

Risk Prediction

Advanced Statistical Analysis

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based on slides by L. Palla, D. Prieto, and E. Williamson

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these slides are available online at:

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

Learning objectives

- Describe the difference between **deterministic** and **probabilistic** methods for prediction
- Create **2x2 contingency table**
- Explain how **ROC curves** are calculated and how they relate to **sensitivity** and **specificity**
- Understand key measures to evaluate **model performance**

The problem

Consider individuals in which a certain **binary event Y** might happen (0=no, 1=yes) by a certain point in time. We also have a set of other variables for each individual.

Some examples:

- A group of patients about to have a surgery: Some will **develop complications after the surgery** and some will not. We have data on their age, sex , severity of disease, comorbidities etc.
- A group of pregnant women: some will **have a child with a malformation** , some will not. We have data on the mothers ' age , medications, diagnostics, life style, etc.

In all these cases we do not know for sure which individuals will get the event.

What we want to do

Ideally we would like to predict who is **going to develop the event**. This can be done in two ways:

- **Deterministic:**

Classify each individual in one of the two possible outcomes: develop the event or not. This is often used in **(Supervised) Machine Learning**

- **Probabilistic:**

Assign each individual a **probability** of developing the event. (This is often used in **Biostatistics** and is known as **Risk Prediction**

Both strategies use data we collected for each individual (age, sex, diagnoses, etc.)

Example

Who will develop myocardial infarction in the next 5 years?

Consider we have the following data

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			

Classify deterministically

Use previous algorithm:

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

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		

Predict probabilistically

Use previous algorithm:

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

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

Observe

... after 5 years follow-up

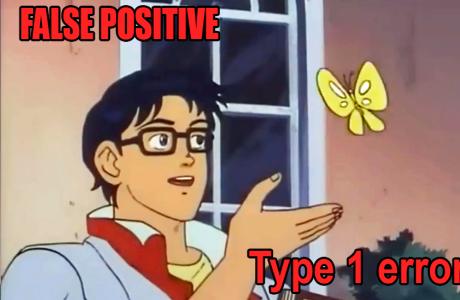
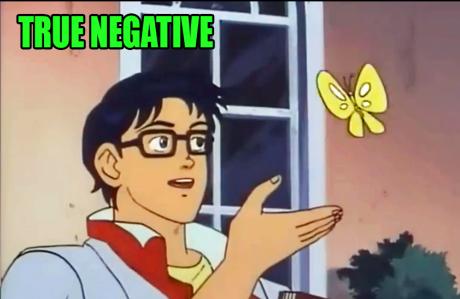
Compare predictions with observed events

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

- Our models have predicted some individuals well but not others
- We want to have a general measure of how good or bad our algorithms are by **comparing the predictions with the actual observed values.**
- This will be done differently for a classification algorithm than for a prediction algorithm.

2x2 Contingency table / Confusion matrix

		OBSERVED
		+
PREDICTED	+	TRUE POSITIVE  Is this a virus?
	-	FALSE POSITIVE  Is this a virus? Type 1 error
-	+	FALSE NEGATIVE  Is this not a virus? Type 2 error
	-	TRUE NEGATIVE  Is this not a virus?

Sensitivity

- a.k.a **True Positive Rate, Recall**
- Probability of **correctly predicting the event**
- Given you are someone who will **have the event**, what is the probability of a **positive classification?**

		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 **True Negative Rate**
- Probability of correctly predicting the *non-event*
- Given you are someone who will *not* have the event, what is the probability of a **negative classification**?

		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 **having the event** given a **positive classification**
- **Positively correlated** with **disease prevalence**

		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 *not* having the event given a **negative classification**
- **Negatively correlated** with **disease prevalence**

		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

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

Sensitivity = ?

PPV = ?

Specificity = ?

NPV = ?

Comparing *classifications* with observations

		Observed		
Predicted	+	-	Total	
+	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

Order by risk 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		
Predicted				Total
	+	-		
+	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 the classification algorithm

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

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

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

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

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

Same contingency table as the classification algorithm

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		
Predicted				Total
	+	-		
+	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 the classification algorithm

All cut-off points

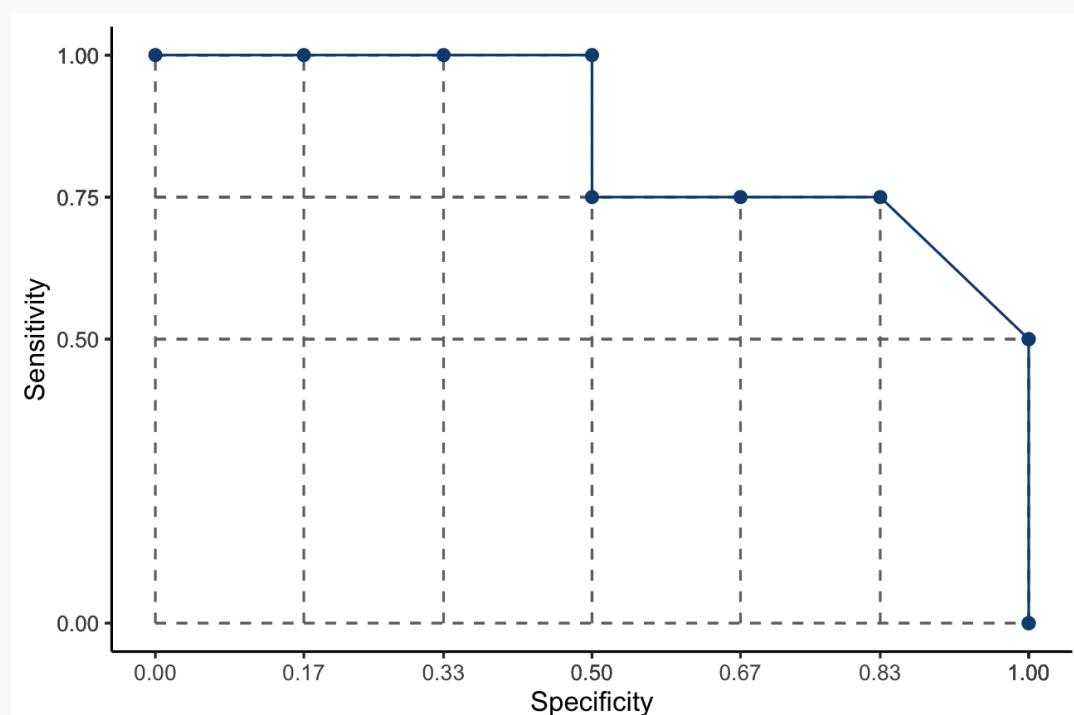
If we repeat this process for each probability value, we can obtain a list of sensitivity and specificity values

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 Characteristic (ROC) Curve

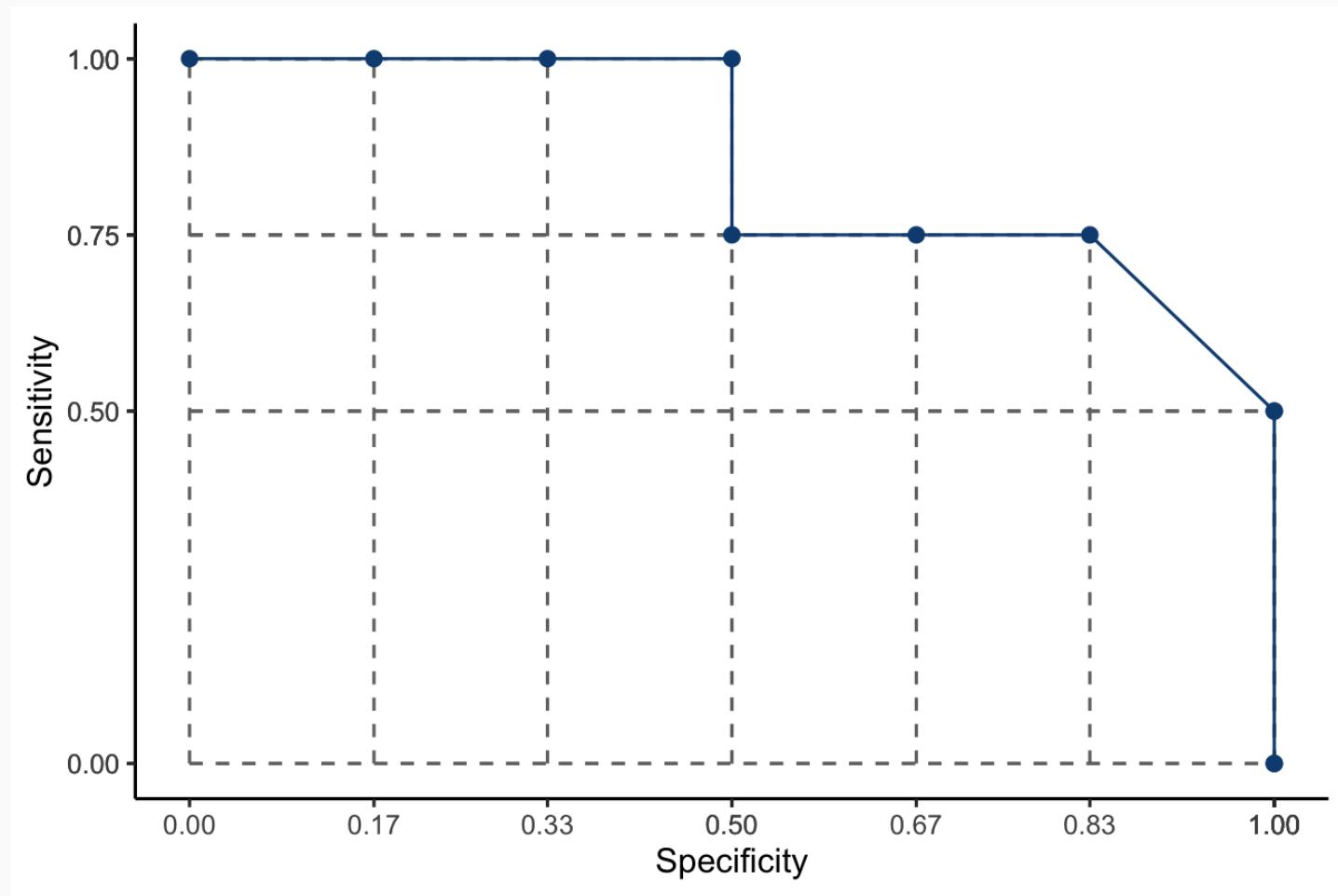
A curve linking all the sensitivity against the specificity values

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?

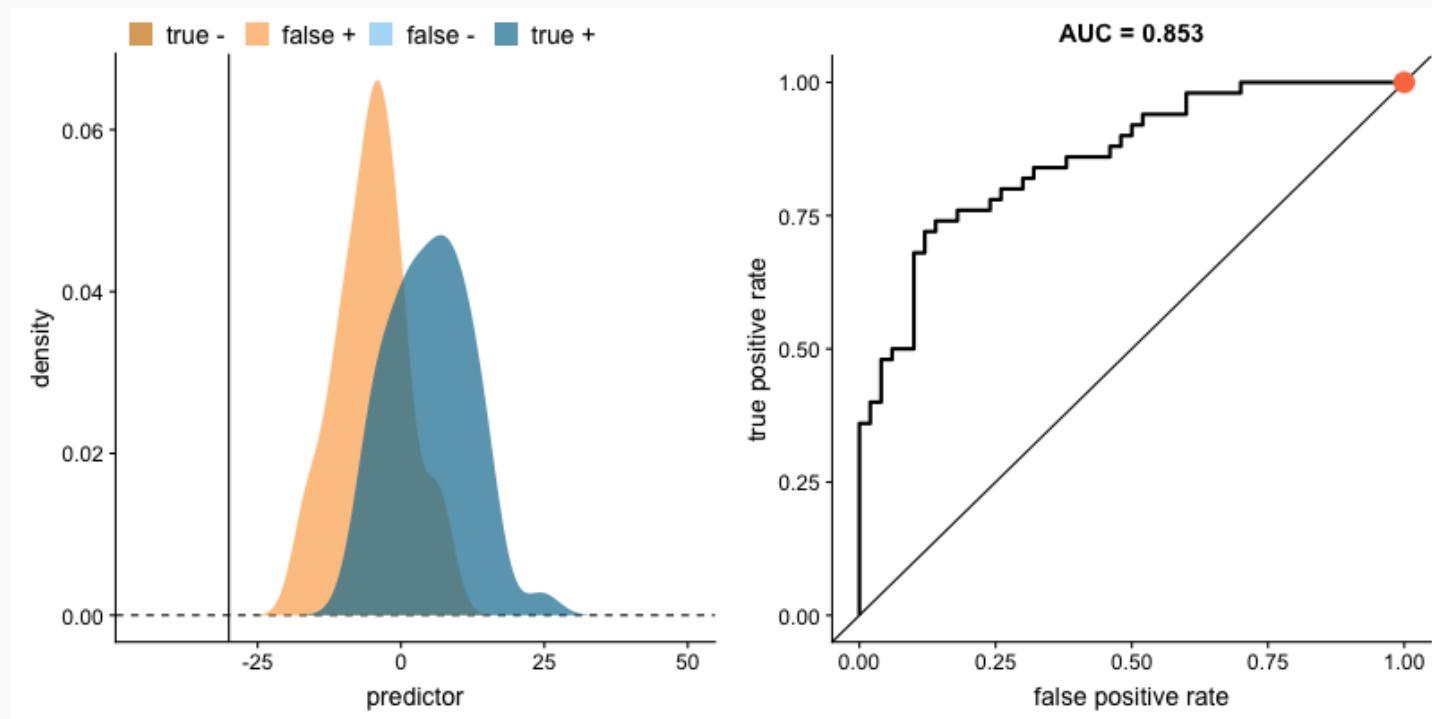
Sample calculation with **yardstick package** in R

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

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

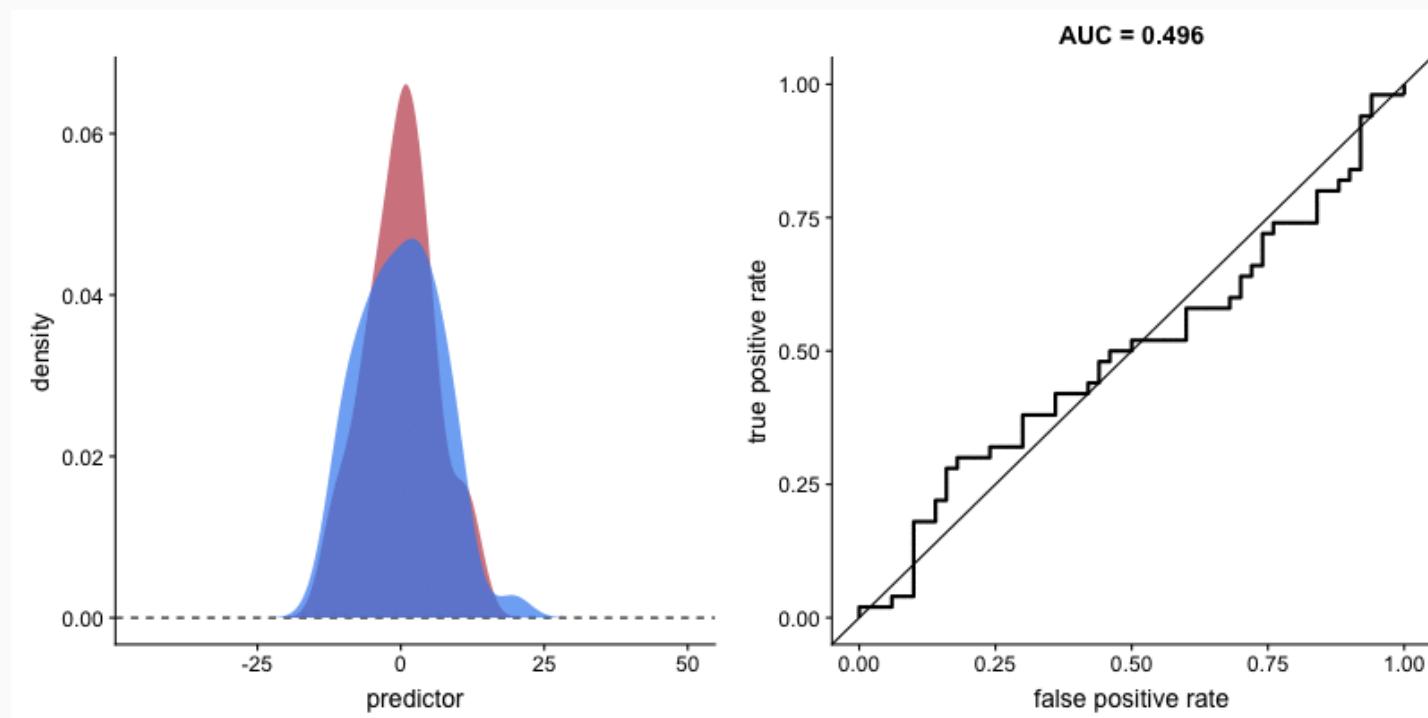
AUC = 0.8541667

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



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

AUC as a measure of model discrimination



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

What does AUC tell us?

- AUC can be interpreted as the **probability that an observed "yes" was assigned a higher probability than an observed "no"**
- If the model was **useless** (same as assigning probabilities "at random"), then an observed "yes" would have only 50% chances of having higher predicted risk than an observed "no" (**AUC = 0.5**)
- **AUC = 1** for a model that would give higher predictions to all the observed "yes" than to all the observed "no" (**perfect separation** between "yes" and "no").
- Any real world model will have **AUC between 0.5 and 1**. 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**

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

Model validation

Internal validation

- The validity of claims for the underlying **population that the data originated from (reproducibility)**
- **Split sample validation:** split dataset randomly into **training** (for model development) and **test** set (for validation)
👉 **today's practical**
- 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

Steyerberg EW, Vergouwe Y (2014)

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 ($P = 0.185$) but let's stay with this model for now

Make predictions from Model M1

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

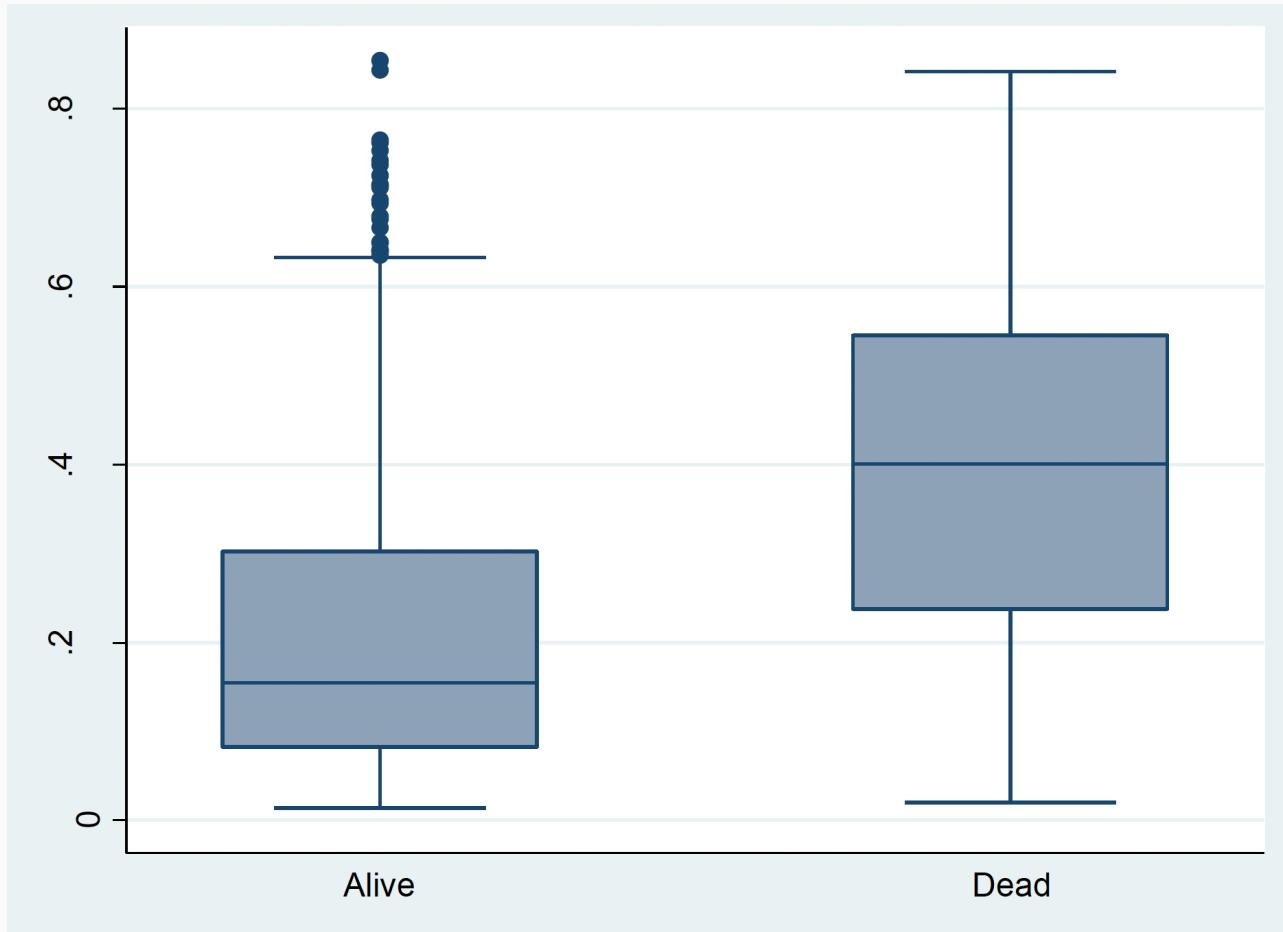
```
predict m1lp, xb
```

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
```

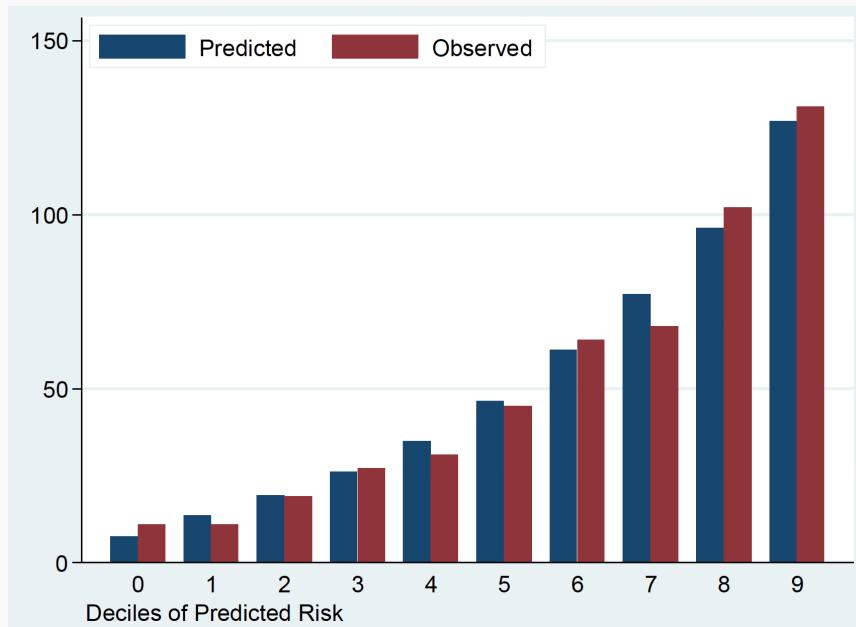
Logistic model for dead, goodness-of-fit test
(Table collapsed on quantiles of estimated probabilities)

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



Note: Hosmer-Lemeshow test can not tell the direction of micalibration and relies on arbitrary grouping (see Steyerberg EW, Vergouwe Y (2014) for discussion on the limitations and suggested alternatives)

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

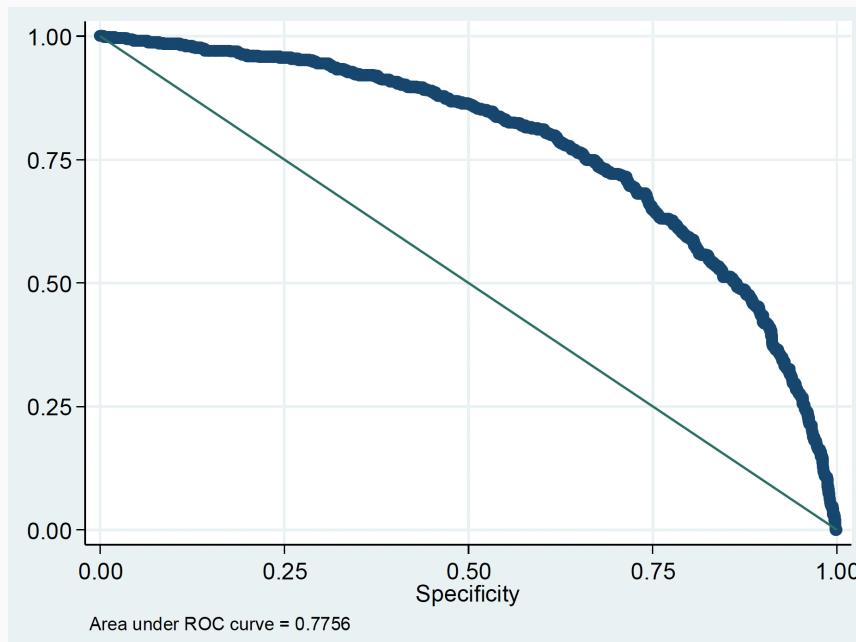
estat classification, cutoff(0.3)

		True			
Classified		D	~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%

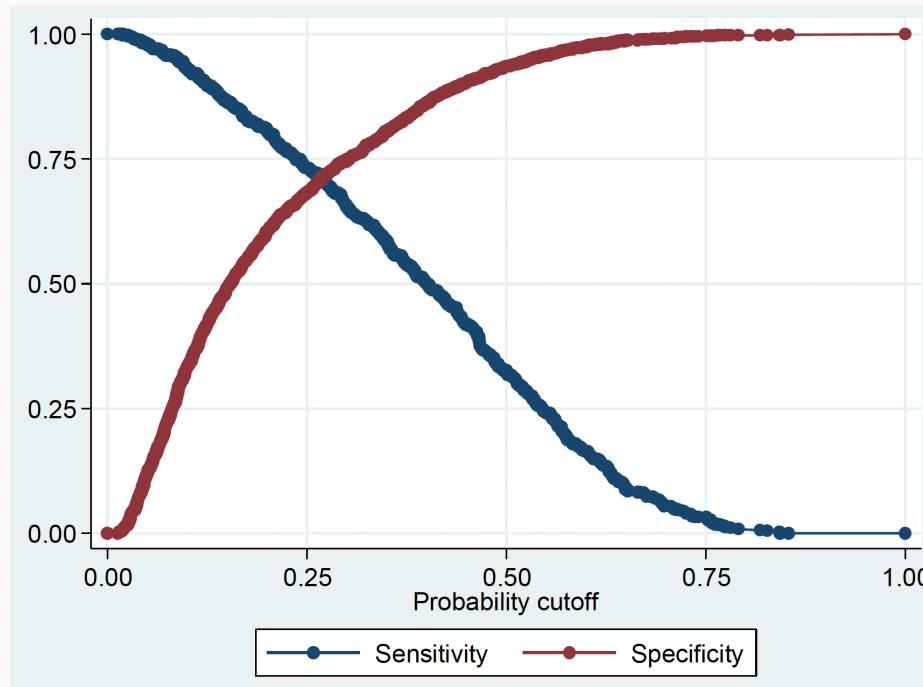
ROC curve from model M_1



$$\text{AUC} = 0.78$$

There is a 78% probability that a person that actually dies gets a higher predicted risk by the model than a person that did not die 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

For discussion

Consider the following scenarios:

- Screening for diabetes & pre-diabetes
- Diagnosing coeliac disease
- Screening suspect for coronavirus infection COVID-2019

Which model would you choose:

1. High-sensitivity, low-specificity
2. Low-sensitivity, high-specificity

Key measures to evaluate model performance

Calibration

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

Discrimination

- The ability of the model to distinguish between "event" and "non-event"
- 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 x 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

- 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.
- 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.
- ROC curve animation by Dariya Sydykova
- A Twitter thread on AUC by Cecile Janssens