Measuring the Prediction Performance for Risk Scores in the Era of Clinical Preventive Care

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2017 Lifetime Data Science Conference

Outline

- Motivation
  - The clinical preventative care focuses on earlier intervention through *personalized* risk prediction
- Measures for evaluating prediction performance of risk scores
- Simulation study
- Data analysis example
- Summary and future work

Examples of Prevention and Early Detection in Clinical Practice

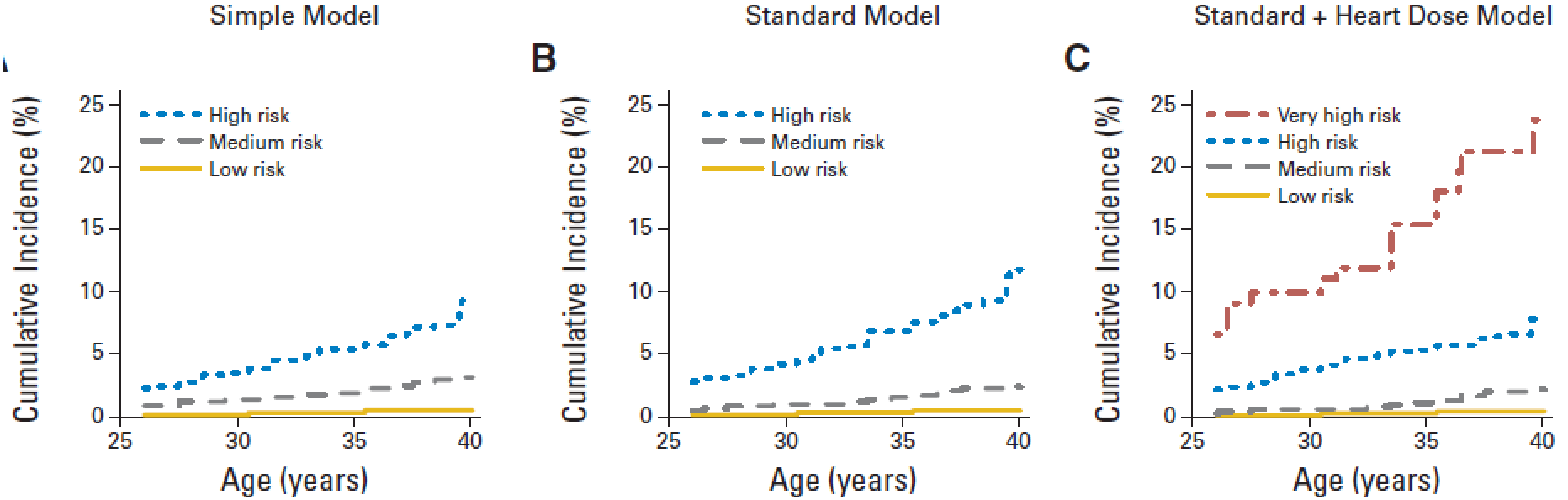
- Framingham risk score for CVD in general population
- CHA_2DS_2-Vasc scores for stroke risk in patients with atrial fibrillation
- Multiple risk score systems (n>40) for diabetes risk in general population
- BIRADS scores for breast cancer early detection

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

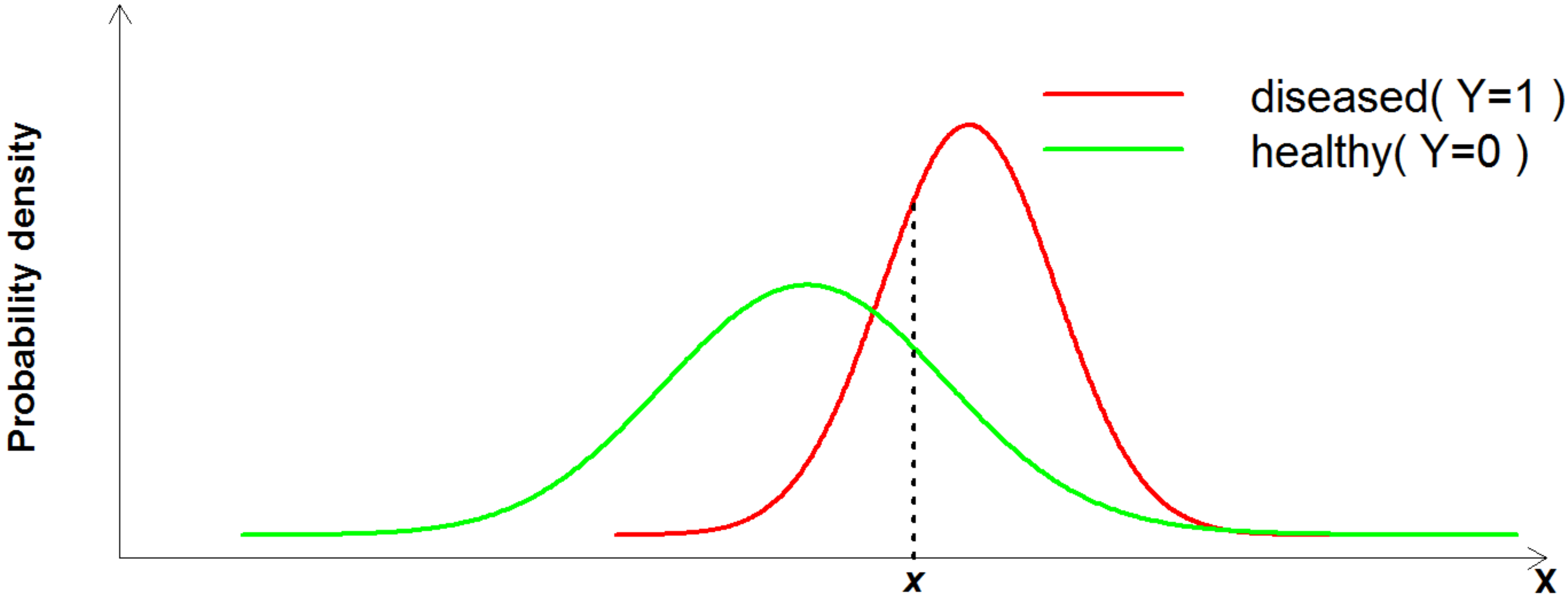
- Late effects of cancer treatments in childhood cancer survivors – e.g. Congestive heart failure (Chow et al. JCO, 2015)
- Cumulative risk of CHF is ~3% by 35 years post diagnosis



Evaluating Model Performance for Predicting Rare Events

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

How about when predictor is continuous or ordinal?



Risk score

Threshold Independent Measure

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

$$\text{AUC} \equiv \int_0^1 \text{TPF}(s)\text{dFPF}(s)$$

- 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

*Receiver Operating Characteristic

Alternatives to AUC_{t_0} for Time-to-event Outcome

- Time-dependent PPV – PPV_{t_0}
  - Needs binary predictor or equivalently a threshold for continuous / ordinal predictor
- Time-dependent Average Positive predictive value (AP_{t_0})

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

Note that AP_{t_0} is Threshold Independent

Nonparametric Estimator

Let (X, δ, Z) be the standard survival time notation,
X: the censored event time, δ: the censoring indicator
Z: the risk score

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

where

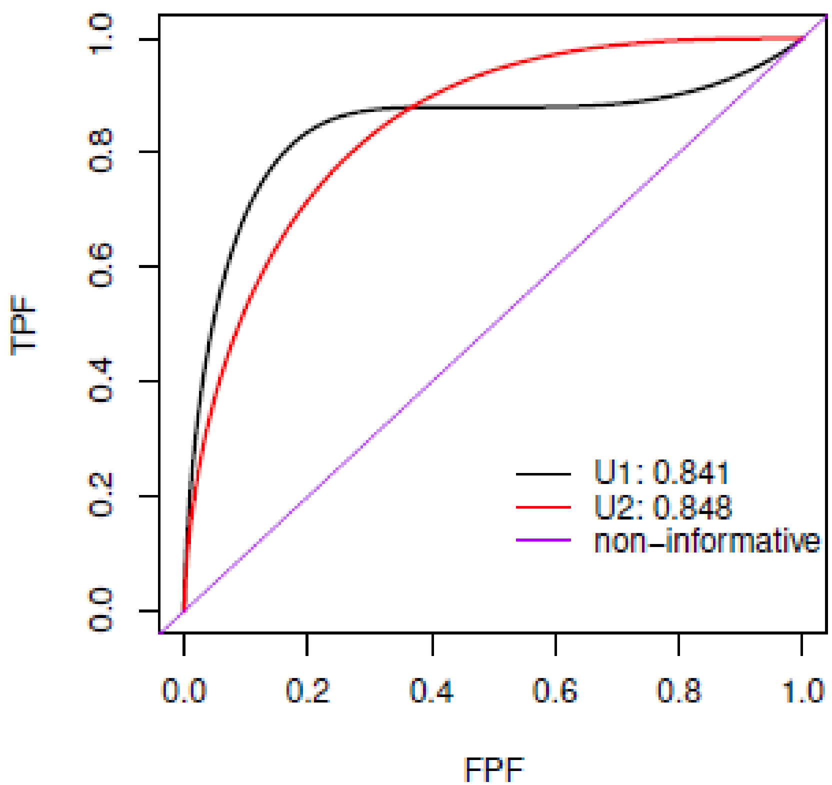
$$\widehat{w}_{t_0,i} = \frac{I(X_i < t_0)\delta_i}{\widehat{\mathcal{G}}(X_i)} + \frac{I(X_i \geq t_0)}{\widehat{\mathcal{G}}(t_0)}$$

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

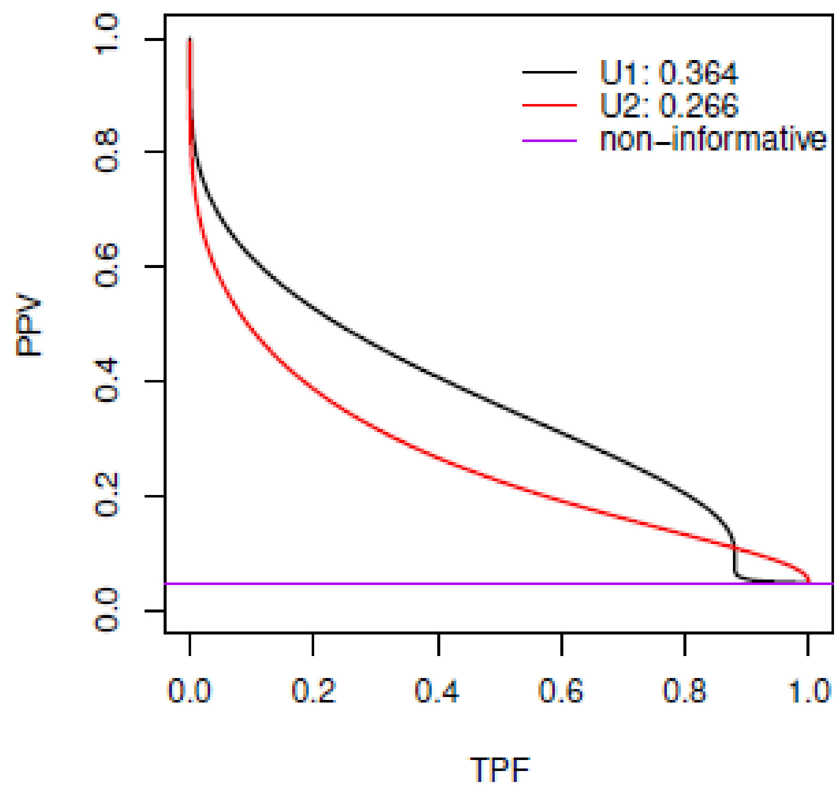
Simulation Study

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

$ROC_{t_0=8}$



$PR_{t_0=8}$



Results (n=2000)

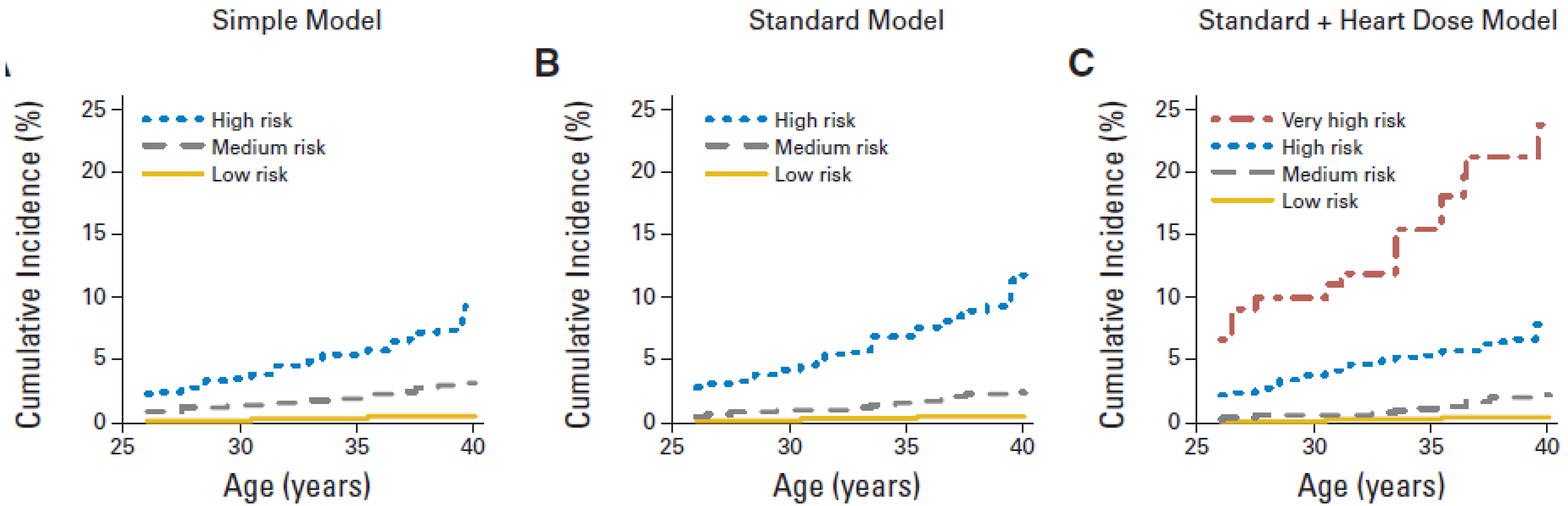
t_0	Event rate		TRUE	BIAS	ESE	ASE^b	$ECOVP^b(\%)$
0.5	0.0101	AP_1	0.182	0.0365	0.0810	0.0795	92.3
		AP_2	0.124	0.0339	0.0689	0.0678	93.0
		rAP	1.47	0.4890	1.5300	1.7600	95.1
8	0.0495	AP_1	0.364	0.0096	0.0527	0.0516	92.5
		AP_2	0.266	0.0129	0.0452	0.0450	93.4
		rAP	1.37	0.0140	0.3290	0.3320	95.7
36	0.0991	AP_1	0.462	0.0098	0.0534	0.0558	95.9
		AP_2	0.375	0.0118	0.0493	0.0501	94.5
		rAP	1.23	0.0135	0.2310	0.2420	94.9

where $rAP_{t_0} = \frac{AP_{u_1,t_0}}{AP_{u_2,t_0}}$

Results (n=5000)

t_0	Event rate		TRUE	BIAS	ESE	ASE^b	$ECOVP^b(\%)$
0.5	0.0101	AP_1	0.182	0.0185	0.0500	0.0504	93.1
		AP_2	0.124	0.0155	0.0416	0.0417	94.8
		rAP	1.47	0.1550	0.7060	0.7600	93.8
8	0.0495	AP_1	0.364	0.0042	0.0337	0.0333	92.9
		AP_2	0.266	0.0049	0.0291	0.0288	93.7
		rAP	1.37	0.0060	0.2160	0.2100	95.4
36	0.0991	AP_1	0.462	0.0034	0.0354	0.0346	95.5
		AP_2	0.375	0.0037	0.0310	0.0313	94.1
		rAP	1.23	0.0051	0.1490	0.1510	95.0

CCSS CHF risk prediction

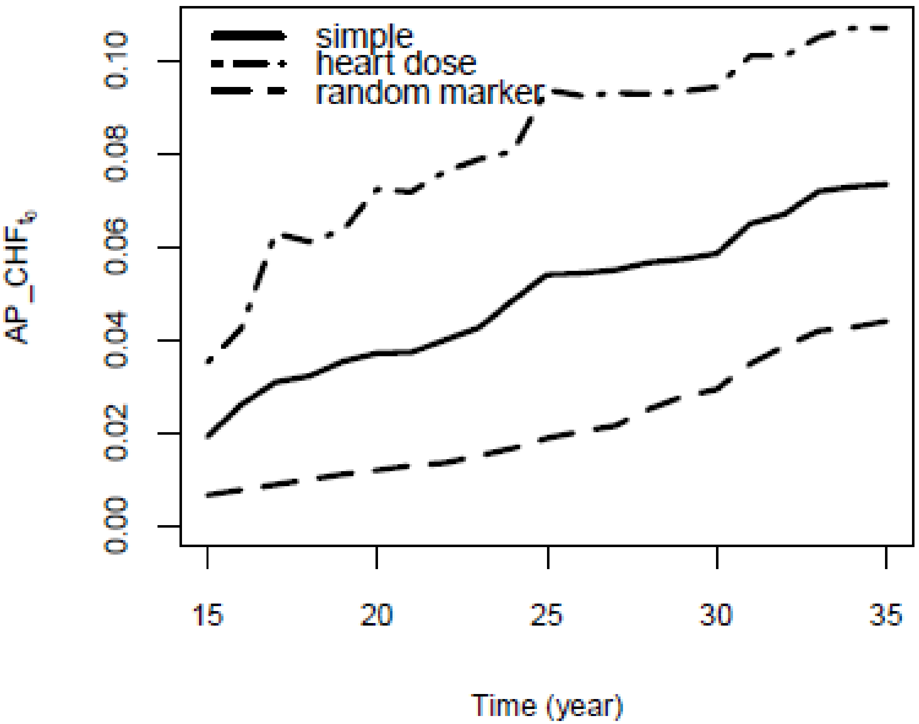


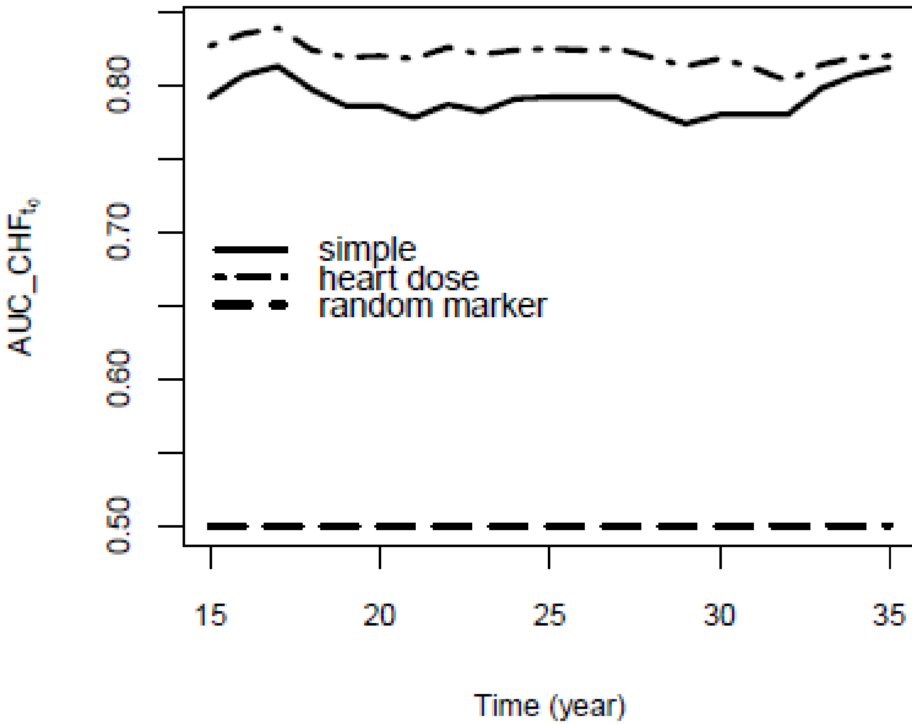
$$\mathrm{PPV}_{t_0}^{\mathrm{CHF}}(z) = Pr\{T < t_0, \Delta = 1 \mid Z \geq z\} \quad \text{and} \quad \mathrm{TPF}_{t_0}^{\mathrm{CHF}}(z) = Pr\{Z \geq z \mid T < t_0, \Delta = 1\}.$$

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

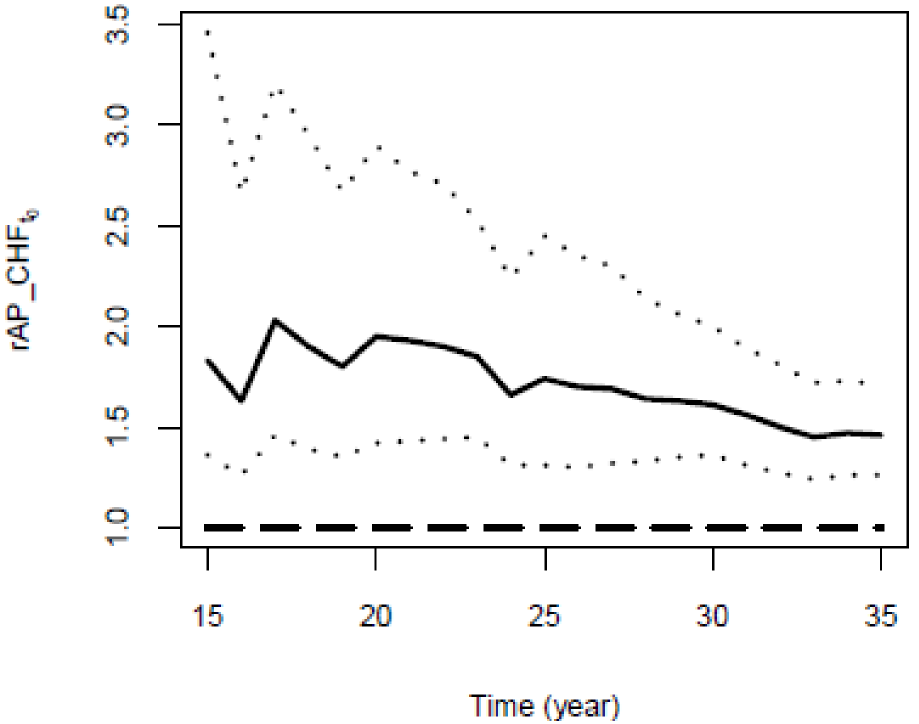
$$\widehat{\mathrm{TPF}}_{t_0}^{\mathrm{CHF}}(z) = \frac{\sum_{i=1}^{n} \widehat{w}_{t_0,i} I(Z_i \geq z) I(X_i < t_0) I(\Delta_i = 1)}{\sum_{i=1}^{n} \widehat{w}_{t_0,i} I(X_i < t_0) I(\Delta_i = 1)}$$

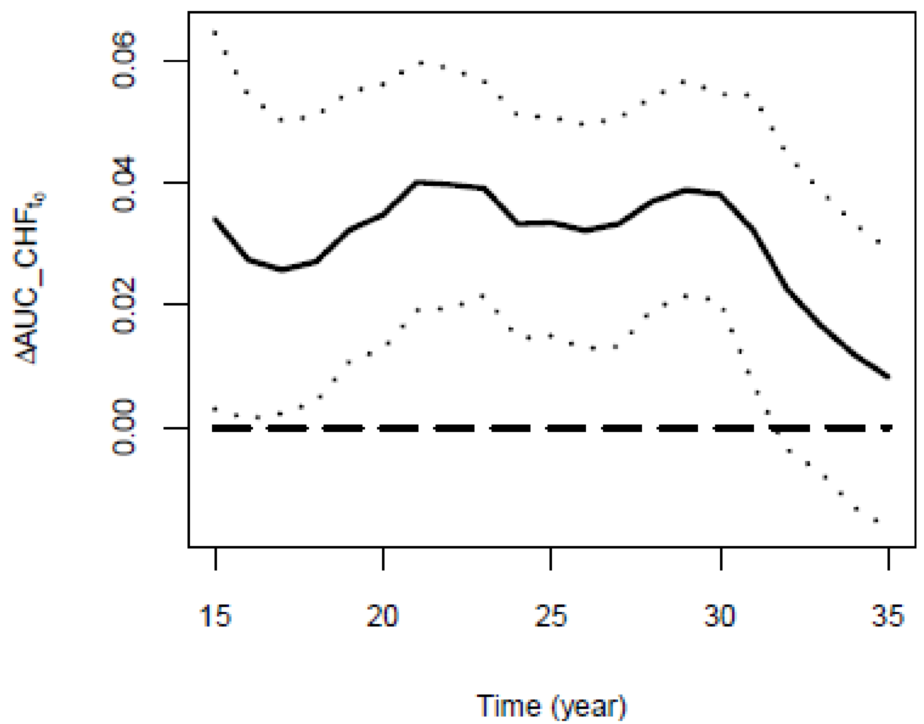
AP_{t_0} vs. t_0 | AUC_{t_0} vs. t_0





Comparison using rAP and ΔAUC





t_0	Event Rate	Risk Score System	AP_{t_0}	AUC_{t_0}
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)
		Comparison	1.46 (1.26, 1.71)	0.008 (-0.016, 0.029)

Summary

Contributions

- Nonparametric estimator of AP_{t_0} for censored event status and in the presence of competing risks
- 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 <u>single numerical measure</u>, 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

- Incremental value of biomarkers in risk prediction model as evaluated by AP
- Evaluating the sensitivity of AP with simulated biomarkers that have moderate effect size and are considered clinically significant
- Partial AP

Acknowledgement

Collaborators

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

Students

- Doris Li
- Hengrui Cai

CIHR IRSC

Canadian Institutes of Health Research
Instituts de recherche en santé du Canada