

Risk Prediction

Advanced Statistics for Records Research

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<https://ihi-risk-teaching.netlify.app/>

Learning objectives

This lecture will cover:

- Types of prediction
- 2x2 contingency table
- Metrics to evaluate model performance
- Model development and validation

in the context of binary risk prediction

Acknowledgements

Materials and data presented are based on previous slides prepared by L. Palla, D. Prieto, and E. Williamson

Scenario

Consider a dataset consisting some variables collected from a group of individuals. We want to predict which individuals develop a certain **binary outcome Y** .

Examples

Population	Available data	Outcome to predict
Surgical patients	age, sex, comorbidities, medications, severity of disease	complications after surgery
Covid-19 patients	age, sex, vaccination status, virus variant, chest X-ray	ICU admission within 10 days
Healthy individuals	body mass index, lifestyle, socioeconomic status, genotypes, lipid profile	myocardial infarction in 10-year follow-up

* **Note:** prediction modelling is *not* limited to biomedical problems

Types of prediction: deterministic vs probabilistic

- **Deterministic:**

- **Classify** each individual into one of the two possible outcomes.
- Often used in **(Supervised) Machine Learning**

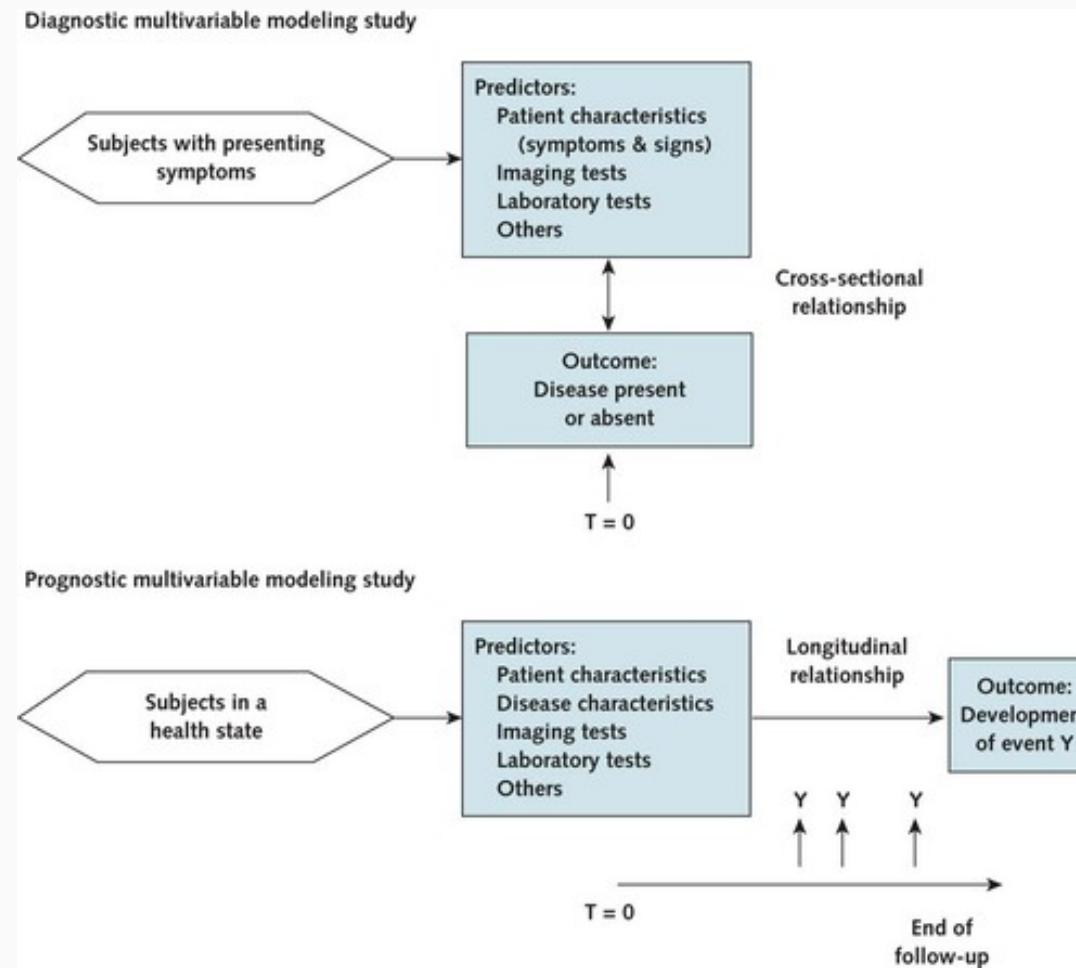
- **Probabilistic:**

- Assign each individual a **probability** of developing the outcome.
- Often used in **Biostatistics** and is known as **Risk Prediction***

Both methods use individual-level data on a set of variables (or **predictors**) to develop a prediction model

*Other names: risk prediction model, predictive model, prognostic (or prediction) index or rule, and risk score

Types of prediction: diagnostic vs prognostic



Example

Who will develop myocardial infarction in the next 5 years?

	id	age	sex	diabet	SBP	Classify	Predict	Observed
	1	35	F	Yes	145			
	2	35	M	No	130			
	3	55	F	No	115			
	4	55	M	Yes	170			
	5	65	F	No	135			
	6	65	M	Yes	140			
	7	75	M	Yes	160			
	8	75	F	No	130			
	9	85	F	Yes	130			
	10	85	M	No	160			

Deterministic classification

Suppose we have a pre-defined deterministic classification model C :

$$C(\text{age}, \text{sex}, \text{diabet}, \text{SBP}) = 0 \text{ or } 1$$

id	age	sex	diabet	SBP	Classify	Predict	Observed
1	35	F	Yes	145	No		
2	35	M	No	130	No		
3	55	F	No	115	No		
4	55	M	Yes	170	Yes		
5	65	F	No	135	No		
6	65	M	Yes	140	Yes		
7	75	M	Yes	160	Yes		
8	75	F	No	130	No		
9	85	F	Yes	130	Yes		
10	85	M	No	160	Yes		

Probabilistic prediction

Suppose we have a pre-defined probabilistic prediction model P :

$$P(\text{age}, \text{sex}, \text{diabet}, \text{SBP}) = [0, 1]$$

id	age	sex	diabet	SBP	Classify	Predict	Observed
1	35	F	Yes	145	No	0.15	
2	35	M	No	130	No	0.05	
3	55	F	No	115	No	0.10	
4	55	M	Yes	170	Yes	0.55	
5	65	F	No	135	No	0.30	
6	65	M	Yes	140	Yes	0.52	
7	75	M	Yes	160	Yes	0.60	
8	75	F	No	130	No	0.40	
9	85	F	Yes	130	Yes	0.55	
10	85	M	No	160	Yes	0.60	

Observation

... after 5 years follow-up

id	age	sex	diabet	SBP	Classify	Predict	Observed
1	35	F	Yes	145	No	0.15	No
2	35	M	No	130	No	0.05	No
3	55	F	No	115	No	0.10	No
4	55	M	Yes	170	Yes	0.55	No
5	65	F	No	135	No	0.30	Yes
6	65	M	Yes	140	Yes	0.52	No
7	75	M	Yes	160	Yes	0.60	Yes
8	75	F	No	130	No	0.40	No
9	85	F	Yes	130	Yes	0.55	Yes
10	85	M	No	160	Yes	0.60	Yes

Model validation

- Both **C** and **P** models are not always correct in predicting the outcome
- The goal of model validation is to evaluate model performance by **comparing predictions against observed values.**
- For binary prediction, model validation usually starts with creating a 2x2 contingency table / confusion matrix consisting all four possible **pairs of predicted-observed values**

2x2 Contingency table / Confusion matrix

id	Predicted	Observed
1	No	No
2	No	No
3	No	No
4	Yes	No
5	No	Yes
6	Yes	No
7	Yes	Yes
8	No	No
9	Yes	Yes
10	Yes	Yes

Predicted	Observed	Count
Yes	Yes	3
Yes	No	2
No	Yes	1
No	No	4

Predicted	Observed	Term
+	+	True Positive
+	-	False Positive
-	+	False Negative
-	-	True Negative

2x2 Contingency table / Confusion matrix

		Observed	
Predicted	+	-	
+	3	2	
-	1	4	

		Observed	
Predicted	+	-	
+	True Positive	False Negative	
-	False Positive	True Negative	

With 2 x 2 contingency table, we can calculate several useful metrics* to evaluate model performance, including:

- sensitivity, recall, hit / detection rate, or true positive rate (TPR)
- specificity, selectivity, or true negative rate (TNR)
- precision or positive predictive value (PPV)
- negative predictive value (NPV)

*for a full list, refer to [Wikipedia entry for Confusion matrix](#)

Sensitivity

- a.k.a **True Positive Rate**, **Recall**, **Hit / Detection Rate**
- Probability of **correctly predicting positive outcome**
- What is the probability of a **positive classification**, given a **positive outcome**?
- $P(\hat{Y} = 1 \mid Y = 1)$

		Observed	
		+	-
Predicted	+	TP	FP
	-	FN	TN

$$\text{Sensitivity} = \frac{\sum \text{True Positive}}{\sum \text{Observed Positive}}$$

$$\text{Sensitivity} = \frac{TP}{TP + FN}$$

Specificity

- a.k.a **Selectivity, True Negative Rate**
- Probability of **correctly predicting negative outcome**
- What is the probability of a **negative classification**, given a **negative outcome?**
- $P(\hat{Y} = 0 \mid Y = 0)$

		Observed	
Predicted	+	-	
	+	TP	FP
-	FN		TN

$$\text{Specificity} = \frac{\sum \text{True Negative}}{\sum \text{Observed Negative}}$$

$$\text{Specificity} = \frac{TN}{TN + FP}$$

Positive predictive value (PPV)

- Probability of a **positive outcome** given a **positive classification**
- $P(Y = 1 | \hat{Y} = 1)$
- For a given model (e.g. diagnostic test) with fixed sensitivity and specificity, **PPV** is **positively correlated** with **disease prevalence**
- Intuition: as **prevalence increases, true positive increases** while **false positives decreases**

		Observed	
Predicted	+	TP	FP
	-	FN	TN

$$PPV = \frac{\sum \text{True Positive}}{\sum \text{Predicted Positive}}$$

$$PPV = \frac{TP}{TP + FP}$$

Negative predictive value (NPV)

- Probability of a **negative outcome** given a **negative classification**
- $P(Y = 0 | \hat{Y} = 0)$
- For a given model (e.g. diagnostic test) with fixed sensitivity and specificity, **NPV** is **negatively correlated** with **disease prevalence**
- Intuition: as **prevalence increases, true negative decreases** while **false negative increases**

		Observed	
		+	-
Predicted	+	TP	FP
	-	FN	TN

$$NPV = \frac{\sum \text{True Negative}}{\sum \text{Predicted Negative}}$$

$$NPV = \frac{TN}{TN + FN}$$

Comparing *classifications* with observations

Suppose we have the following contingency table for classification model C:

		Observed		Total
Predicted	+	-		
+	3	2	5	
-	1	4	5	
Total	4	6	10	

Sensitivity = ?

PPV = ?

Specificity = ?

NPV = ?

Comparing *classifications* with observations

Suppose we have the following contingency table for classification model C:

		Observed		Total
Predicted	+	-		
+	3	2	5	
-	1	4	5	
Total	4	6	10	

$$\text{Sensitivity} = 3/4 = 0.75$$

$$\text{PPV} = 3/5 = 0.6$$

$$\text{Specificity} = 4/6 = 0.67$$

$$\text{NPV} = 4/5 = 0.8$$

Comparing *predictions* with observations

For prediction model P , we order by predicted probability and choose a **cut-off point** to classify as "Yes", e.g.

"Yes" if probability (P) > 0.1

id	Predict	Observed	Prob >0.1
2	0.05	No	No
3	0.10	No	No
1	0.15	No	Yes
5	0.30	Yes	Yes
8	0.40	No	Yes
6	0.52	No	Yes
4	0.55	No	Yes
9	0.55	Yes	Yes
7	0.60	Yes	Yes
10	0.60	Yes	Yes

Cut-off point: Yes if $P > 0.1$

		Observed		Total
Predicted	+	-		
+	4	4	8	
-	0	2	2	
Total	4	6	10	

$$\text{Sensitivity} = 4/4 = 1$$

$$\text{PPV} = 4/8 = 0.5$$

$$\text{Specificity} = 2/6 = 0.33$$

$$\text{NPV} = 2/2 = 1$$

Higher sensitivity, lower specificity than classification model C

Cut-off point: Yes if $P > 0.4$

id	Predict	Observed	Prob >0.4
2	0.05	No	No
3	0.10	No	No
1	0.15	No	No
5	0.30	Yes	No
8	0.40	No	No
6	0.52	No	Yes
4	0.55	No	Yes
9	0.55	Yes	Yes
7	0.60	Yes	Yes
10	0.60	Yes	Yes

Cut-off point: Yes if $P > 0.4$

		Observed		Total
Predicted	+	-		
+	3	2	5	
-	1	4	5	
Total	4	6	10	

$$\text{Sensitivity} = 3/4 = 0.75$$

$$\text{PPV} = 3/5 = 0.6$$

$$\text{Specificity} = 4/6 = 0.67$$

$$\text{Same } \text{NPV} = 4/5 = 0.8$$

contingency table as classification model [C](#)

Cut-off point: Yes if $P > 0.55$

id	Predict	Observed	Prob >0.55
2	0.05	No	No
3	0.10	No	No
1	0.15	No	No
5	0.30	Yes	No
8	0.40	No	No
6	0.52	No	No
4	0.55	No	No
9	0.55	Yes	No
7	0.60	Yes	Yes
10	0.60	Yes	Yes

Cut-off point: Yes if $P > 0.55$

		Observed		Total
Predicted	+	-		
+	2	0	2	
-	2	6	8	
Total	4	6	10	

$$\text{Sensitivity} = 2/4 = 0.5$$

$$\text{PPV} = 2/2 = 1$$

$$\text{Specificity} = 6/6 = 1$$

$$\text{NPV} = 6/8 = 0.75$$

Lower sensitivity, higher specificity than classification model C

All cut-off points

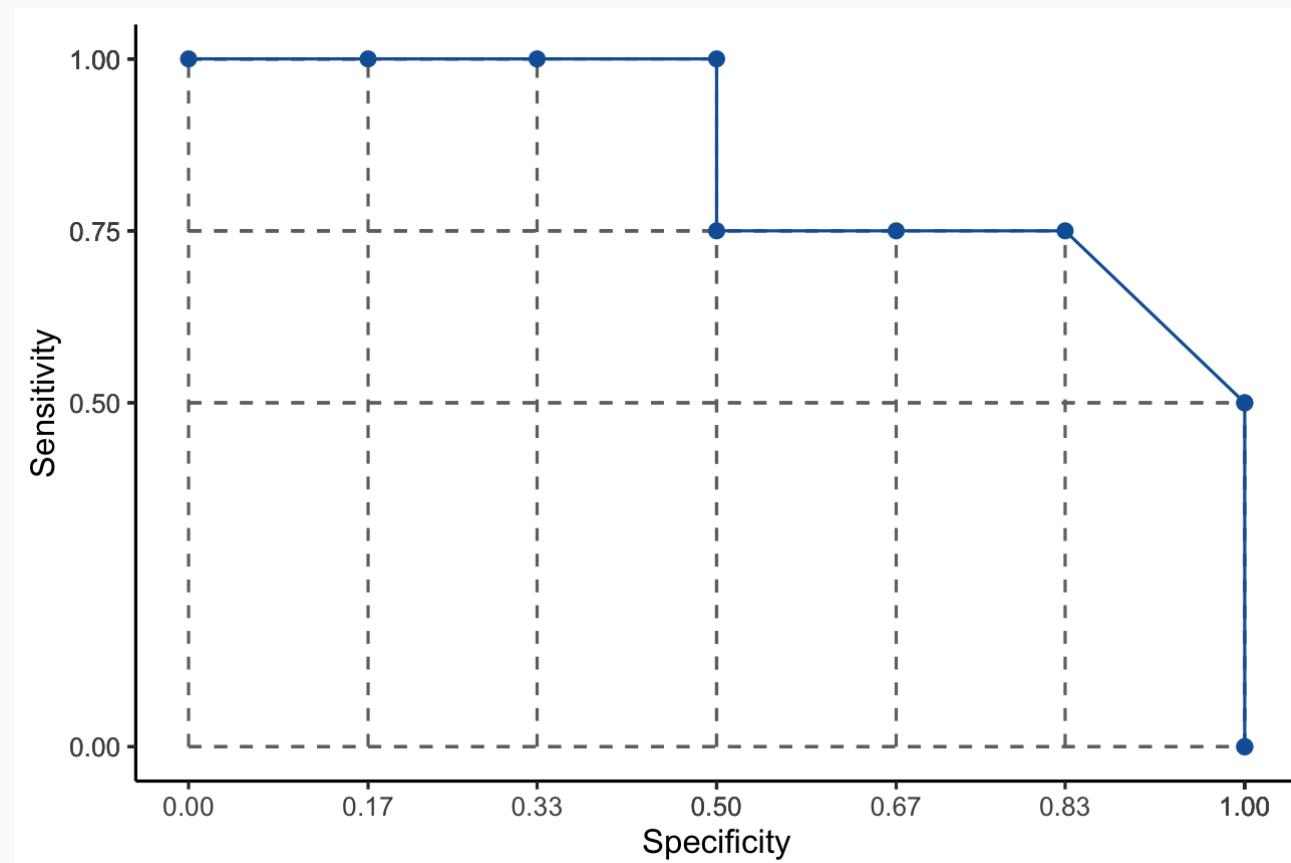
If we repeat this process for each probability value, we can obtain a list of sensitivity and specificity values

id	Predict	Observed	Cut-off	Sensitivity	Specificity
2	0.05	No	P >0.05	1.00	0.17
3	0.10	No	P >0.1	1.00	0.33
1	0.15	No	P >0.15	1.00	0.50
5	0.30	Yes	P >0.3	0.75	0.50
8	0.40	No	P >0.4	0.75	0.67
6	0.52	No	P >0.52	0.75	0.83
4	0.55	No	P >0.55	0.50	1.00
9	0.55	Yes	P >0.55	0.50	1.00
7	0.60	Yes	P >0.6	0.00	1.00
10	0.60	Yes	P >0.6	0.00	1.00

Receiver Operating Characterictic (ROC) Curve

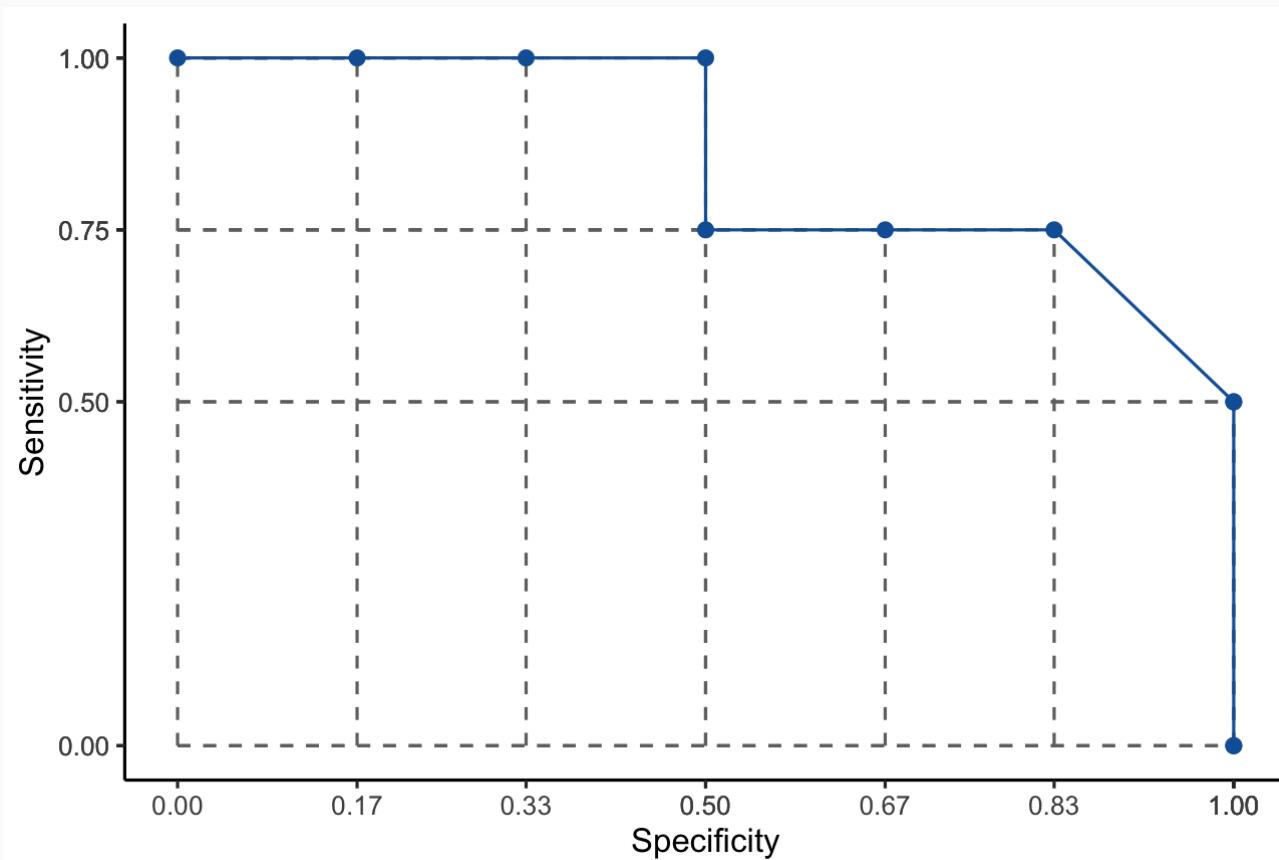
A curve linking all the sensitivity against the specificity values

Sens	Spec
1.00	0.17
1.00	0.33
1.00	0.50
0.75	0.50
0.75	0.67
0.75	0.83
0.50	1.00
0.50	1.00
0.00	1.00
0.00	1.00



Area Under the [ROC] Curve (AUC / AUROC)

What is the AUC?



Area Under the [ROC] Curve (AUC / AUROC)

What is the AUC?

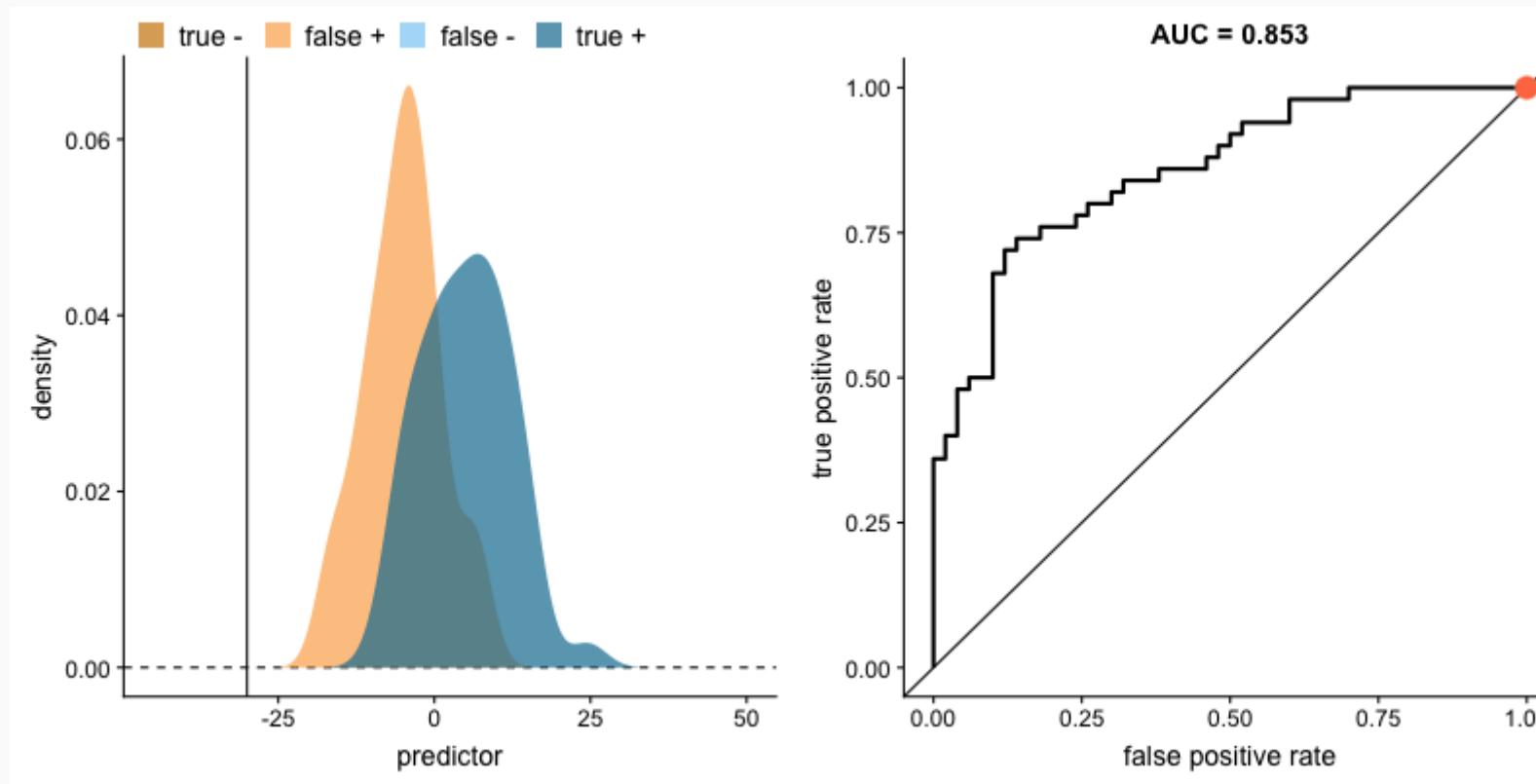
Sample calculation with **yardstick** package in R

```
# df = the dataset shown in previous slides
roc <- yardstick::roc_auc(df, truth = Observed, Predict)
roc
```

```
## # A tibble: 1 × 3
##   .metric .estimator .estimate
##   <chr>   <chr>       <dbl>
## 1 roc_auc binary     0.854
```

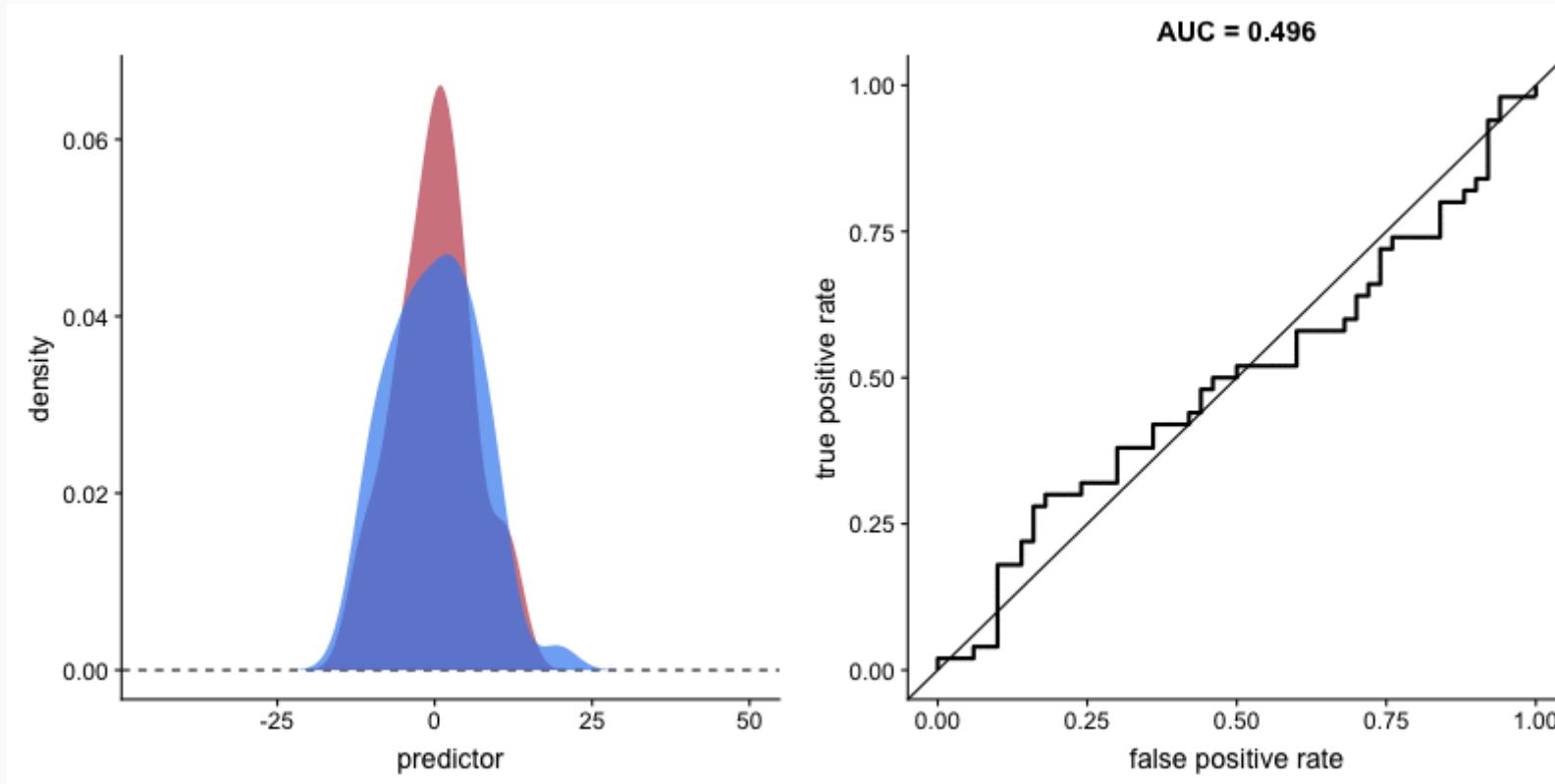
AUC = 0.8541667

AUC and the distributions of predictors in the two outcome groups at different cut-off values



by Dariya Sydykova ([follow link for more info](#))

AUC as a measure of model discrimination



by Dariya Sydykova ([follow link for more info](#))

What does AUC tell us?

- AUC estimates the **probability that a randomly chosen observed “yes” was assigned a higher probability than a randomly observed “no”** by the model
- Real world models will have **AUC from 0.5 to 1**. A value closer to 1 indicates better performance in separating "yes" and "no".
- For binary classification, AUC is equal to **concordance (C) statistic**

How do we come up with predictions?

- We propose a statistical model for the **probability of the event happening** $P(Y_i = 1)$ depending on the other variables
- For example a **logistic model**:

$$\log\left(\frac{P(Y_i = 1)}{1 - P(Y_i = 1)}\right) = \beta_0 + \beta_1 X_i + \beta_2 Z_i + \dots \quad (1)$$

- We need a **training set** where we can observe all the variables Y_i, X_i, Z_i, \dots to estimate the **coefficients** $\beta_0, \beta_1, \beta_2, \dots$
- Once we have the coefficients that best fit the data we can **calculate the predicted risk for each individual i**

$$\hat{P}(Y_i = 1) = \frac{e^{\hat{\beta}_0 + \hat{\beta}_1 X_i + \hat{\beta}_2 Z_i + \dots}}{1 + e^{\hat{\beta}_0 + \hat{\beta}_1 X_i + \hat{\beta}_2 Z_i + \dots}} \quad (2)$$

Dataset for model development & model validation

Internal validation

- The validity of claims for the underlying population where the data originated from (reproducibility)
- Split sample validation: split dataset randomly into training (for model development) and test set (for validation)
- Other methods: cross validation and bootstrap resampling

External validation

- Generalizability of claims to 'plausibly related' populations not included in the initial study population (transportability)
- e.g. temporal or geographical validation

A larger example with 2000 individuals

We will use the variables `Age`, `Sex`, `SBP`, and `BMI` to predict if the person will be dead (`Death = 1`) or alive (`Death= 0`) in 5 years time

	id	Age	SBP	BMI	Sex	Death	
	1	47	116.8	25.6	Female	Alive	
	2	71	113.8	21.1	Male	Dead	
	3	41	130.7	25.6	Male	Alive	
	4	71	118.2	25.9	Male	Alive	
	5	54	120.3	20.7	Male	Alive	
	6	67	126.4	22.8	Male	Alive	
	7	71	129.3	32.9	Female	Dead	
	8	73	117.4	27.5	Male	Alive	
	
	2000	46	111.1	24	Male	Alive	
+-----+							

Model M1: Logistic regression

Stata command:

```
logistic dead age sex sbp bmi
```

Logistic regression				Number of obs = 2,000		
LR chi2(4) = 377.64						
Prob > chi2 = 0.0000						
Log likelihood = -945.62964				Pseudo R2 = 0.1664		

dead	Odds Ratio	Std. Err.	Z	P> z	[95% Conf. Interval]	
-----	-----	-----	-----	-----	-----	
age	1.09391	.0062246	15.77	0.000	1.081778	1.106178
sex	1.301071	.1484571	2.31	0.021	1.040341	1.627145
sbp	1.050522	.0061981	8.35	0.000	1.038444	1.062741
bmi	1.025531	.0195045	1.33	0.185	.9880064	1.06448
_cons	1.39e-06	1.38e-06	-13.52	0.000	1.96e-07	9.81e-06
-----	-----	-----	-----	-----	-----	

Note that BMI is not statistically significant ($P = 0.185$)

Make predictions from Model M1

Create variable: **logit of the probability of death - equation (1)**

```
predict m1lp, xb
```

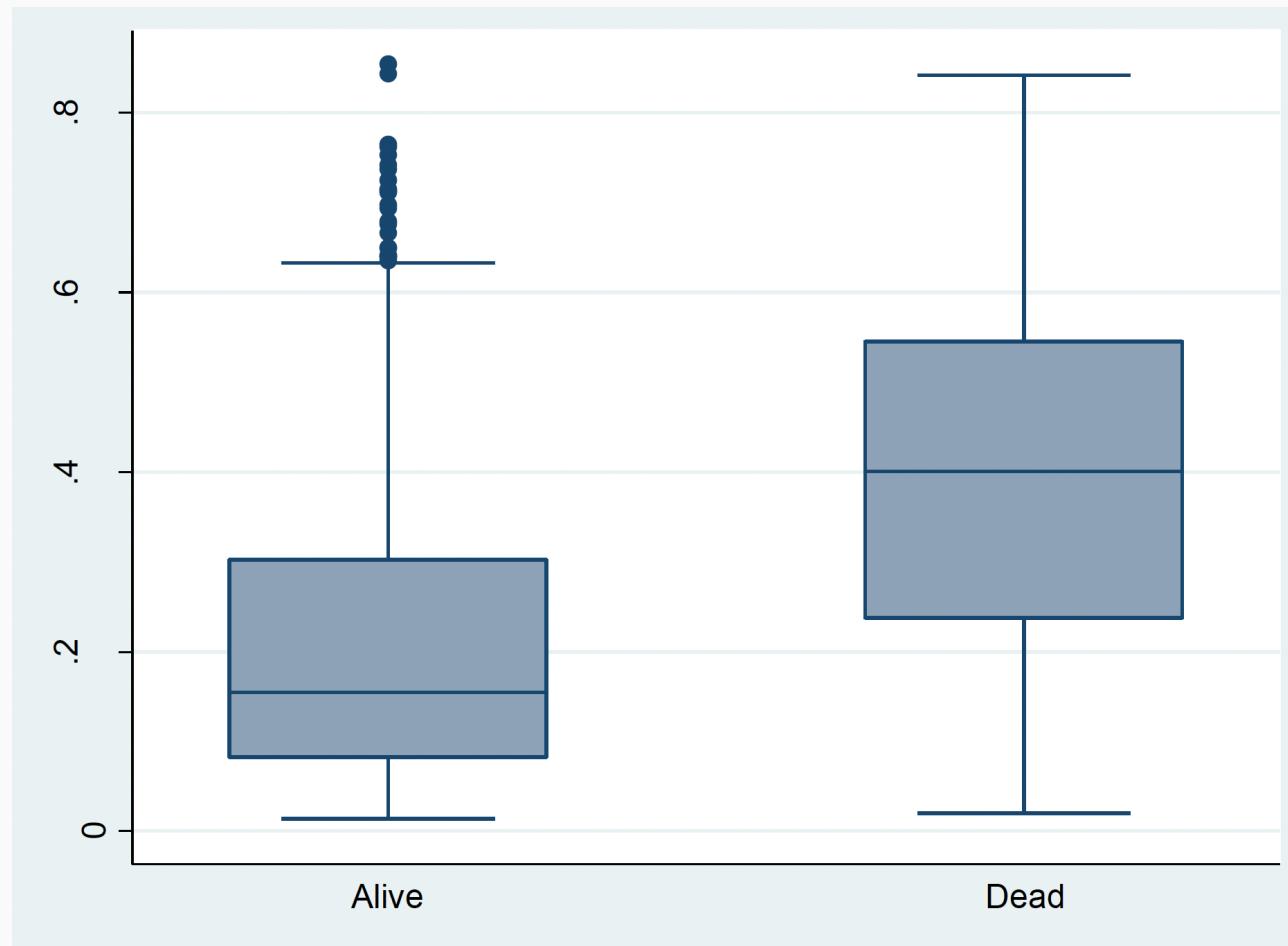
Create variable: **predicted probability of death - equation (2)**

```
predict m1pr
```

+-----+		id	age	sbp	bmi	sex	dead	m1lp	m1pr	

		10	46	111.1	24	Male	Alive	-3.014752	.0467639	
		11	79	117.5	28.7	Male	Dead	.381197	.594162	
		12	72	113.2	24.2	Male	Alive	-.572492	.3606619	
		13	54	123.4	26.1	Female	Alive	-1.900696	.1300298	
		14	45	105.7	24.7	Female	Alive	-3.616203	.0261807	

Predicted probability of death in **dead** and **alive** group



Model calibration

Evaluate **goodness of fit** with **Hosmer-Lemeshow test**

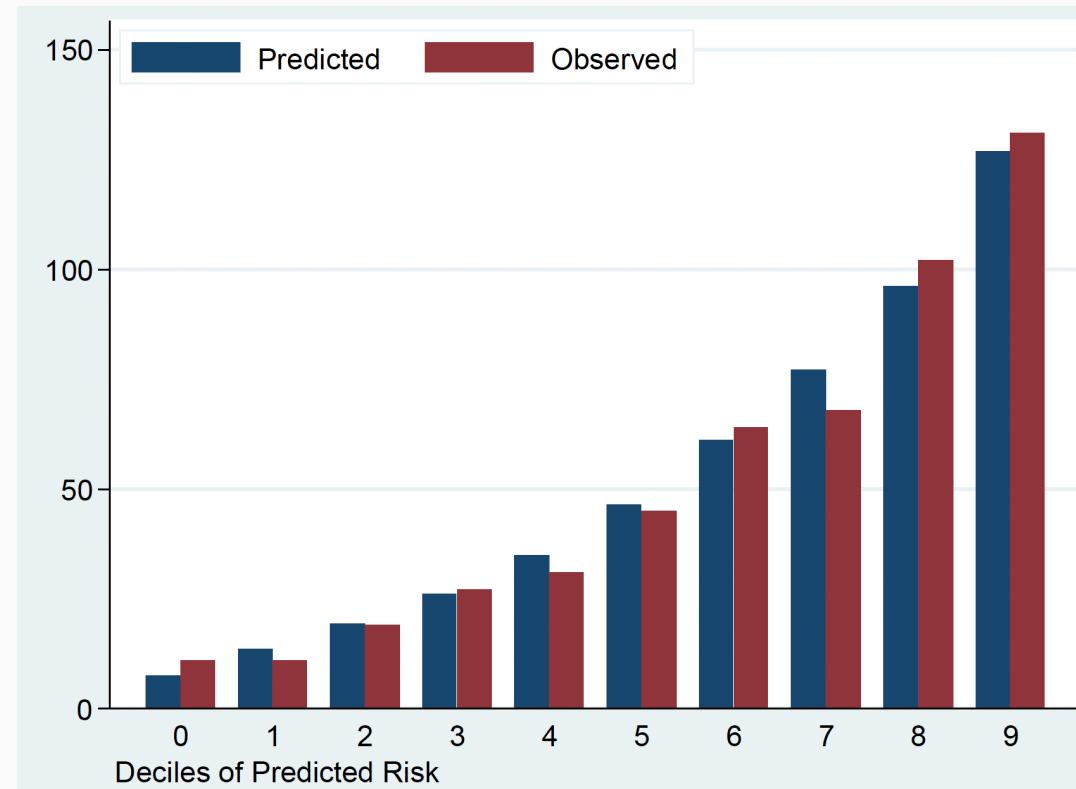
`estat gof, group(10) table`

Logistic model for dead, goodness-of-fit test (Table collapsed on quantiles of estimated probabilities)						
Group	Prob	Obs_1	Exp_1	Obs_0	Exp_0	Total
1	0.0520	11	7.4	189	192.6	200
2	0.0831	11	13.6	189	186.4	200
3	0.1133	19	19.3	181	180.7	200
4	0.1504	27	26.1	173	173.9	200
5	0.2011	31	35.0	169	165.0	200
6	0.2670	45	46.4	155	153.6	200
7	0.3460	64	61.1	136	138.9	200
8	0.4277	68	77.0	132	123.0	200
9	0.5384	102	96.2	98	103.8	200
10	0.8544	131	126.7	69	73.3	200

Hosmer-Lemeshow chi2(8) = 5.98 Prob > chi2 = 0.6499

Model calibration

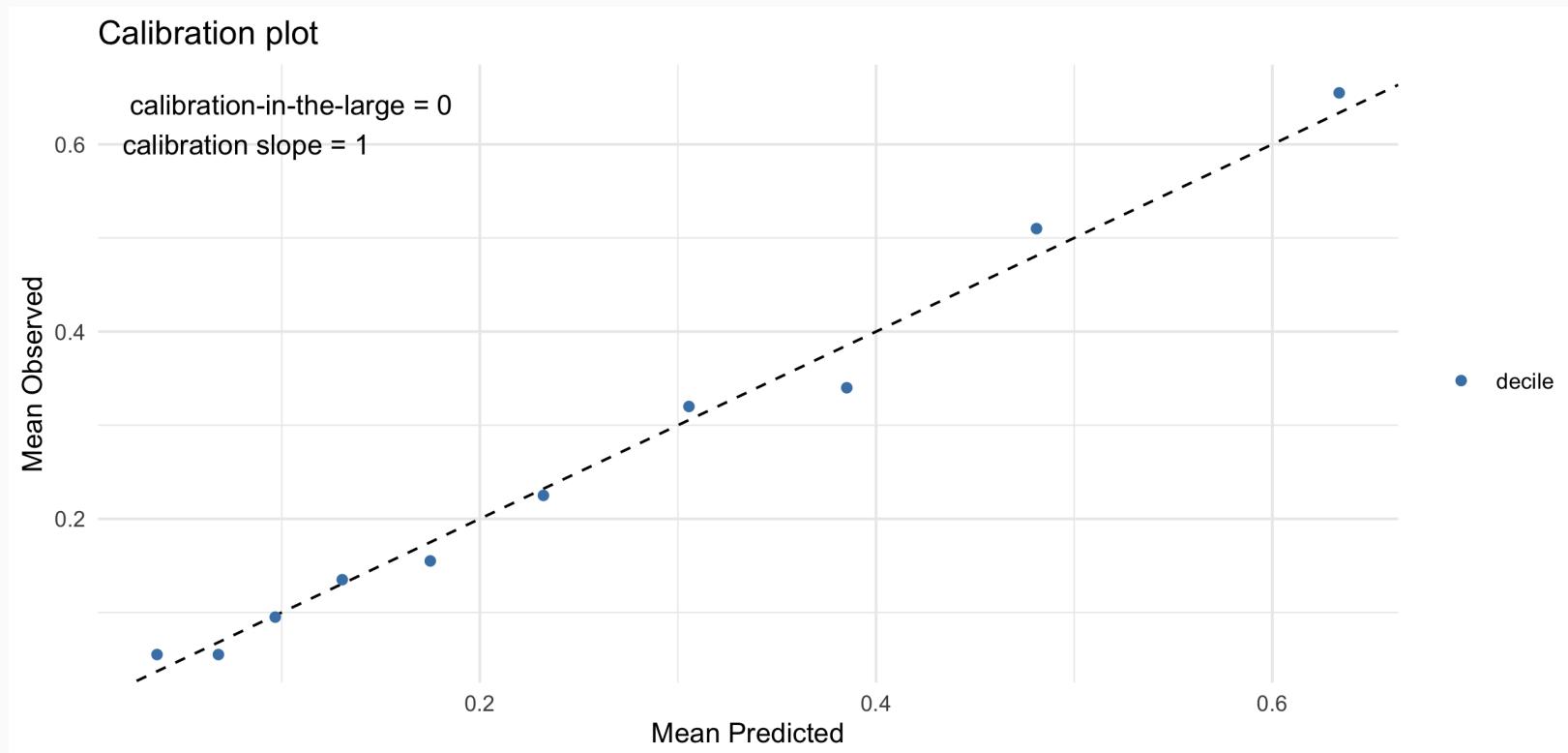
Goodness of fit: Observed and expected events by deciles of risk



Limitation: Hosmer-Lemeshow test can not tell the direction of miscalibration and relies on arbitrary grouping

Model calibration with calibration plot

- **Calibration-in-the-large**: compares average predicted risk with observed risk (**0**: ideal, **<0**: underestimation, **>0**: overestimation)
- **Calibration slope**: evaluate spread of estimated risk (**1**: ideal, **<1**: too extreme, **>1**: too moderate)



Further discussion: Steyerberg EW, Vergouwe Y (2014) and Calster BV *et al.* (2019)

Contingency table: cut-off $P(Y = 1) \geq 0.3$

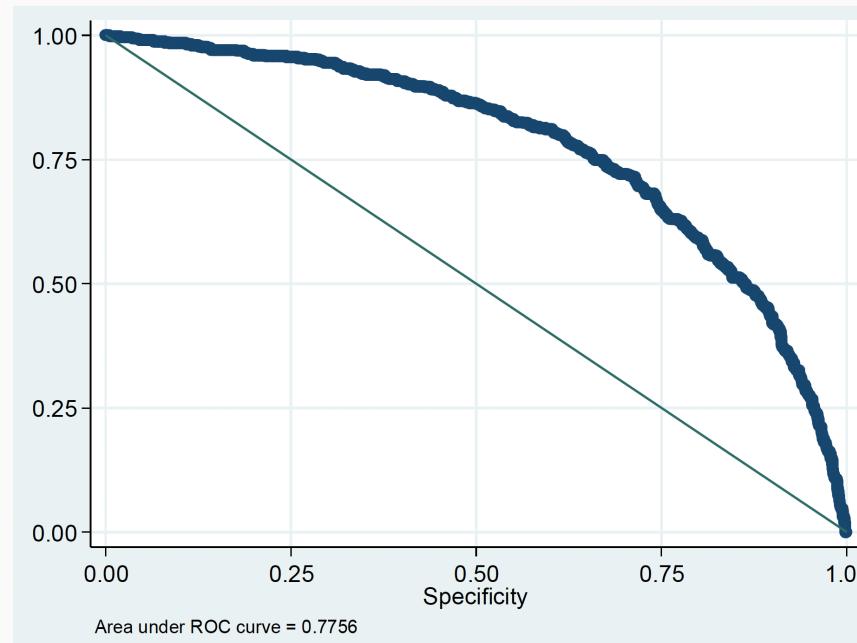
estat classification, cutoff(0.3)

		True			
Classified		D	$\sim D$	Total	
+		333	375	708	
-		176	1116	1292	
Total		509	1491	2000	

Classified + if predicted $\Pr(D) \geq .3$

Sensitivity	$\Pr(+ D)$	65.42%
Specificity	$\Pr(- \sim D)$	74.85%
Positive predictive value	$\Pr(D +)$	47.03%
Negative predictive value	$\Pr(\sim D -)$	86.38%
False + rate for classified +	$\Pr(\sim D +)$	52.97%
False - rate for classified -	$\Pr(D -)$	13.62%
Correctly classified		72.45%

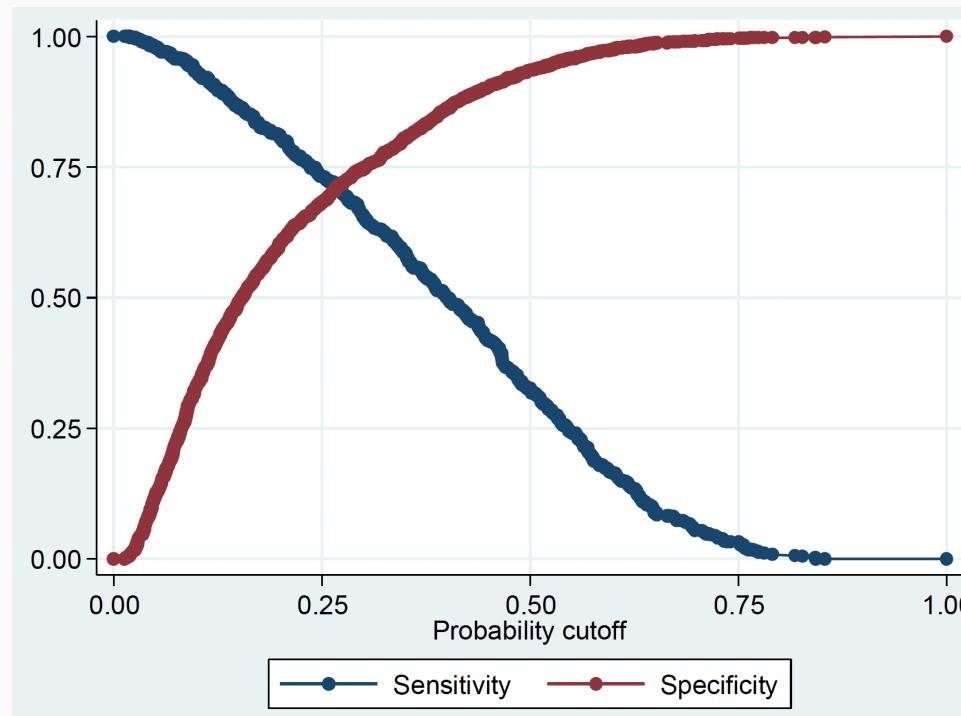
ROC curve from model *M1*



$$\text{AUC} = 0.78$$

There is a 78% probability that a person who died is assigned a higher predicted risk by the model than a person was alive by the end of the follow up

Sensitivity and Specificity for model M_1 by cut-off value



Plotting **sensitivity and specificity against cut-off value** can help to select the most appropriate cut-off

In practice, this trade-off often needs to be decided on a **case-by-case** basis

Evaluating prediction model performance

Calibration

- The agreement between the predicted & observed outcomes
- For a group of patients with 10% predicted risk, do 10% experience the outcome?
- e.g. Goodness of fit test, calibration curve

Discrimination

- The ability of the model to distinguish between *positive* and *negative* outcome
- e.g. AUC / C statistic

Clinical usefulness

- Does the model provide accurate predictions at the patient level that can be used to guide clinical decision making?
- e.g. **Decision curve analysis**

Summary

- Prediction modelling can be broadly categorised into **deterministic** and **probabilistic** methods
- **2×2 contingency table / confusion matrix** is useful as a first step to evaluate model performance
- **AUC** is a useful measure of the model **discrimination**
- Comparing observed and predicted risks is useful for model **calibration**
- Assessing **clinical usefulness** requires other approaches and often requires insights from ***beyond the data***

References and further reading

- Textbook: Steyerberg EW. Clinical Prediction Models: A Practical Approach to Development, Validation, and Updating. Springer, New York, NY; 2009.
- Practical article: Steyerberg EW, Vergouwe Y. Towards better clinical prediction models: seven steps for development and an ABCD for validation. Eur Heart J. 2014 Aug 1;35(29):1925–1931.
- Reporting guide: Moons KG, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD): Explanation and Elaboration. Ann Intern Med. 2015;162:W1–W73.
- Comparison with machine learning: Breiman L. Statistical Modeling: The Two Cultures (with comments and a rejoinder by the author). Stat Sci. Institute of Mathematical Statistics; 2001 Aug;16(3):199–231.