UNIVERSITY OF ALBERTA
SCHOOL OF PUBLIC HEALTH

# A Summary Index of Prediction Accuracy for Censored Time to Event Data

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June 5, 2018 Montreal

Joint work with Michelle Zhou et al.

# Outline

- Motivation
- Measures for evaluating prediction performance of risk scores
- Estimator and simulation
- Data analysis
- Summary and future work

# Examples of Prevention and Early Detection in Clinical Practice

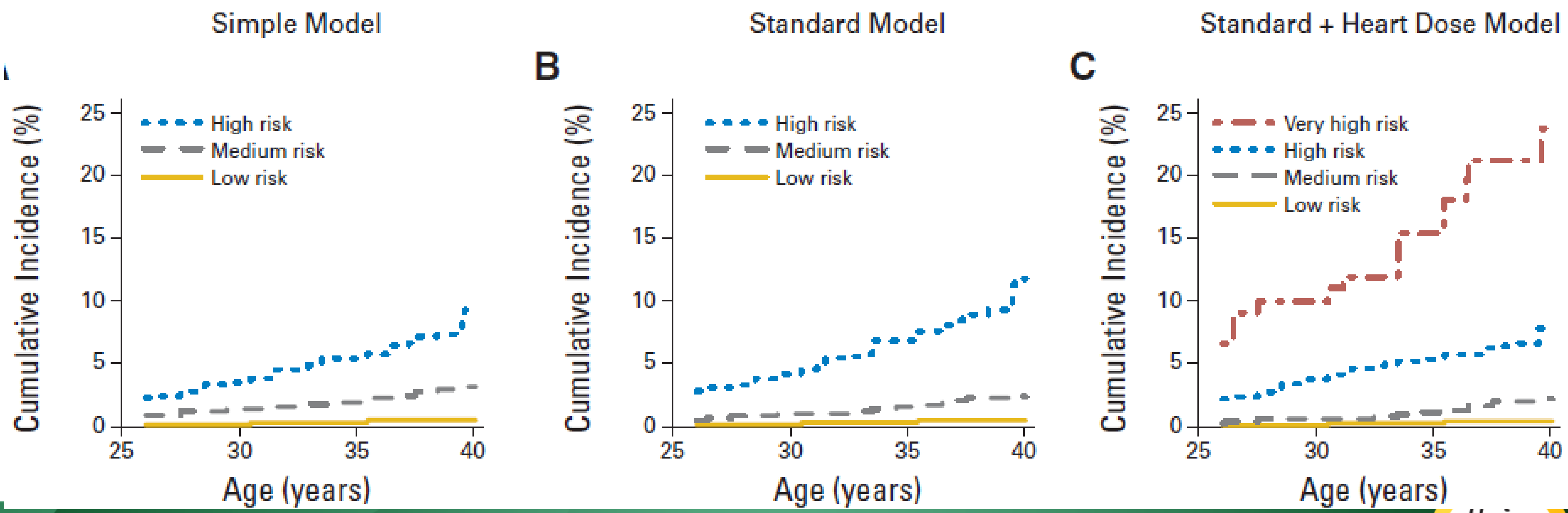
- The Prism risk tool (for re-hospitalization within a year)
- Risk charts for 182 countries to predict future risk of cardiovascular disease
- Multiple risk score systems (n>40) for diabetes risk in general population
- Risk prediction models for acute kidney injury in critically ill patients (2018)

# Risk Score as a Screening Tool

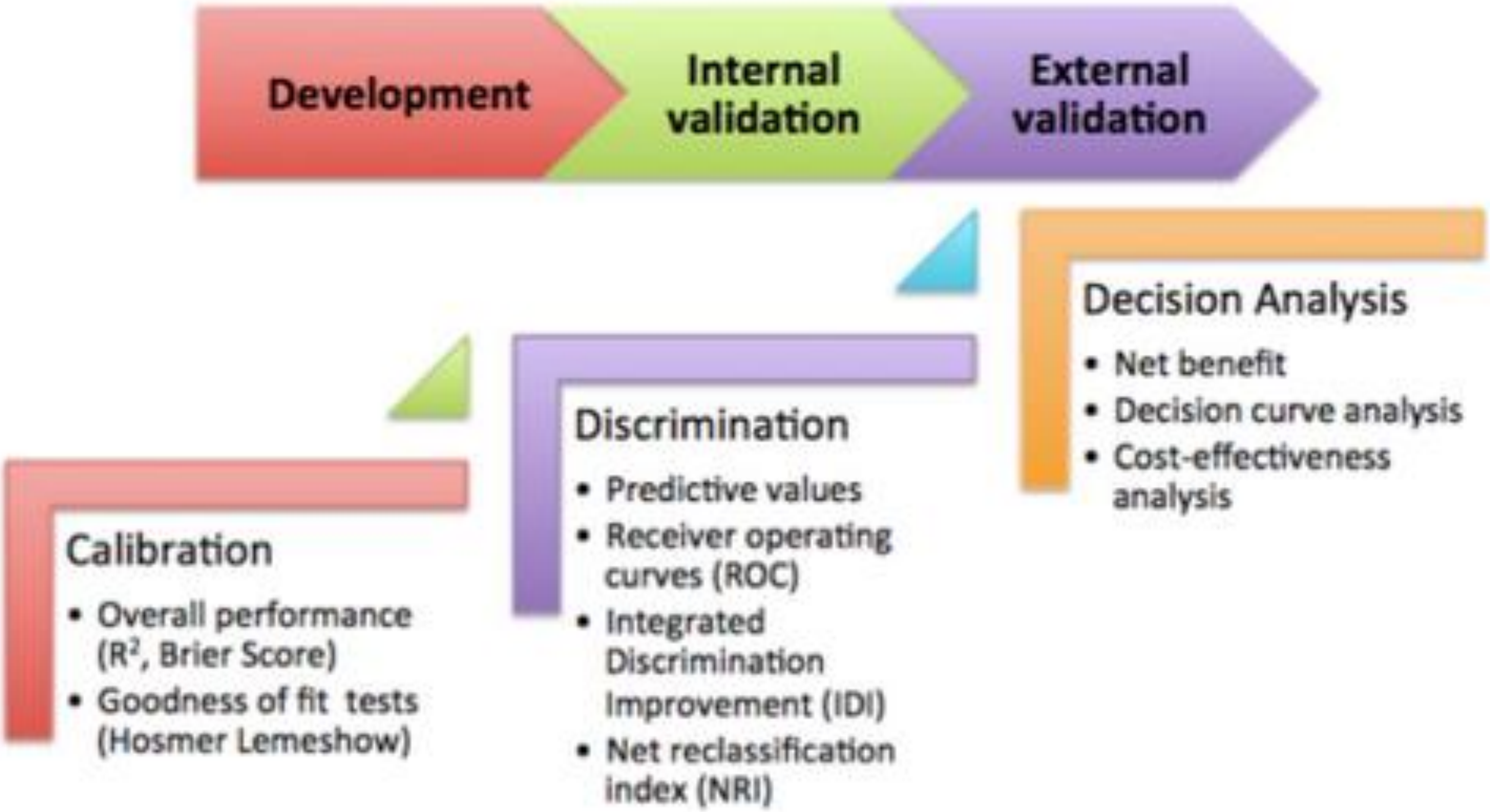
- Typical condition that risk scores are used/ developed for have the following characteristics
  - seriousness may result in a high risk of mortality or significantly affect the quality of life;
  - early detection/intervention can make a difference in disease prognosis;
  - the event rate is <u>low</u>

# Motivating Data

- Late effects of cancer treatments in childhood cancer survivors – e.g. Congestive heart failure (Chow et al. 2015, *Journal of Clinical Oncology*)
- Cumulative risk of CHF is ~3% by 35 years post diagnosis



# Prediction Performance Measure

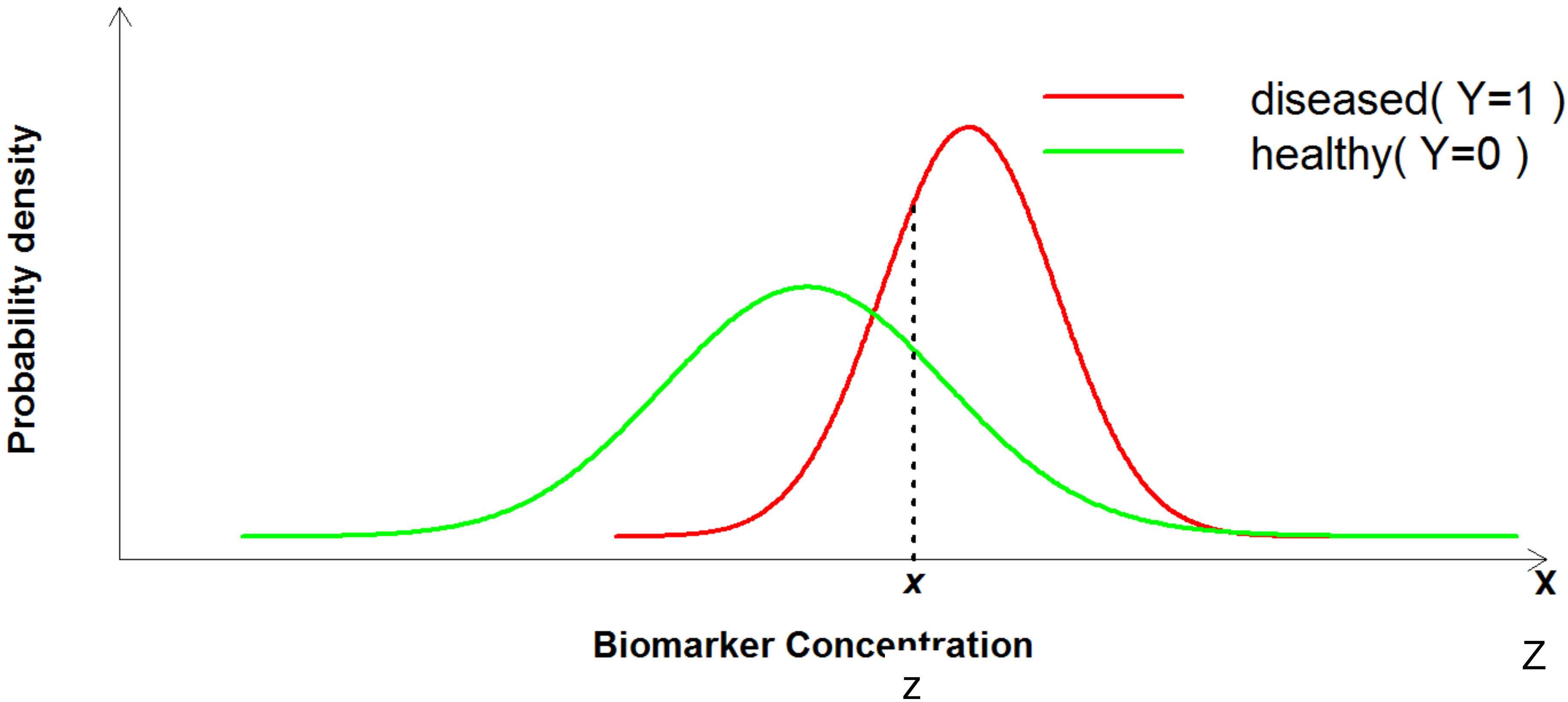



[Columbia University Mailman School of Public Health]

# Evaluating Model Performance when Predicting Low Prevalence Events

- Threshold Dependent Measure (predictor needs to be binary)
  - ~~Misclassification rate~~
  - Sensitivity (TPF): P(test positive | diseased) = $\mathrm{P}(\hat{Y} = 1 \mid Y = 1)$
  - Specificity (FPF): P(test negative | healthy) = $\mathrm{P}(\hat{Y} = 0 \mid Y = 0)$
  - Positive Predictive value (PPV): $\mathrm{P}(Y = 1 \mid \hat{Y} = 1)$
  - Negative Predictive Value (NPV): $\mathrm{P}(Y = 0 \mid \hat{Y} = 0)$

# When predictor is continuous or ordinal




Risk score

# Threshold-free Summary Measure

- Area Under the ROC* Curve (AUC, *aROC*)

$$\text{AUC} \equiv \int_R \text{TPF}(z)d\text{FPF}(z)$$

- Extension to event status to accommodate censoring and time to event data -- $AUC_{t_0}$
- Criticisms of AUC as a measure for risk prediction
  - Retrospective measure
  - Insensitive
  - Over-optimistic

# A Threshold-free Alternative to AUC for Binary Outcome

- Average Positive predictive value (AP)

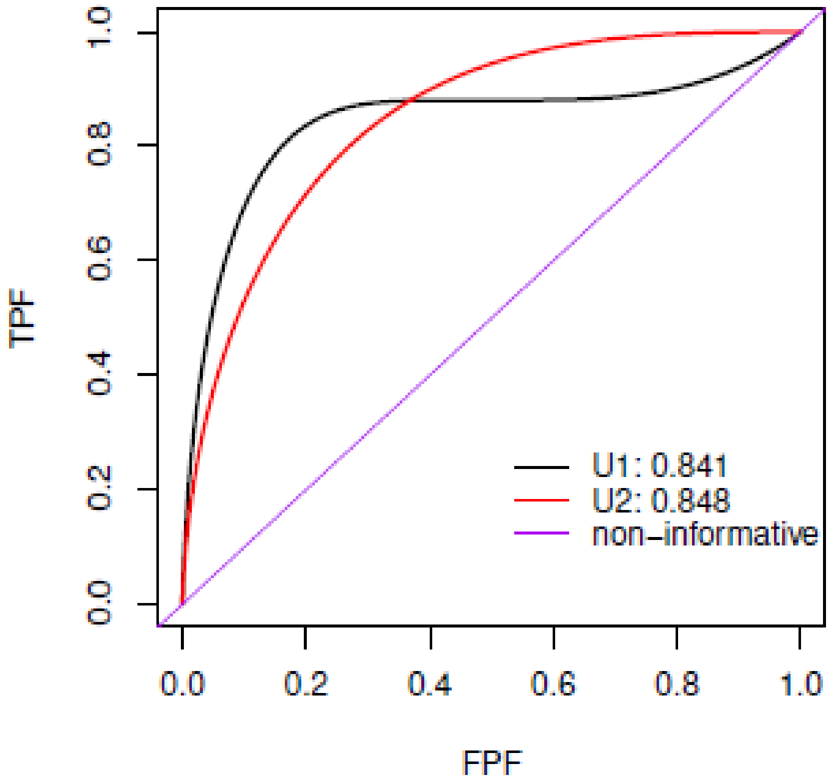
$$\mathrm{A}P \equiv \int_R \mathrm{PPV}(z) d\mathrm{TPF}(z)$$

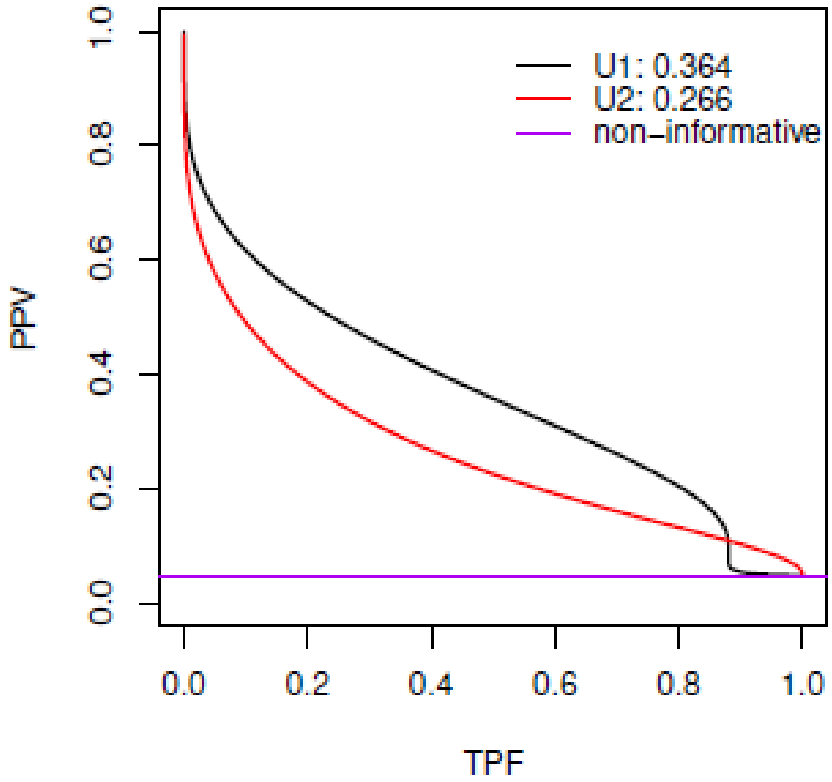
Remark:

– Range: [π, 1] where π is the prevalence rate and corresponds to a random risk score

*Yuan et al. (2015) Frontiers in Public Health 3:57.*

# ROC curve PvR curve



# Relationship to AUC

- When two risk scores $U_1$ and $U_2$ are compared
  - If ROC curve of $U_1$ dominates that of $U_2$ everywhere, the $AUC_1 > AUC_2$ and $AP_1 > AP_2$
  - If ROC curves of $U_1$ and $U_2$ crosses, the ranking of $U_1$ and $U_2$ based on of AUC and AP can differ.

*Su et al. (2015) Proceedings of the 2015 International Conference on Theory of Information Retrieval. pp.349-352.*

# An Alternative to $AUC_{t_0}$ for Time-to-event Outcome

- Time-dependent Average Positive predictive value ($AP_{t_0}$)

$$\mathrm{AP}_{t_0} = \int_{\mathcal{R}} \mathrm{PPV}_{t_0}(z) d\mathrm{TPF}_{t_0}(z).$$

# Nonparametric Estimator for Survival Status

Let $(X, \delta, Z)$ be the standard survival time notation,
*X*: the censored event time, $\delta$: the censoring indicator
*Z*: the risk score

$$\widehat{\mathrm{AP}}_{t_0} = \frac{\sum_{j=1}^{n} I(X_j \le t_0)\hat{w}_{t_0,j}\widehat{\mathrm{PPV}}_{t_0}(Z_j)}{\sum_{j=1}^{n} I(X_j \le t_0)\hat{w}_{t_0,j}}.$$

where

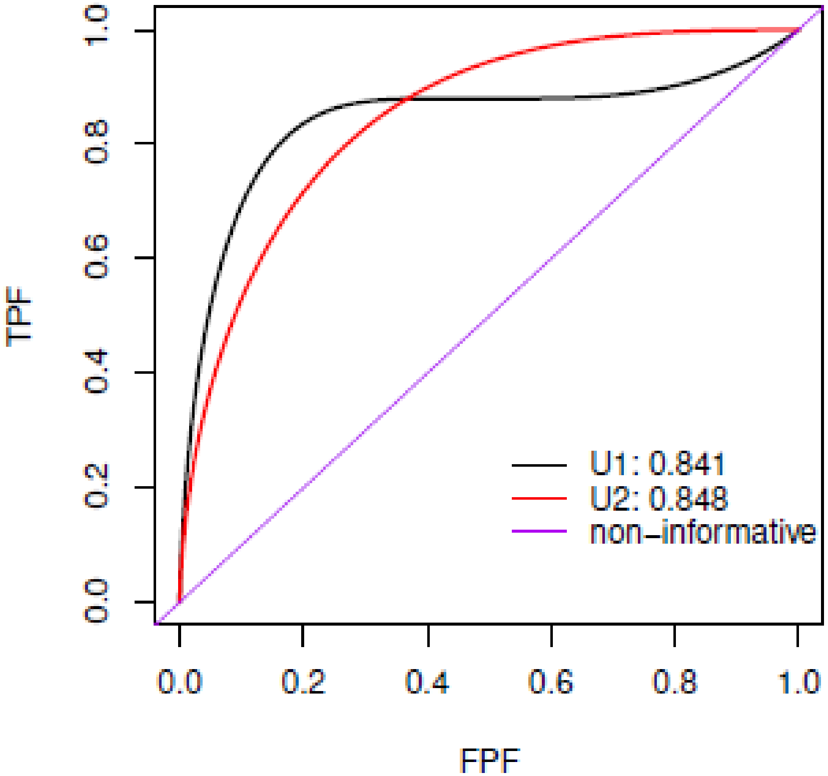
$$\widehat{w}_{t_0,i} = \frac{I(X_i < t_0)\delta_i}{\widehat{\mathcal{G}}(X_i)} + \frac{I(X_i \ge t_0)}{\widehat{\mathcal{G}}(t_0)}$$

$$\widehat{\mathrm{PPV}}_{t_0}(z) = \frac{\sum_{i=1}^{n} \widehat{w}_{t_0,i} I(Z_i \ge z) I(X_i < t_0)}{\sum_{i=1}^{n} I(Z_i \ge z)}$$

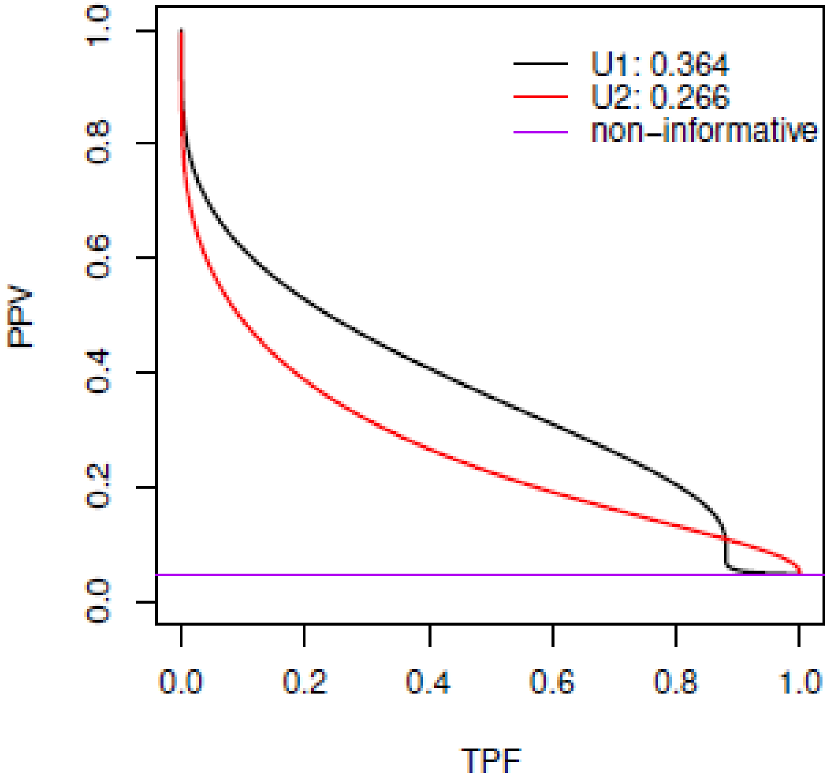
# Simulation Study

$$\log(T_i) = 7.2 - 1.1U_{i1} - 2.5U_{i2} - 1.5log(U_{i1}^2) + \epsilon_T,$$

$ROC_{t_0=8}$




$PR_{t_0=8}$



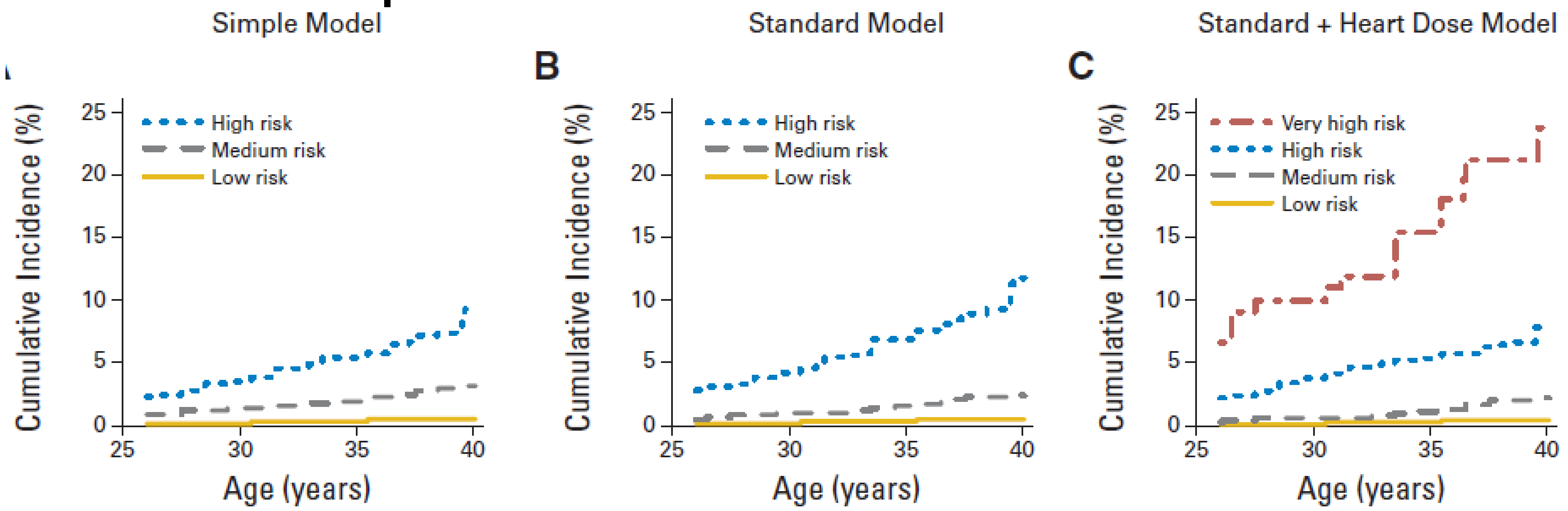
# Results (n=2000)

| $t_0$ | Event rate | Risk score | AP | | | | | AUC |
|---|---|---|---|---|---|---|---|---|
| | | | TRUE | BIAS | ESE | $ASE^b$ | $ECOVP^b(\%)$ | TRUE |
| 0.5 | 0.0101 | $U_1$ | 0.182 | 0.0361 | 0.0806 | 0.0794 | 92.2 | 0.920 |
| | | $U_2$ | 0.124 | 0.0339 | 0.0687 | 0.0679 | 94.1 | 0.904 |
| | | $\Delta$ | 0.058 | 0.0251 | 0.102 | 0.116 | 96.1 | 0.016 |
| | | Ratio | 1.47 | 0.4820 | 1.470 | 1.740 | 92.4 | 1.02 |
| 8 | 0.0495 | $U_1$ | 0.364 | 0.0085 | 0.0508 | 0.0499 | 94.4 | 0.841 |
| | | $U_2$ | 0.266 | 0.0121 | 0.0435 | 0.0439 | 94.8 | 0.848 |
| | | $\Delta$ | 0.098 | -0.0028 | 0.0707 | 0.072 | 96.3 | -0.007 |
| | | Ratio | 1.37 | 0.0123 | 0.310 | 0.322 | 95.8 | 0.99 |
| 36 | 0.0991 | $U_1$ | 0.462 | 0.0060 | 0.0416 | 0.0431 | 94.2 | 0.786 |
| | | $U_2$ | 0.375 | 0.0074 | 0.0387 | 0.0393 | 96.3 | 0.824 |
| | | $\Delta$ | 0.087 | -0.0045 | 0.0655 | 0.0633 | 95.7 | -0.038 |
| | | Ratio | 1.23 | -0.0010 | 0.189 | 0.187 | 94.5 | 0.95 |

# Results (n=5000)

| $t_0$ | Event rate | Risk score | AP | | | | | AUC |
|---|---|---|---|---|---|---|---|---|
| | | | TRUE | BIAS | ESE | $ASE^b$ | $ECOVP^b(\%)$ | TRUE |
| 0.5 | 0.0101 | $U_1$ | 0.182 | 0.0185 | 0.0498 | 0.0503 | 93.6 | 0.920 |
| | | $U_2$ | 0.124 | 0.0154 | 0.0415 | 0.0415 | 93.6 | 0.904 |
| | | $\Delta$ | 0.058 | 0.0056 | 0.0696 | 0.0712 | 94.2 | 0.016 |
| | | Ratio | 1.47 | 0.1490 | 0.709 | 0.756 | 92.9 | 1.02 |
| 8 | 0.0495 | $U_1$ | 0.364 | 0.0041 | 0.0327 | 0.0324 | 94.0 | 0.841 |
| | | $U_2$ | 0.266 | 0.0043 | 0.0285 | 0.0280 | 95.5 | 0.848 |
| | | $\Delta$ | 0.098 | -0.0005 | 0.0473 | 0.0460 | 96.3 | -0.007 |
| | | Ratio | 1.37 | 0.0099 | 0.209 | 0.204 | 94.5 | 0.99 |
| 36 | 0.0991 | $U_1$ | 0.462 | 0.0023 | 0.0273 | 0.0275 | 95.0 | 0.786 |
| | | $U_2$ | 0.375 | 0.0015 | 0.0247 | 0.0251 | 95.5 | 0.824 |
| | | $\Delta$ | 0.087 | 0.0003 | 0.0398 | 0.0402 | 95.1 | -0.038 |
| | | Ratio | 1.23 | 0.0058 | 0.117 | 0.120 | 95.0 | 0.95 |

# Example: CCSS CHF Risk Prediction

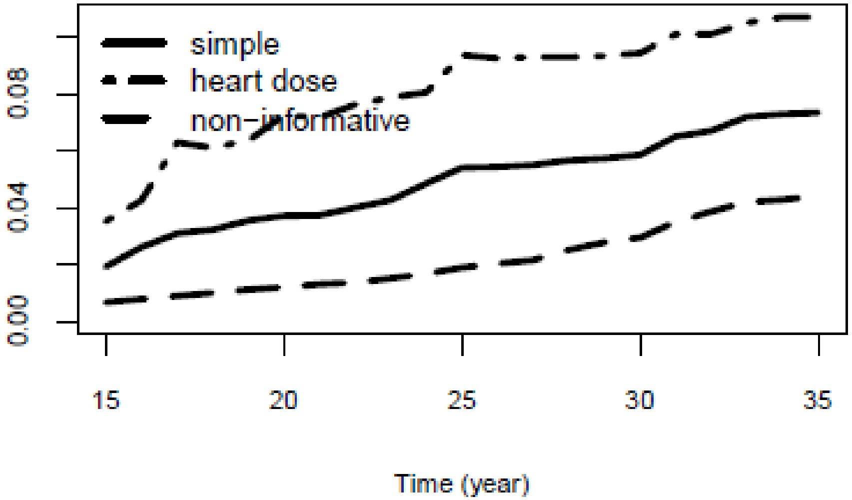


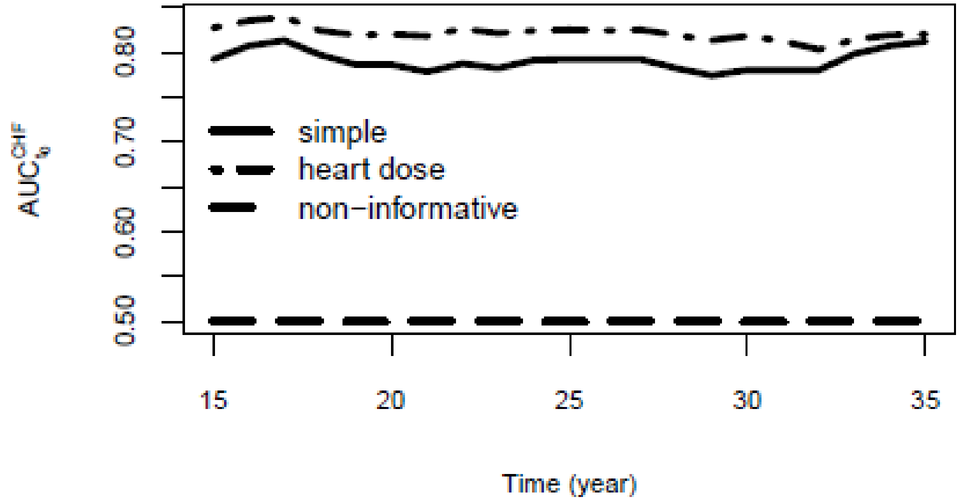

$$\mathrm{PPV}_{t_0}^{\mathrm{CHF}}(z) = Pr\{T < t_0, \Delta = 1 \mid Z \geq z\} \quad \text{and} \quad \mathrm{TPF}_{t_0}^{\mathrm{CHF}}(z) = Pr\{Z \geq z \mid T < t_0, \Delta = 1\}.$$

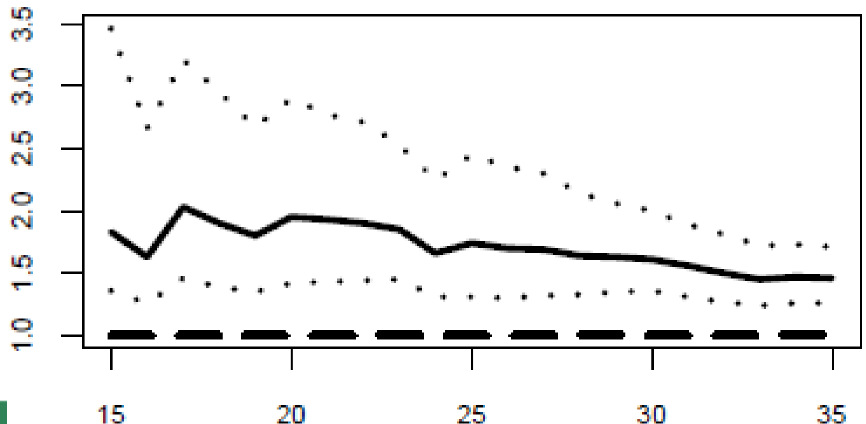
$$\widehat{\mathrm{PPV}}_{t_0}^{\mathrm{CHF}}(z) = \frac{\sum_{i=1}^{n} \widehat{w}_{t_0,i} I(Z_i \geq z) I(X_i < t_0) I(\Delta_i = 1)}{\sum_{i=1}^{n} I(Z_i \geq z)}$$

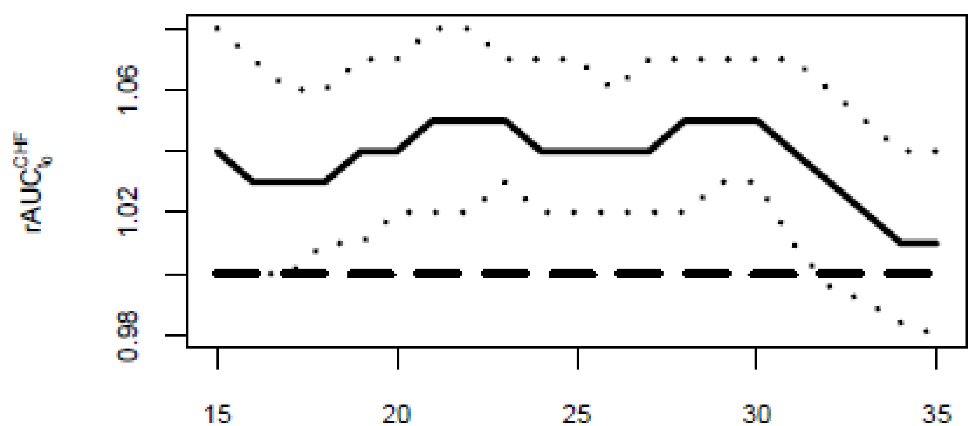
$$\widehat{\mathrm{TPF}}_{t_0}^{\mathrm{CHF}}(z) = \frac{\sum_{i=1}^{n} \widehat{w}_{t_0,i} I(Z_i \geq z) I(X_i < t_0) I(\Delta_i = 1)}{\sum_{i=1}^{n} \widehat{w}_{t_0,i} I(X_i < t_0) I(\Delta_i = 1)}$$

## $AP_{t_0}\ vs.\ t_0$      $AUC_{t_0}\ vs.\ t_0$



# Comparison

| $t_0$ | Event rate | Risk score system | $AP^{CHF}$ | $AUC^{CHF}$ |
|---|---|---|---|---|
| 20 years | 0.0120 | Simple | 0.037 (0.028, 0.051) | 0.786 (0.746, 0.824) |
| | | Heart dose | 0.072 (0.047, 0.120) | 0.820 (0.780, 0.859) |
| | | $\Delta$ | 0.035 (0.015, 0.077) | 0.035(0.013, 0.056) |
| | | Ratio | 1.95 (1.42, 2.90) | 1.04 (1.02, 1.07) |
| 35 years | 0.0440 | Simple | 0.073 (0.062, 0.088) | 0.812 (0.778, 0.846) |
| | | Heart dose | 0.107 (0.088, 0.135) | 0.820 (0.784, 0.856) |
| | | $\Delta$ | 0.034(0.020, 0.055) | 0.008 (-0.016, 0.029) |
| | | Ratio | 1.46 (1.26, 1.71) | 1.01 (0.98, 1.04) |

# Summary

- Point and interval estimators of AP for binary outcome (ordinal risk score);
- Nonparametric estimator of $AP_{t_0}$ for censored event status and in the presence of competing risks (continuous risk score);
- Inference procedure to compare $AP_{t_0}$ for two risk scores;
- APtools: an R package for binary and survival time data.

# Discussion

- AP is a single numerical measure, in this respect it is similar to AUC.
- A summary measure of positive predictive value, better suited in comparing prospective prediction performance of competing risk scores
- More sensitive than AUC as illustrated by the data analysis
- Event rate dependent, AP should be estimated in a prospective cohort or population-based study

# Future Work

- To evaluate how sensitive and robust the AP is as a measure of prediction accuracy Partial AP
- To extend the AP for evaluation of multicategory outcomes
- Partial AP

# Acknowledgement

Collaborators

- Dr. Qian Michelle Zhou
- Dr. Eric Chow
- Dr. Greg Armstrong

Students

- Doris Li
- Hengrui Cai