Improving risk prediction in heart failure using multivariate analysis techniques from high energy physics

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How did this start

Conversations between exp high energy physicists and clinical cardiologists:

- Attempts to predict heart failure (HF) mortality using clinical variables or risk scores have not been very successful
- Fails in one or more of the following ways:
  - limited predictive power (poor AUC, typically < 0.7)
  - loss of accuracy when applied to other cohorts or populations
  - dependence on variables that are subjective or not readily available

There are many many risk-scores on the market

to the point that "risk-score fatigue" is prevalent

Today's buzzword…Machine Learning (ML)

- In HEP have been using (simple) ML for > 20 years to categorize "events" or "objects" as "signal" vs. "background"
  - Event = final state of decay or of interaction
  - Object = electrons, photons, bottom quarks, etc

- Can our experience be brought to bear?
  - Signal/Background → Early death/Long term Survival

Primary Objective

Define a risk score aiming to avoid common pitfalls by:

- Using strict data collection and cleanup methodology that ensures maintaining the correlations that define the physical state of the system (patient) within a relatively limited period of time
- Having precise definitions of outcomes.
- Avoiding imputation by requiring all covariates used in the creation of the model to be present.
- Limiting the number of inputs to a small number of widely available covariates that are checked routinely in HF patients.
- Capturing the multi-dimensional correlations between the covariates and the outcomes.

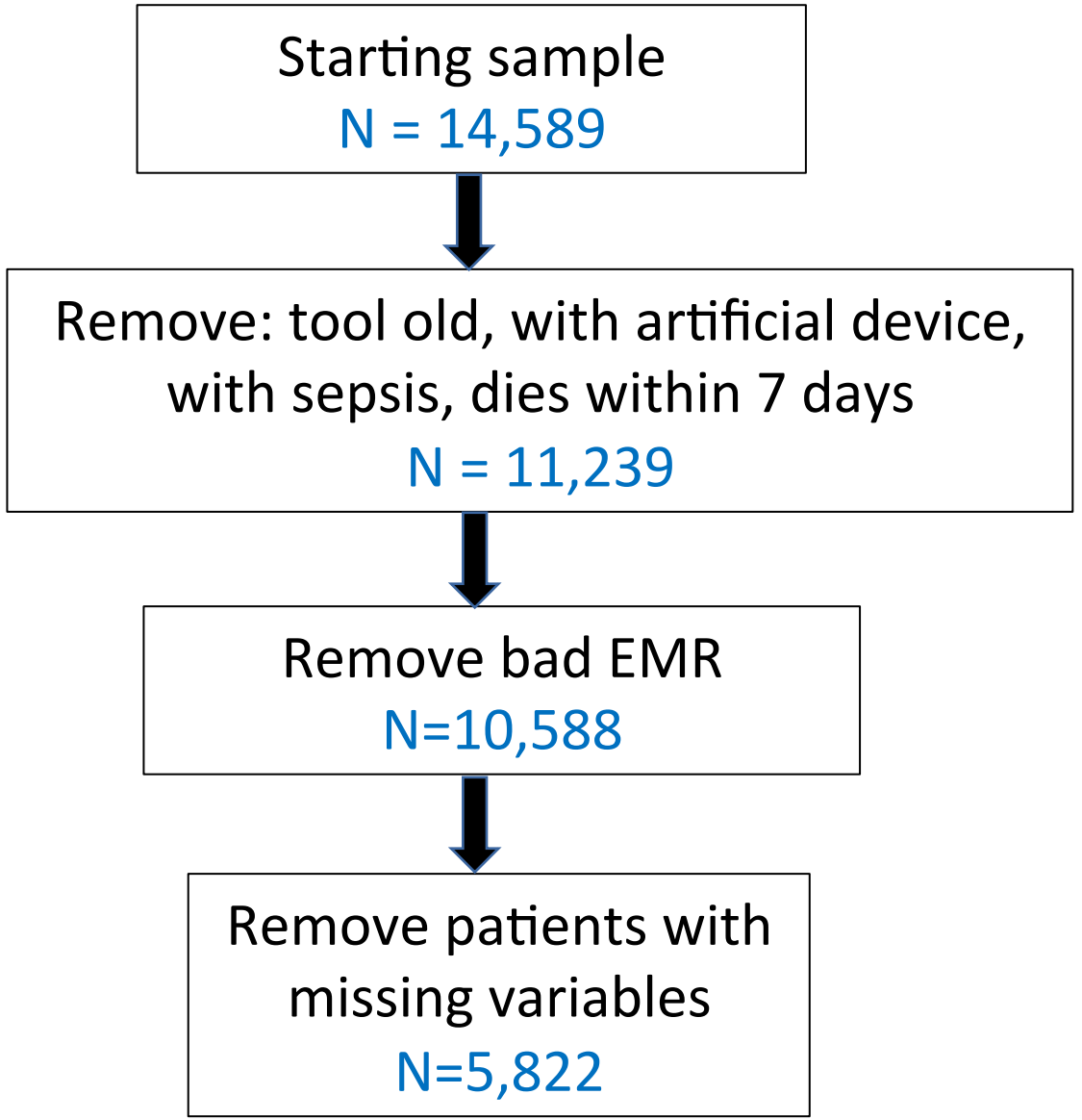
Methods and Study definition

- Retrospectively extracted de-identified EMR of patients in the UCSD health system with 1st recorded diagnosis of Heart Failure.
- Used an iterative process to select a minimal, most common, and discriminating set of variables (only 8)
  - HEP software, TMVA in CERN Root package
- For patient to be included in the analysis ***all*** variables needed to be present using data collected over a narrow time window (<7 days)
- Excluded patients: over 80, with an ICD, with indication of Sepsis
  - Minimize dilution of outcomes

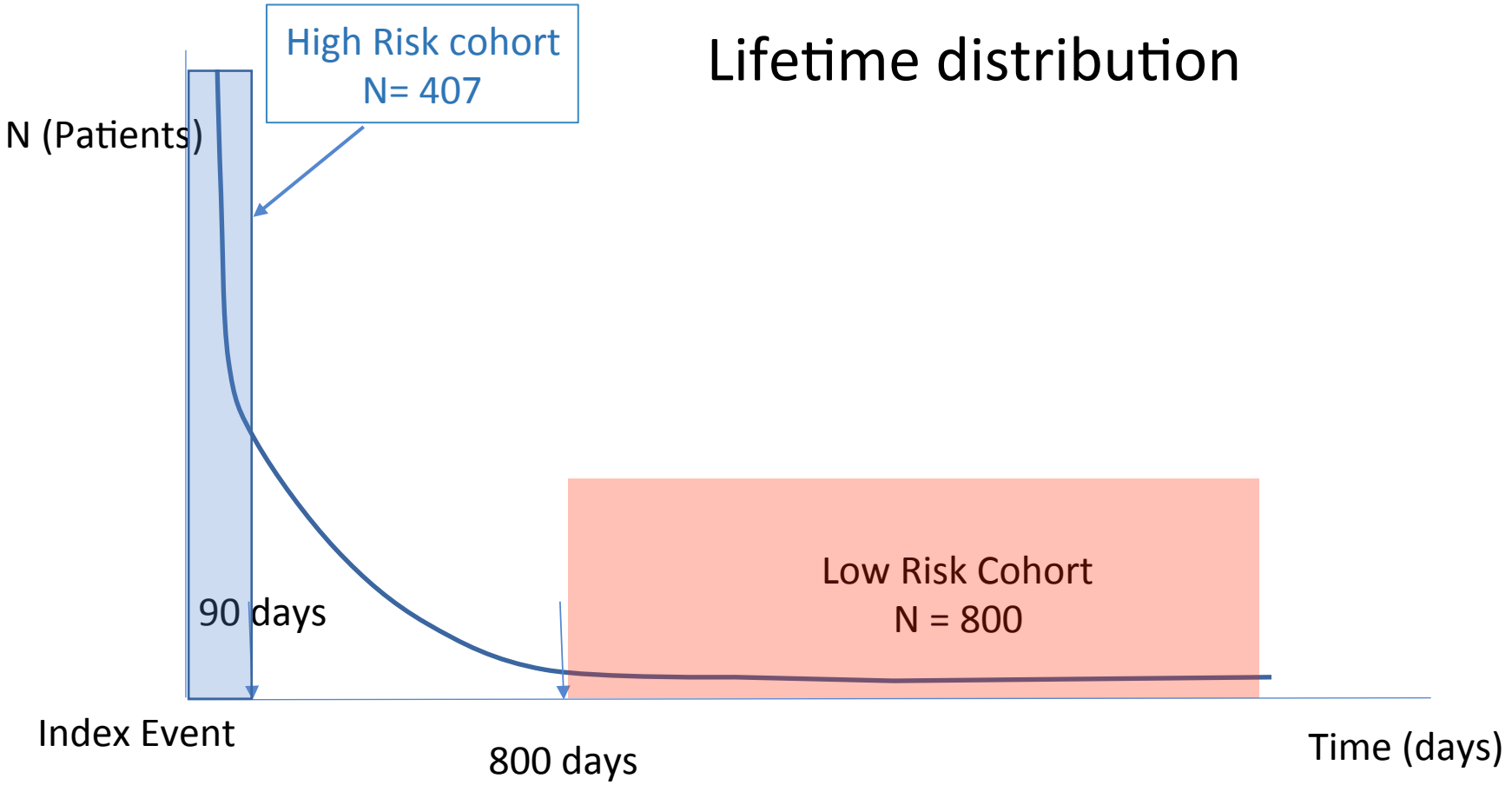
Statistics

Comments:

- Low statistics compared to typical HEP problem
- Dirty data, big loss from missing variables
  - Systematics?
- Extracting data from the EMR was a bit of an “adventure”



Cartoon of samples definition



Variables Used:

Diastolic blood pressure
Creatinine
Blood Urea Nitrogen
Hemoglobin
White blood cell count
Platelets
Albumin
Red Blood Cell Distribution Width

Input Variables

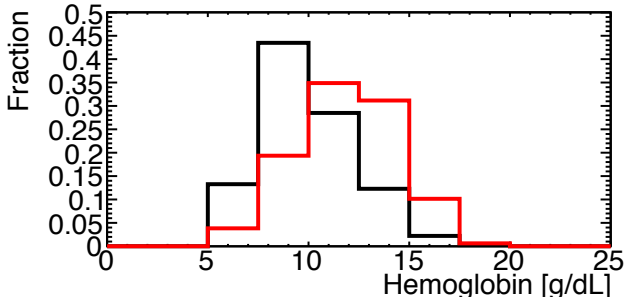
Red - Low risk cohort

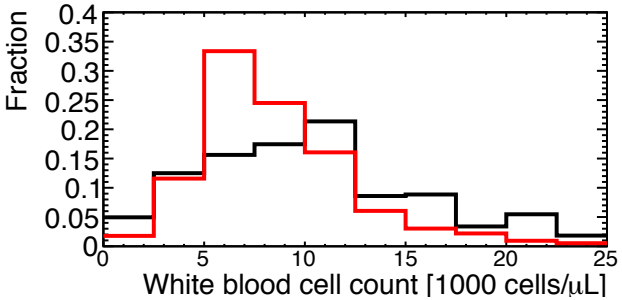
Black - High risk cohort

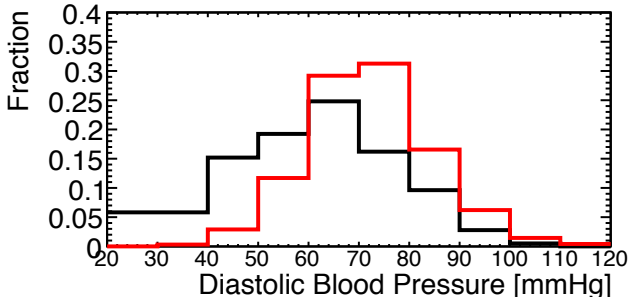
Important: No ”silver bullet”:

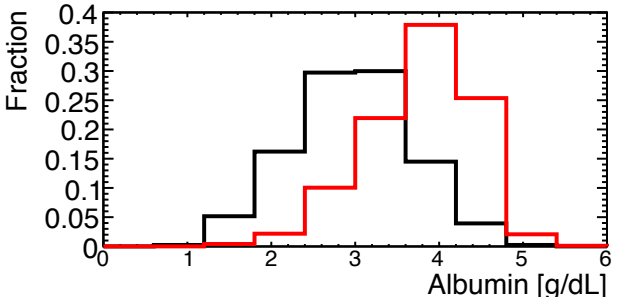
- No single discriminating variable.
- Each shows some separation.
- But poor AUC, individually.

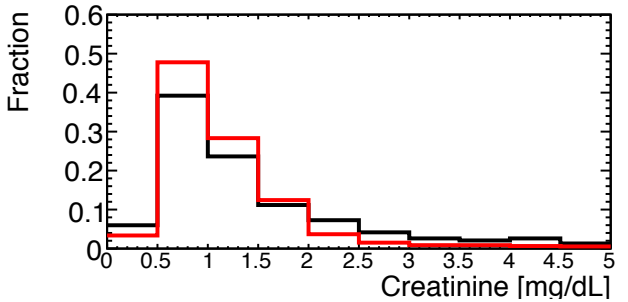
Key is the combination and correlations between the whole set

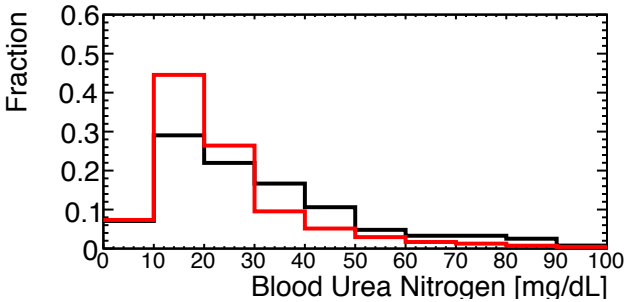


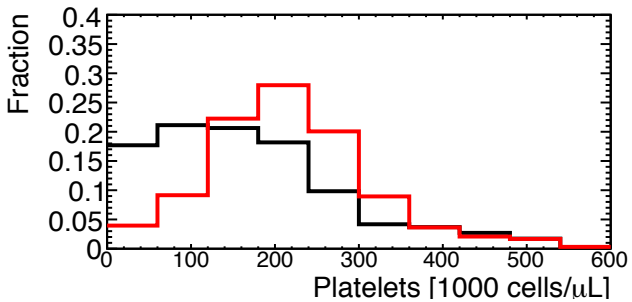


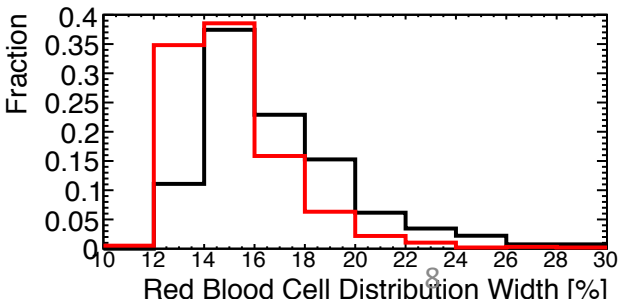






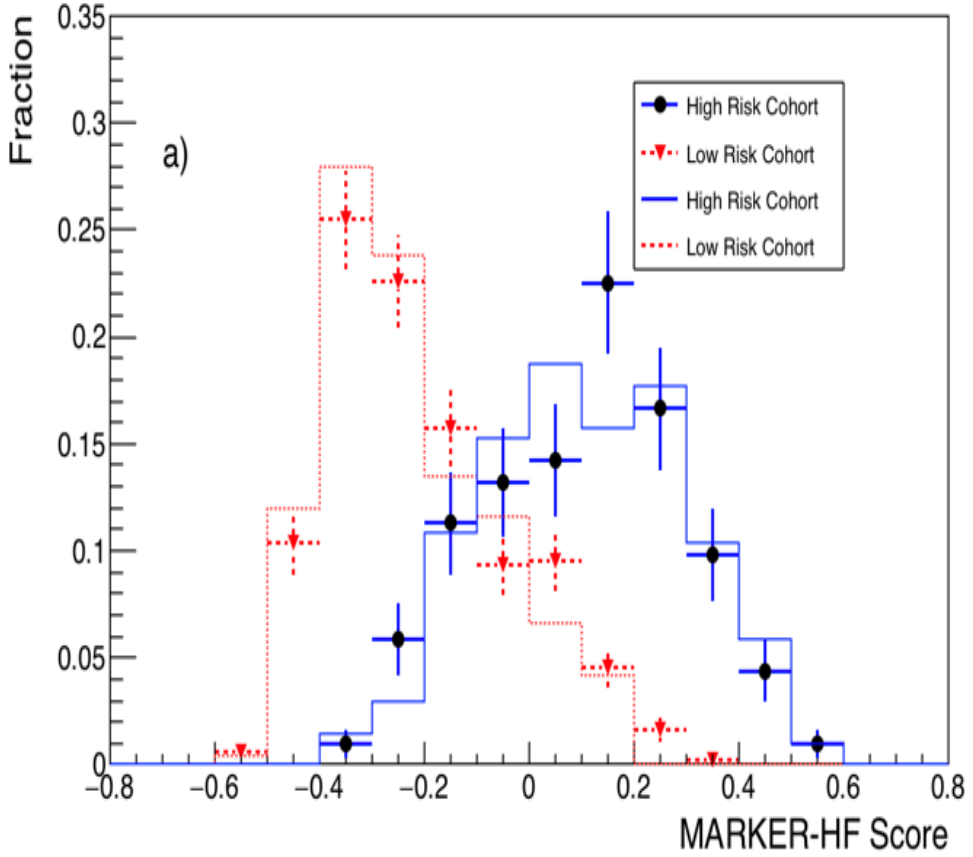


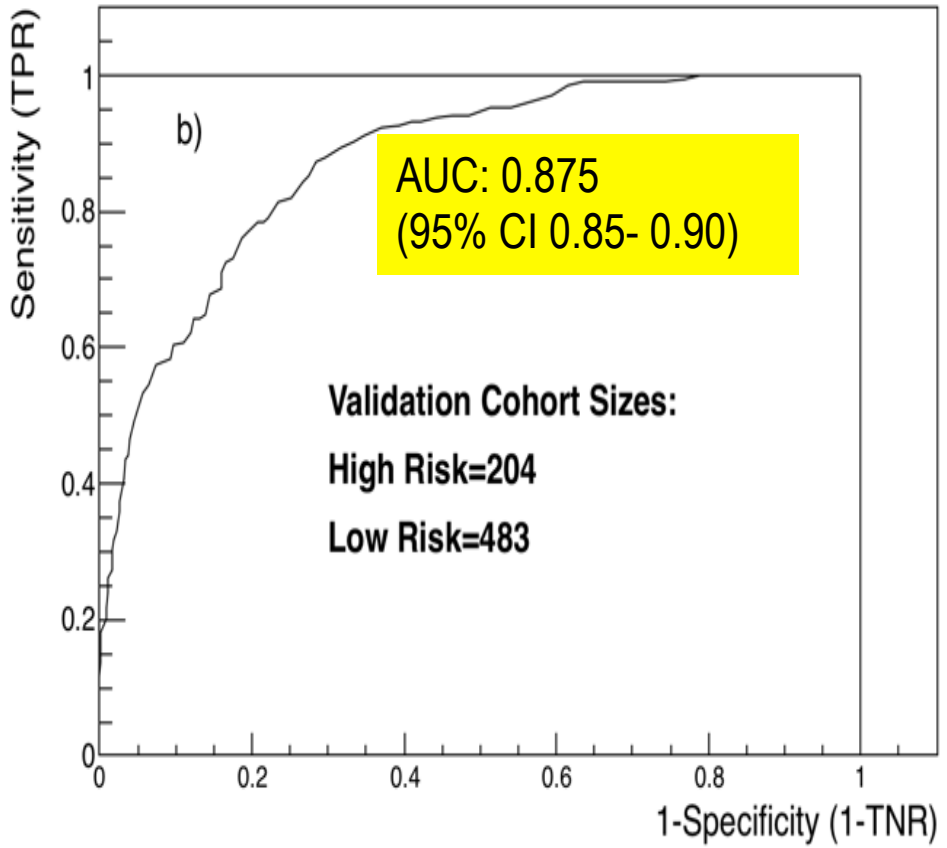




MARKER-HF Training and Performance

A Boosted Decision Tree algorithm was used (200 trees, maximum depth of 2) to derive a model and relate variables to the known outcome using the training subset of the sample only. *Similar results obtained with ANN)





TPR = True Positive Rate
TNR = True Negative Rate

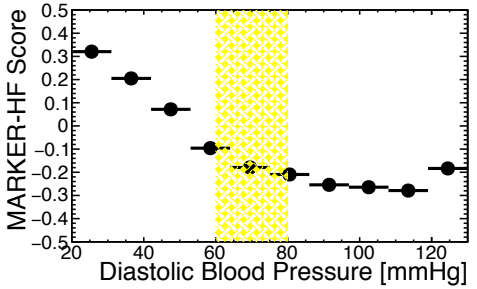
Does it make sense clinically?

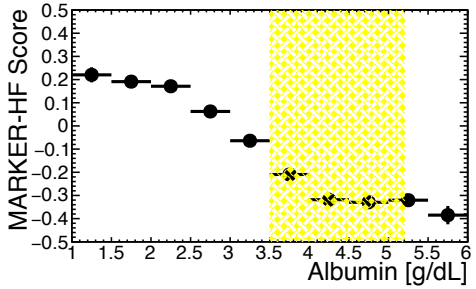
Does a high score corresponds to abnormal values of the measured inputs??

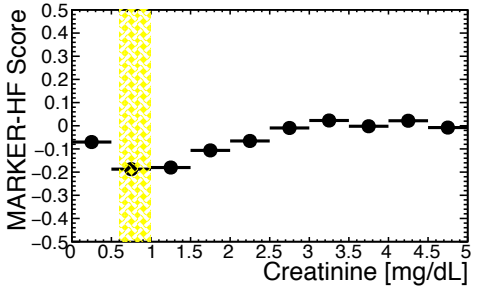
- Input variables plotted against the mean score

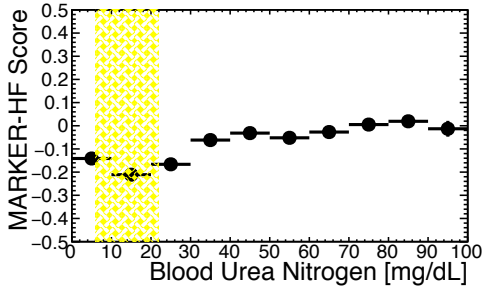
- The yellow bands represent the normal ranges.

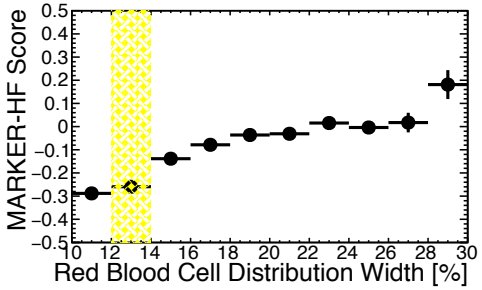
➔ **NOT an explicit input to the model. "Learned" by the training**

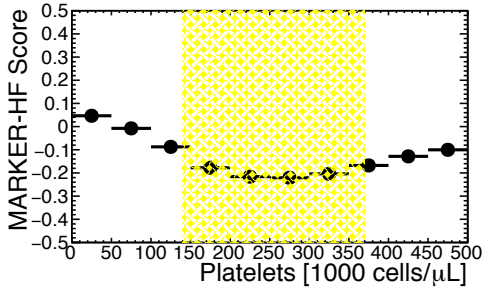


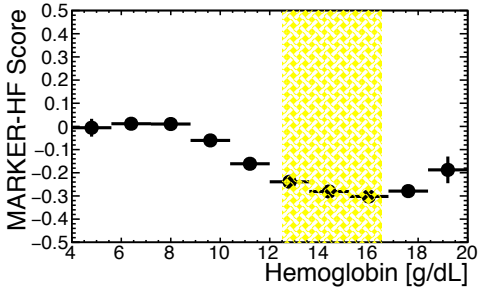


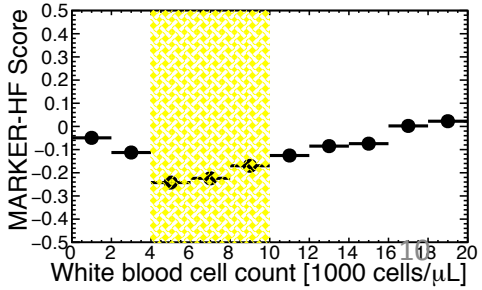




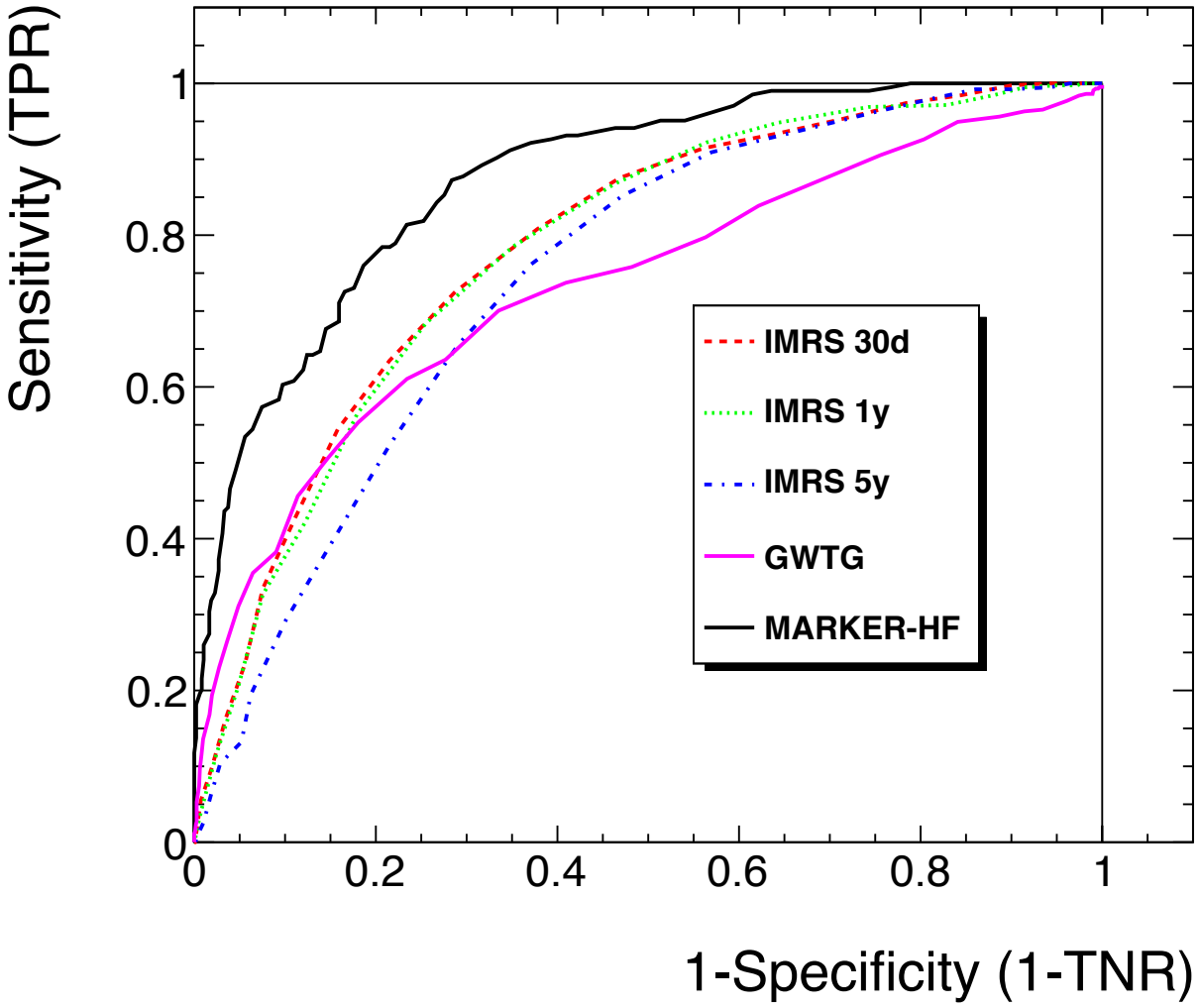








Comparisons with similar risk scores

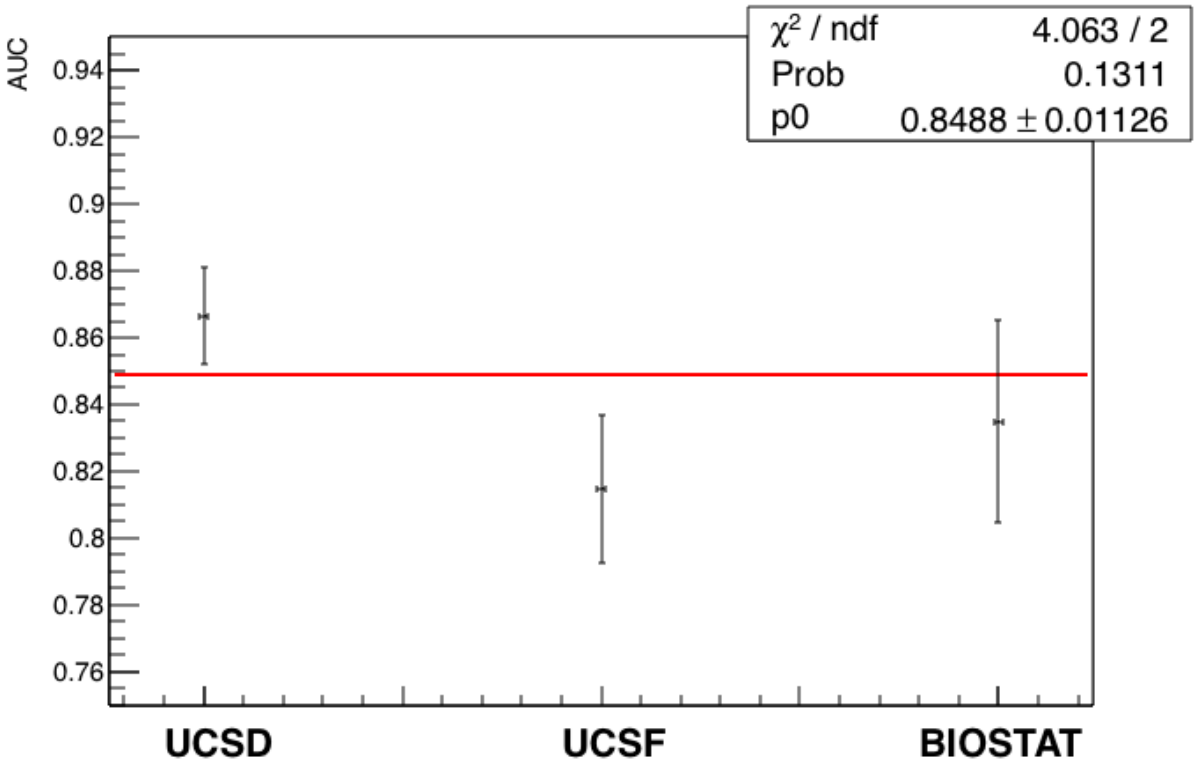


IMRS: *American Journal of Medicine*, 122(6)L550-558, 2009

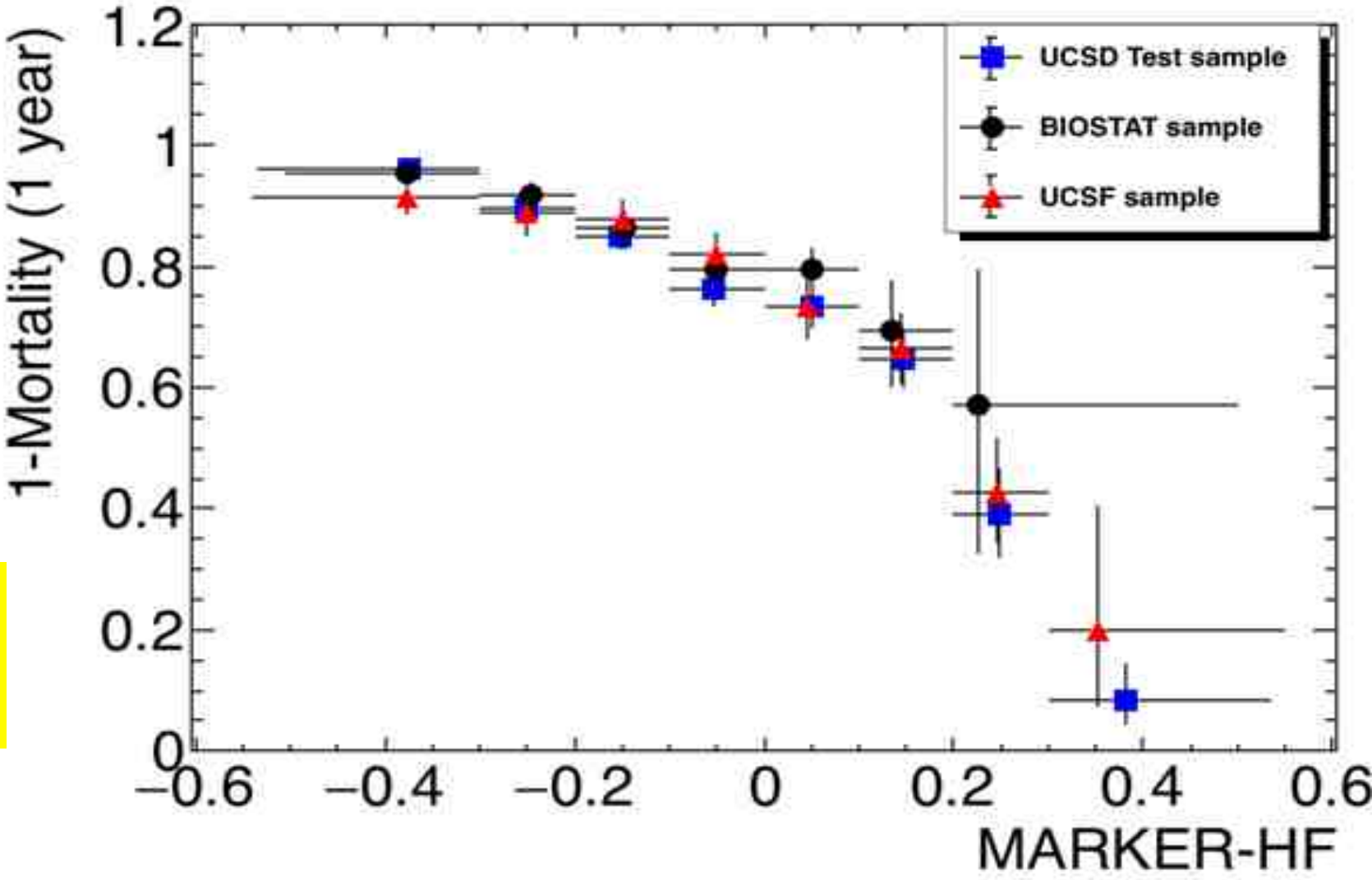
GWTG: Circulation: Cardiovascular Quality and Outcomes, 3(1):25-32, 2010

Reproducibility with patients not from UCSD

- "Local" bias of studies major concern in medical field
- Applied model derived on UC San Diego patients on patients from
  - UC San Francisco EMR
  - BIOSTAT—CHF
    - A study from 69 centers in 11 EU countries
- **<u>AUC is statistically consistent in the 3 cohorts of patients</u>**



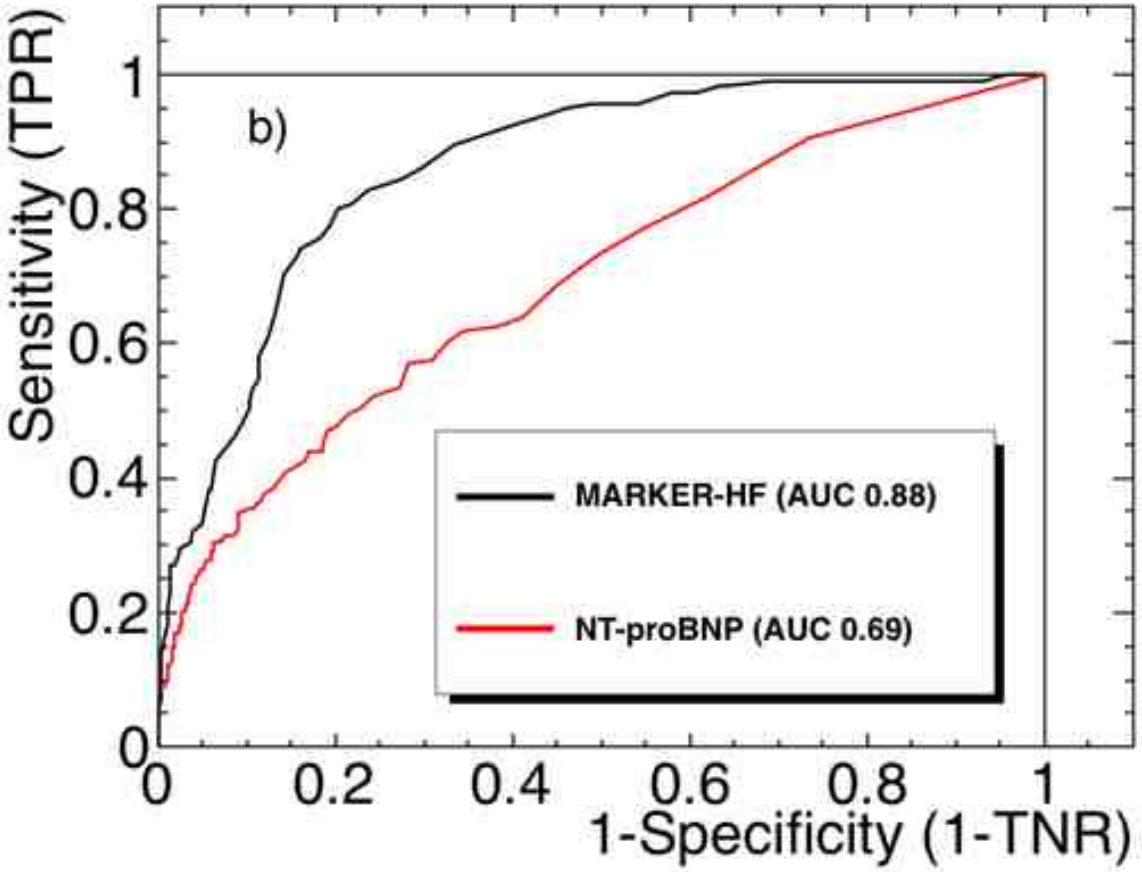
Applicability to all patients, ie, not just the “high risk” and “low risk”



Consistency between the 3 cohorts

Comparing NT-proBNP and Marker-HF

Amino-terminal pro-B-type natriuretic peptide, (NT-proBNP) is a well validated biomarker associated with HF



Other features that did not have time to cover

Consistent performance in

- Men vs. Women
- As a function of ethnicity
- As a function of age
- For in- vs. out-patients (proxy for health status)
- Patients with pulmonary edema vs. other HF diagnoses
- No detectale bias due to excluding patients with missing variables

Conclusion

- Succeeded in designing predictive risk score algorithm for HF using ML
- Key features, some based on HEP experience
  - Tight data collection requirements → Clean training/testing samples
  - Clear definition of outcomes using the extrema
  - Automatic inclusion of correlations (potentially non-linear)
- Paper submitted to medical journal
- Starting to think about further studies, still in cardiology, e.g., can we predict which patients will suffer major bleeding with anticoagulants?