table>

PVD = peripheral vascular disease
HF hosp = heart failure hospitalization
BMI = body mass index
SBP = systolic blood pressure
DBP = diastolic blood pressure
MBP = mean blood pressure
JVP = jugular venous pressure
WBC = white blood cell
ALT = alanine transferase
Table 2. Numbers of events and their components contributing to the four outcomes analysed

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Events / Evaluable Patients</th>
<th>Events rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (1-30 days)</td>
<td>106#/2033</td>
<td>5.2%*</td>
</tr>
<tr>
<td>30 day death or all-cause re-hospitalization</td>
<td>382/2033</td>
<td>18.8%*</td>
</tr>
<tr>
<td>Death as first event</td>
<td>96</td>
<td>4.7%</td>
</tr>
<tr>
<td>All-cause hospitalisation (first-event)</td>
<td>286</td>
<td>14.1%</td>
</tr>
<tr>
<td>Cardiovascular/Renal hospitalization (first event)</td>
<td>226</td>
<td>11.1%</td>
</tr>
<tr>
<td>Re-hospitalization for Heart Failure (first-event)</td>
<td>130</td>
<td>6.4%</td>
</tr>
<tr>
<td>30 day death or CV/renal re-hospitalization</td>
<td>326/2033</td>
<td>16.0%*</td>
</tr>
<tr>
<td>Death as first event</td>
<td>96</td>
<td>4.7%</td>
</tr>
<tr>
<td>Cardiovascular/Renal hospitalization (first event)</td>
<td>230</td>
<td>11.3%</td>
</tr>
<tr>
<td>Re-hospitalization for Heart Failure (first-event)</td>
<td>132</td>
<td>6.5%</td>
</tr>
<tr>
<td>180 day mortality</td>
<td>358/2033</td>
<td>17.6%*</td>
</tr>
</tbody>
</table>

Note that each patient could have several different types of non-fatal events

# 93 deaths occurred during the index admission of which 84 were within 30 days.

CV = cardiovascular

* Kaplan-Meier event rate estimates for the outcomes in the shaded rows were 5.2%, 18.9%, 16.2%, and 17.7% respectively.
Table 3. Multi-variable Analysis Showing Baseline Predictors of All-Cause Mortality at 30 Days#

<table>
<thead>
<tr>
<th>Variable</th>
<th>8-item model</th>
<th>Unit* Increase for HR</th>
<th>HR</th>
<th>95% CI for HR</th>
<th>Chi-sq</th>
<th>p</th>
<th>Q1 (0.001-0.014)</th>
<th>Q2 (0.014-0.030)</th>
<th>Q3 (0.030-0.061)</th>
<th>Q4 (0.061-0.752)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin, g/dL</td>
<td>✔</td>
<td>0.5</td>
<td>0.551</td>
<td>(0.445, 0.683)</td>
<td>29.7</td>
<td>&lt;.0001</td>
<td>4.1 (3.9 - 4.4)</td>
<td>4 (3.7 - 4.2)</td>
<td>3.7 (3.5 - 4)</td>
<td>3.6 (3.3 - 3.8)</td>
</tr>
<tr>
<td>BUN*, mg/dL</td>
<td>✔</td>
<td>20% increase</td>
<td>1.38</td>
<td>(1.22, 1.56)</td>
<td>25.5</td>
<td>&lt;.0001</td>
<td>22 (18 - 27)</td>
<td>28 (21 - 36)</td>
<td>32 (25 - 43)</td>
<td>44 (33 - 58.5)</td>
</tr>
<tr>
<td>Creatinine*, mg/dL</td>
<td>✔</td>
<td>20% increase</td>
<td>0.776</td>
<td>(0.660, 0.912)</td>
<td>9.5</td>
<td>0.0021</td>
<td>1.3 (1.1 - 1.6)</td>
<td>1.4 (1.1 - 1.7)</td>
<td>1.4 (1.1 - 1.8)</td>
<td>1.5 (1.2 - 2)</td>
</tr>
<tr>
<td>Age, years</td>
<td>✔</td>
<td>5</td>
<td>1.14</td>
<td>(1.04, 1.26)</td>
<td>7.21</td>
<td>0.0073</td>
<td>65 (55 - 73)</td>
<td>72 (62 - 79)</td>
<td>73.5 (66 - 79.5)</td>
<td>76 (69 - 81)</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>✔</td>
<td>3</td>
<td>0.843</td>
<td>(0.737, 0.965)</td>
<td>6.10</td>
<td>0.0135</td>
<td>141 (139 - 143)</td>
<td>140 (138 - 143)</td>
<td>139 (136 - 142)</td>
<td>137 (134 - 140)</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>✔</td>
<td>5</td>
<td>1.08</td>
<td>(1.02, 1.14)</td>
<td>6.05</td>
<td>0.0139</td>
<td>77 (69 - 88)</td>
<td>78 (69 - 90)</td>
<td>80 (70 - 90)</td>
<td>80 (70 - 92)</td>
</tr>
<tr>
<td>Respiration*, bpm</td>
<td>✔</td>
<td>Below 20</td>
<td>5</td>
<td>0.524</td>
<td>(0.334, 0.823)</td>
<td>7.96</td>
<td>0.0187</td>
<td>21 (19 - 24)</td>
<td>21 (18 - 24)</td>
<td>21 (18 - 24)</td>
</tr>
<tr>
<td>IHD</td>
<td></td>
<td>Above 20</td>
<td>5</td>
<td>1.14</td>
<td>(0.914, 1.43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC, x10^9/L</td>
<td>y/n</td>
<td>5</td>
<td>1.23</td>
<td>(1.02, 1.47)</td>
<td>4.83</td>
<td>0.0280</td>
<td>7.38 (6.08 - 8.84)</td>
<td>7.48 (6.15 - 9.11)</td>
<td>7.28 (5.9 - 9.26)</td>
<td>7.75 (6.16 - 9.89)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>✔</td>
<td>10</td>
<td>0.882</td>
<td>(0.781, 0.995)</td>
<td>4.14</td>
<td>0.0418</td>
<td>130 (120 - 143)</td>
<td>129 (112 - 140)</td>
<td>120 (110 - 134)</td>
<td>115 (105 - 130)</td>
</tr>
</tbody>
</table>

# Variables are ranked according to their strength of association (p-value) with 30-day mortality. The overall model C-index was 0.79, 0.78 when corrected for optimism and 0.77 using the simplified 8-item model (items checked ✔). Two items from the 8-item model (hospitalization for heart failure in the past year and severity of oedema) did not contribute to the multivariable model for this endpoint. The last four columns summarize the univariable distribution of the selected baseline predictors for patients grouped by quartiles of predicted risk.

* Units are absolute unless specified as % increase. y/n = yes versus no. HR = hazard ratio, CI = confidence interval KM% = Kaplan-Meier estimator of the event rate. BUN = blood urea nitrogen, bpm = beats per minute, IHD = ischaemic heart disease, WBC = white blood cell count, BP = blood pressure, HF = heart failure, hosp = hospitalization. 1. The relationships with BUN and creatinine were non-linear and modelled on the log scale. The HR quantifies the increased risk for a 20% higher lab value. 2. The relationship with respiration rate was non-linear and modelled using a two-piece linear spline with a knot at 20 breathes/min. The association was summarized with two HR components: the first quantifying the effect of higher respiration rate when respiration is below 20 breathes/min; and the second when respiration is above 20 breathes/min.
<table>
<thead>
<tr>
<th>Variable</th>
<th>8-item model</th>
<th>Unit* Increase in HR</th>
<th>HR</th>
<th>95% CI for HR</th>
<th>Chi-sq</th>
<th>p</th>
<th>Q1 (0.018 – 0.113)</th>
<th>Q2 (0.113 – 0.165)</th>
<th>Q3 (0.165 – 0.242)</th>
<th>Q4 (0.242 – 0.886)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN, mg/dL</td>
<td>✓</td>
<td>20% increase</td>
<td>1.10</td>
<td>(1.06 – 1.15)</td>
<td>20.5</td>
<td>&lt; 0.0001</td>
<td>22 (18 – 27)</td>
<td>27 (21 – 34)</td>
<td>33 (24 – 43)</td>
<td>45 (32 – 61)</td>
</tr>
<tr>
<td>Age, years</td>
<td>✓</td>
<td>5</td>
<td>1.15</td>
<td>(1.08 – 1.23)</td>
<td>18.8</td>
<td>&lt; 0.0001</td>
<td>66 (57 – 73)</td>
<td>71 (62 – 78)</td>
<td>74 (65 – 80)</td>
<td>76 (70 – 82)</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>✓</td>
<td>3</td>
<td>0.869</td>
<td>(0.807 – 0.936)</td>
<td>13.7</td>
<td>0.0002</td>
<td>142 (139 – 143)</td>
<td>141 (138 – 143)</td>
<td>139 (137 – 141)</td>
<td>137 (134 – 140)</td>
</tr>
<tr>
<td>Oedema</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td>18.0</td>
<td>0.0004</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>33 (6.5)</td>
<td>63 (12.4)</td>
<td>72 (14.2)</td>
<td>116 (23.0)</td>
</tr>
<tr>
<td>1+</td>
<td>1+/none</td>
<td>0.689</td>
<td>(0.488 – 0.973)</td>
<td>6.93</td>
<td>0.0085</td>
<td>110 (21.7)</td>
<td>94 (18.6)</td>
<td>93 (18.4)</td>
<td>69 (13.6)</td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>2+/none</td>
<td>0.833</td>
<td>(0.621 – 1.12)</td>
<td>7.74</td>
<td>0.0061</td>
<td>154 (30.3)</td>
<td>216 (42.7)</td>
<td>221 (43.7)</td>
<td>224 (44.4)</td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>3+/none</td>
<td>0.517</td>
<td>(0.368 – 0.725)</td>
<td>7.94</td>
<td>0.0049</td>
<td>211 (41.5)</td>
<td>133 (26.3)</td>
<td>120 (23.7)</td>
<td>96 (19.0)</td>
<td></td>
</tr>
<tr>
<td>NYHA class 1 month prior to admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.34</td>
<td>0.0094</td>
<td>101 (19.9)</td>
<td>129 (25.4)</td>
<td>113 (22.3)</td>
<td>107 (21.1)</td>
</tr>
<tr>
<td>&lt; III</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>147 (28.9)</td>
<td>233 (45.9)</td>
<td>283 (55.8)</td>
<td>219 (62.8)</td>
</tr>
<tr>
<td>III</td>
<td>III / none-I-II</td>
<td>1.13</td>
<td>(0.873 – 1.46)</td>
<td>8.02</td>
<td>0.0048</td>
<td>260 (51.2)</td>
<td>146 (28.7)</td>
<td>111 (21.9)</td>
<td>82 (16.1)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>IV / none-I-II</td>
<td>0.760</td>
<td>(0.558 – 1.03)</td>
<td>7.62</td>
<td>0.0055</td>
<td>145 (28.5)</td>
<td>238 (46.9)</td>
<td>289 (56.9)</td>
<td>330 (64.8)</td>
<td></td>
</tr>
<tr>
<td>HF Hosp in past year</td>
<td>✓</td>
<td>y/n</td>
<td>1.32</td>
<td>(1.07 – 1.63)</td>
<td>6.54</td>
<td>0.0104</td>
<td>135 (20 – 140)</td>
<td>130 (112 – 140)</td>
<td>120 (110 – 139)</td>
<td>114 (104 – 130)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>✓</td>
<td>10</td>
<td>0.921</td>
<td>(0.865 – 0.981)</td>
<td>6.54</td>
<td>0.0104</td>
<td>135 (20 – 140)</td>
<td>130 (112 – 140)</td>
<td>120 (110 – 139)</td>
<td>114 (104 – 130)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>✓</td>
<td>5</td>
<td>1.12</td>
<td>(1.03 – 1.23)</td>
<td>6.46</td>
<td>0.0110</td>
<td>27.7 (24.1 – 32.7)</td>
<td>27.8 (24.7 – 31.6)</td>
<td>27.6 (24.4 – 31.6)</td>
<td>28.0 (24.7 – 31.8)</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>✓</td>
<td>0.5</td>
<td>0.854</td>
<td>(0.755 – 0.965)</td>
<td>6.40</td>
<td>0.0114</td>
<td>3.9 (3.7 – 4.2)</td>
<td>4.0 (3.7 – 4.2)</td>
<td>3.8 (3.5 – 4.1)</td>
<td>3.7 (3.5 – 4.0)</td>
</tr>
<tr>
<td>iHDL</td>
<td>y/n</td>
<td>1.29</td>
<td>(1.02 – 1.64)</td>
<td>4.43</td>
<td>0.0353</td>
<td>281 (55.3)</td>
<td>342 (67.6)</td>
<td>366 (72.2)</td>
<td>428 (84.1)</td>
<td></td>
</tr>
<tr>
<td>ALT, U/L</td>
<td>✓</td>
<td>5.38</td>
<td>0.0678</td>
<td>(24 – 36)</td>
<td>22 (15 – 31)</td>
<td>20 (14 – 29)</td>
<td>18 (14 – 28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 35, U/L</td>
<td>20</td>
<td>0.749</td>
<td>(0.569 – 0.986)</td>
<td></td>
<td></td>
<td>53 (10.5)</td>
<td>42 (8.3)</td>
<td>41 (8.1)</td>
<td>61 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Above 35, U/L</td>
<td>20</td>
<td>1.07</td>
<td>(0.993 – 1.16)</td>
<td></td>
<td></td>
<td>142 (28.0)</td>
<td>155 (30.6)</td>
<td>157 (31.1)</td>
<td>139 (27.6)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
<td>6.64</td>
<td>0.0845</td>
<td>53 (10.5)</td>
<td>42 (8.3)</td>
<td>41 (8.1)</td>
<td>61 (12.1)</td>
</tr>
<tr>
<td>&lt; 1/3</td>
<td>&lt;1/3 / none</td>
<td>1.00</td>
<td>(0.692 – 1.45)</td>
<td></td>
<td></td>
<td>142 (28.0)</td>
<td>155 (30.6)</td>
<td>157 (31.1)</td>
<td>139 (27.6)</td>
<td></td>
</tr>
<tr>
<td>1/3 – 2/3</td>
<td>1/3-2/3 / none</td>
<td>0.989</td>
<td>(0.693 – 1.41)</td>
<td></td>
<td></td>
<td>288 (56.8)</td>
<td>277 (54.7)</td>
<td>247 (48.9)</td>
<td>221 (43.8)</td>
<td></td>
</tr>
<tr>
<td>&gt; 2/3</td>
<td>&gt;2/3 / none</td>
<td>1.49</td>
<td>(0.966 – 2.29)</td>
<td></td>
<td></td>
<td>24 (4.7)</td>
<td>32 (6.3)</td>
<td>60 (11.9)</td>
<td>83 (16.5)</td>
<td></td>
</tr>
</tbody>
</table>

# Ranked according to strength of association (p-value) with for death or hospitalisation for any Reason by 30 days. The overall model C-index was 0.660, 0.644 when corrected for optimism and 0.644 using the simplified 8-item model (items checked ✓). One item from the 8-item model (serum creatinine) did not contribute to the model for this endpoint. The last four columns summarize the univariable distribution of the selected baseline predictors for patients grouped by quartiles of predicted risk.
ALT = alanine transferase. NYHA = New York Heart Association functional class. 1/3 – means rales heard over less than one third of chest height 1+ means score for oedema. See table 2 for other abbreviations.

1. The relationship with BUN was nonlinear and modelled on the log scale. The HR quantifies the increased risk for a 20% higher higher lab value.

2. The relationship with age was nonlinear. Below 62 years, differences in age had little effect on outcome; above 62 years the tabulated HR quantifies the effect of a 5 year increase in age.

3. The relationship with ALT was non-linear and modelled using a two-piece linear spline with a knot at 35 U/L. The association was summarized with two HR components: the first quantifying the effect of higher ALT when ALT is below 35 U/L; and the second when ALT is above 35 U/L.
Table 5. Multi-variable Analysis Showing Baseline Predictors for Death or Re-hospitalisation for Cardiovascular or Renal Reasons at 30 Days #

<table>
<thead>
<tr>
<th>Variable</th>
<th>8-item model</th>
<th>Unit* Increase in HR</th>
<th>HR</th>
<th>95% CI for HR</th>
<th>Chi-sq</th>
<th>p</th>
<th>Quartile of Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Q1 (0.021 – 0.098)</td>
</tr>
<tr>
<td>BUN¹, mg/dL</td>
<td>✓</td>
<td>20% increase</td>
<td>1.11</td>
<td>(1.06 – 1.16)</td>
<td>20.8</td>
<td>&lt;0.0001</td>
<td>22 (18 – 26)</td>
</tr>
<tr>
<td>Sodium, mEq/L</td>
<td>✓</td>
<td>3</td>
<td>0.833</td>
<td>(0.769 – 0.902)</td>
<td>20.5</td>
<td>&lt;0.0001</td>
<td>142 (140 – 144)</td>
</tr>
<tr>
<td>Age², years</td>
<td>✓</td>
<td>5</td>
<td>1.12</td>
<td>(1.05 – 1.20)</td>
<td>10.5</td>
<td>0.0011</td>
<td>67 (58 – 74)</td>
</tr>
<tr>
<td>HF Hosp in past year</td>
<td>✓</td>
<td>y/n</td>
<td>1.35</td>
<td>(1.08 – 1.70)</td>
<td>6.85</td>
<td>0.0089</td>
<td>126 (24.8)</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>✓</td>
<td>0.5</td>
<td>0.857</td>
<td>(0.751 – 0.977)</td>
<td>5.32</td>
<td>0.0211</td>
<td>4.0 (3.7 – 4.2)</td>
</tr>
<tr>
<td>Oedema</td>
<td>✓</td>
<td></td>
<td>9.18</td>
<td></td>
<td></td>
<td>0.0269</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td>5</td>
<td>1.11</td>
<td>(1.01 – 1.23)</td>
<td>4.71</td>
<td>0.0300</td>
<td>27.1 (24.0 – 31.6)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>✓</td>
<td>10</td>
<td>0.934</td>
<td>(0.872 – 0.999)</td>
<td>3.92</td>
<td>0.0476</td>
<td>130 (120 – 140)</td>
</tr>
<tr>
<td>NYHA class 1 month prior to admission</td>
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<tr>
<td>&lt; III</td>
<td></td>
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</tr>
<tr>
<td>III / none-I-II</td>
<td></td>
<td>1.10</td>
<td>0.834</td>
<td>(0.834 – 1.46)</td>
<td>1.10</td>
<td>0.2737</td>
<td>161 (31.7)</td>
</tr>
<tr>
<td>IV / none-I-II</td>
<td></td>
<td>0.791</td>
<td>0.568</td>
<td>(0.568 – 1.10)</td>
<td>1.27</td>
<td>0.2646</td>
<td>243 (47.8)</td>
</tr>
<tr>
<td>IHD y/n</td>
<td></td>
<td>1.27</td>
<td>0.985</td>
<td>(0.985 – 1.64)</td>
<td>3.39</td>
<td>0.0657</td>
<td>283 (55.7)</td>
</tr>
<tr>
<td>Pulmonary rales</td>
<td></td>
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<tr>
<td>Actual Events (KM%)</td>
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<td></td>
</tr>
</tbody>
</table>

See table 3 for abbreviations.
Ranked according to strength of association (p-value) with death or re-hospitalisation for cardiovascular or renal reasons at 30 Days. The overall model C-index was 0.66, 0.64 when corrected for optimism and 0.65 using the simplified 8-item model (items checked ✔). One item from the 8-item model (serum creatinine) did not contribute to the multivariable model for this endpoint. The last four columns summarize the univariable distribution of the selected baseline predictors for patients grouped by quartiles of predicted risk.

The relationship with BUN was nonlinear and modelled on the log scale. The HR quantifies the increased risk for a 20% higher lab value.

The relationship with age was nonlinear. Below 62 years, differences in age had little effect on outcome; above 62 years the tabulated HR quantifies the effect of a 5 year increase in age.
Variable  | 8-item model | Unit* Increase | Risk Estimate | 95% CI for HR | Chi-sq | p        | Quartile of Risk |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN¹ mg/dL</td>
<td>✓</td>
<td>20% increase</td>
<td>1.24</td>
<td>(1.16, 1.32)</td>
<td>41.6798</td>
<td>&lt;.0001</td>
<td>Q1 (0.008-0.080)</td>
</tr>
<tr>
<td>Age, years</td>
<td>✓</td>
<td>5</td>
<td>1.17</td>
<td>(1.11, 1.24)</td>
<td>35.3270</td>
<td>&lt;.0001</td>
<td>Q2 (0.080-0.135)</td>
</tr>
<tr>
<td>Systolic BP, mmHg</td>
<td>✓</td>
<td>10</td>
<td>0.836</td>
<td>(0.871, 0.949)</td>
<td>27.0781</td>
<td>&lt;.0001</td>
<td>Q3 (0.135-0.232)</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>✓</td>
<td>0.5</td>
<td>0.778</td>
<td>(0.690, 0.877)</td>
<td>16.7578</td>
<td>&lt;.0001</td>
<td>Q4 (0.232-0.932)</td>
</tr>
<tr>
<td>Creatinine² mg/dL</td>
<td>✓</td>
<td>3</td>
<td>0.867</td>
<td>(0.802, 0.936)</td>
<td>13.2941</td>
<td>0.003</td>
<td>None</td>
</tr>
</tbody>
</table>

The relationships with BUN and creatinine were nonlinear and modelled on the log scale. The HR quantifies the increased risk for a 20% higher lab value.

1. The relationship with bicarbonate was non-linear and modelled using a two-piece linear spline with a knot at 27 mEq/L. The association was summarized with two HR components: the first quantifying the effect of higher bicarbonate when bicarbonate is below 27 mEq/L; and the second when bicarbonate is above 27 mEq/L.
Figure Legends

Figure 1. Plots showing strengths of relationship, as expressed by the univariable c-index, between all 37 variables included in the model and the four outcomes of interest. Variables have been ranked by the univariable c-index for all-cause mortality at 180 days.

Figure 2. Hazard ratios and 95% CI for variables selected for the multivariable models for each of the four outcomes of interest. Only variables that contributed independent predictive information are shown. For instance, age contributed information to all four outcomes but white blood cell count predicted only 30-day mortality.
30-Day Mortality

- BUN
- BUN/creatinine
- eGFR
- SBP
- MDR
- Sodium
- Cholesterol
- Creatinine
- Albumin
- DBP
- Age
- Pulse pressure
- Bicarbonate
- Uric acid
- Triglycerides
- HF Hosp. in prior year
- eGFR
- BMI
- Orthopnoea
- Anemia
- Oedema
- Ischemic Heart Disease
- Mitral regurgitation
- WBC Count
- Potassium
- Respiratory Rate
- NYHA in prior month
- Prior stroke or PVD
- JVP
- Respiratory Disease
- History of Atrial fibrillation/Flutter
- Male sex
- History of Angina
- Heart rate
- Diabetes Mellitus
- Glucose
- ALT

Univariable c-index

30-day death or AC Hosp

- eGFR
- SBP
- MDR
- Creatinine
- Albumin
- DBP
- Age
- Pulse pressure
- Bicarbonate
- Uric acid
- Triglycerides
- HF Hosp. in prior year
- eGFR
- BMI
- Orthopnoea
- Anemia
- Oedema
- Ischemic Heart Disease
- Mitral regurgitation
- WBC Count
- Potassium
- Respiratory Rate
- NYHA in prior month
- Prior stroke or PVD
- JVP
- Respiratory Disease
- History of Atrial fibrillation/Flutter
- Male sex
- History of Angina
- Heart rate
- Diabetes Mellitus
- Glucose
- ALT

Univariable c-index

30-day death or CV/Renal Hosp

- eGFR
- SBP
- MDR
- Creatinine
- Albumin
- DBP
- Age
- Pulse pressure
- Bicarbonate
- Uric acid
- Triglycerides
- HF Hosp. in prior year
- eGFR
- BMI
- Orthopnoea
- Anemia
- Oedema
- Ischemic Heart Disease
- Mitral regurgitation
- WBC Count
- Potassium
- Respiratory Rate
- NYHA in prior month
- Prior stroke or PVD
- JVP
- Respiratory Disease
- History of Atrial fibrillation/Flutter
- Male sex
- History of Angina
- Heart rate
- Diabetes Mellitus
- Glucose
- ALT

Univariable c-index

180-day Mortality

- eGFR
- SBP
- MDR
- Creatinine
- Albumin
- DBP
- Age
- Pulse pressure
- Bicarbonate
- Uric acid
- Triglycerides
- HF Hosp. in prior year
- eGFR
- BMI
- Orthopnoea
- Anemia
- Oedema
- Ischemic Heart Disease
- Mitral regurgitation
- WBC Count
- Potassium
- Respiratory Rate
- NYHA in prior month
- Prior stroke or PVD
- JVP
- Respiratory Disease
- History of Atrial fibrillation/Flutter
- Male sex
- History of Angina
- Heart rate
- Diabetes Mellitus
- Glucose
- ALT

Univariable c-index
Predictors of Post-Discharge Outcomes from Information Acquired Shortly After Admission for Acute Heart Failure: A Report from the PROTECT Study

John G. Cleland, Karen Chiswell, John R. Teerlink, Susanna Stevens, Mona Fiuzat, Michael M. Givertz, Beth A. Davison, George A. Mansoor, Piotr Ponikowski, Adriaan A. Voors, Gad Cotter, Marco Metra, Barry M. Massie and Christopher M. O'Connor

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Data Supplement (unedited) at:
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Supplemental Material
Supplemental Figure

a) Calibration plot for models of 30-day mortality

b) Calibration plot for models of 30-day death or all-cause re-hospitalization

c) Calibration plot for models of 30-day death or CV/renal re-hospitalization

d) Calibration plot for models of 180-day mortality

Calibration plots for the four outcomes of interest. Using each model, predicted risk is calculated for each subject and plotted against the risk percentile in the population (X-axis). Subjects are divided into ten groups according to the percentiles of predicted risk, and actual Kaplan-Meier event rates are calculated for each group and plotted for each decile. The horizontal straight line and percentage is the rate for that event in the overall population. Open circles and dotted line indicate calibration using the full multi-variable model constructed for each individual outcome with the line representing predicted risk and the open circles actual risk. Black dots with solid line indicate calibration using only eight selected variables to produce the model with the line representing predicted risk and the open circles actual risk.
Black dot/solid line = smaller model, Open circle/dashed line = best model
Black dot/solid line = smaller model, Open circle/dashed line = best model

Supplemental figure b)
Black dot/solid line= smaller model, Open circle/dashed line= best model
Black dot/solid line = smaller model, Open circle/dashed line = best model

Supplemental figure d)