Survival modeling using deep learning, machine learning and statistical methods: A comparative analysis for predicting mortality after hospital admission

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Background

- Survival analysis often relied on **Cox Proportional hazards**.
- Other techniques include machine learning and deep learning approach.
- Previous literature focused on comparison based on mathematical theory
  - Lack of comparison of traditional vs ML model
  - Lack of comparison of calibration

Objective

- Compare various survival analysis techniques:
  - **Traditional statistic**
  - **Machine learning**
  - **Deep learning**
- On 90-day all-cause mortality after hospital admission.

Method

- **Dataset:**
  - Retrospective cohort from Singapore General Hospital
  - **Inclusion criteria:**
    - All patients hospitalized after visiting the emergency department
    - From January 2017 - December 2019
  - **Exclusion criteria:**
    - Age < 21 years
    - Incomplete medical record
  - **Total 124,873 patients**
- **Data split:**
  - Training cohort 70%
  - Validation cohort 10% (for parameter tuning)
  - Test cohort 20%

Characteristic	Over all	Training cohort	Validation cohort	Test cohort
No. of participants	124,873	87,412	12,487	24,974
Age (years)	65.38 (16.64)	65.34 (16.62)	65.54 (16.69)	65.42 (16.69)
Gender				
Male	61,845 (49.5%)	43,223(49.4%)	6,250 (50.1%)	12,372 (49.5%)
Female	63,018 (50.5%)	44,189 (51.6%)	6,237 (49.9%)	12,602 (50.5%)
Race				
Chinese	92,360 (74.0%)	64,656 (74.0%)	9,251 (74.1%)	18,453 (73.9%)
Indian	12,856 (10.3%)	8,975 (10.3%)	1,335 (10.7%)	2,546 (10.2%)
Malay	14,668 (11.7%)	10,266 (11.7%)	1,398 (11.2%)	3,004 (12.0%)
Others	4,989 (4.0%)	3,515 (4.0%)	503 (4.0%)	971 (3.9%)
Triage class				
P1	28,630 (22.9%)	20,005 (22.9%)	2,887 (23.1%)	5,738 (23.0%)
P2	80,248 (64.3%)	56,165 (64.3%)	8,052 (64.5%)	16,031 (64.2%)
P3 & P4	15,995 (12.8%)	11,242 (12.9%)	1,548 (12.4%)	3,205 (12.8%)
Diastolic blood pressure (mmHg)	72.54 (14.38)	72.51 (14.30)	72.68 (14.49)	72.60 (14.59)
Systolic blood pressure (mmHg)	136.86 (27.50)	136.76 (27.40)	137.34 (27.48)	136.97 (27.86)
FIO2				
=21	124,315 (99.6%)	87,021 (99.6%)	12,431 (99.6%)	24,863 (99.6%)
>21	558 (0.4%)	391 (0.4%)	56 (0.4%)	111 (0.4%)
Pulse (bpm)	85.47 (18.33)	85.50 (18.33)	85.35 (18.48)	85.42 (18.26)
Respiratory rate (cpm)	18.15 (2.11)	18.15 (2.11)	18.13 (2.13)	18.16 (2.11)
SAO2 (%)	97.42 (4.14)	97.42 (4.15)	97.40 (4.34)	97.43 (4.00)
Temperature (°C)	36.71 (0.81)	36.71 (0.82)	36.70 (0.81)	36.70 (0.82)
Blood albumin (g/L)	38.31 (3.80)	38.31 (3.79)	38.30 (3.81)	38.28 (3.84)
Basophils absolute (10^9/L)	0.05 (0.25)	0.04 (0.20)	0.04 (0.11)	0.05 (0.40)
Basophil cell (%)	0.47 (0.33)	0.47 (0.33)	0.47 (0.34)	0.47 (0.33)
Bicarbonate (mmol/L)	23.18 (3.60)	23.16 (3.60)	23.22 (3.57)	23.21 (3.62)
Chloride (mmol/L)	101.72 (5.27)	101.71 (5.25)	101.81 (5.25)	101.68 (5.34)
Serum creatinine (μmol/L)	144.12 (188.33)	143.98 (188.35)	143.33 (189.38)	145.02 (187.75)
Eosinophils absolute (10^9/L)	0.18 (0.39)	0.17 (0.40)	0.17 (0.28)	0.18 (0.41)
Eosinophil cell (%)	2.00 (2.75)	1.99 (2.74)	2.02 (2.74)	2.00 (2.77)
Blood glucose (mmol/L)	8.27 (4.73)	8.28 (4.77)	8.21 (4.47)	8.26 (4.74)
Hematocrit (%)	36.66 (6.52)	36.68 (6.53)	36.63 (6.51)	36.61 (6.50)
Hemoglobin (g/dL)	12.16 (2.32)	12.17 (2.32)	12.15 (2.31)	12.14 (2.31)
Lymph absolute (10^9/L)	1.65 (2.30)	1.64 (1.63)	1.65 (1.52)	1.68 (4.00)
Lymph cell (%)	18.80 (10.37)	18.79 (10.36)	18.82 (10.34)	18.83 (10.41)
MCHB (pg/g)	29.16 (3.08)	29.15 (3.08)	29.20 (3.04)	29.17 (3.07)
MCHC (g/L)	33.10 (1.45)	33.09 (1.45)	33.10 (1.42)	33.10 (1.44)

Method

- **Primary outcome:**
  - Mortality within 90 days
    - If alive after 90 days -> right censored
      - Events (death): 12,755 (10.2%)
- **Feature selection:**
  - 60 candidates based on data availability, expert opinion and literature review
    - Diagnosis from ICD-9, ICD-10
    - Comorbidities: Linked from Charlson Comorbidity Index to ICD with algorithm by Quan et al.

Classification	Variables (Abbreviation)	Categorical/ Continuous
Demographics Information	Age	Continuous
	Gender	Categorical
	Race	Categorical
Vital signs	Triage class	Categorical
	Diastolic blood pressure (Diastolic BP)	Continuous
	Systolic blood pressure (Systolic BP)	Continuous
	Fraction of inspiration oxygen (FIO2)	Categorical
	Heart rate	Continuous
	Respiratory rate	Continuous
	Arterial oxygen saturation (SAO2)	Continuous
	Temperature	Continuous
Laboratory results	Blood albumin (ALB)	Continuous
	Basophils absolute count (BAS#)	Continuous
	Basophils cell (BAS%)	Continuous
	Bicarbonate (HCO3-)	Continuous
	Chloride (Cl-)	Continuous
	Serum creatinine (Cr)	Continuous
	Eosinophils absolute count (EOS#)	Continuous
	Eosinophils cell (EOS%)	Continuous
	Blood glucose (GLU)	Continuous
	Hematocrit (HCT)	Continuous
	Hemoglobin (HGB)	Continuous
	Lymphocytes absolute (LYMPH#)	Continuous
	Lymphocytes cell (LYMPH%)	Continuous
	Mean corpuscular hemoglobin (MCHB)	Continuous
	Mean corpuscular hemoglobin concentration (MCHC)	Continuous
	Mean corpuscular volume (MCV)	Continuous
	Mean platelet volume (MPV)	Continuous
	Monocytes absolute count (MONO#)	Continuous
	Monocytes cell (MONO%)	Continuous
	Neutrophils absolute count (NEUT#)	Continuous
	Neutrophils cell (NEUT%)	Continuous
	Platelet count (PLT)	Continuous
	Potassium (K+)	Continuous
	Red blood cell (RBC)	Continuous
	Red cell distribution width (RDW)	Continuous
	Serum sodium (Na+)	Continuous
	Total absolute count (TAC)	Continuous
	Total blood cells count (TCC)	Continuous
	Troponin T quantitative (Troponin T)	Continuous
	Blood urea nitrogen (BUN)	Continuous
	White blood cell (WBC)	Continuous
Comorbidities	Myocardial infarction (MI)	Categorical
	Congestive heart failure (CHF)	Categorical
	Peripheral vascular diseases (PVD)	Categorical
	Stroke	Categorical
	Dementia	Categorical
	Chronic pulmonary diseases (PulmonaryD)	Categorical
	Rheumatic diseases (RheumaticD)	Categorical
	Peptic ulcer disease (PUD)	Categorical
	Hemiplegia or paraplegia (Paralysis)	Categorical
	Renal diseases (Renal)	Categorical
	Malignancy	Categorical
	Liver diseases (LiverD)	Categorical
	Diabetes	Categorical
History information	Emergency admissions in the past year (ED#)	Continuous
	Inpatient admission in the past year (INP#)	Continuous
	Surgeries in the past year (SURG#)	Continuous
	HUD admission in the past year (HD#)	Continuous
	ICU admission in the past year (ICU#)	Continuous

Models

- **Traditional statistic:**
  - CoxPH
  - Step-wise CoxPH
  - Elastic net penalty Cox model
- **Machine learning:**
  - AutoScore-Survival
  - Random survival forest
  - Gradient boosting
- **Deep learning:**
  - DeepSurv
  - CoxTime
  - DeepHit

Table 1. Description of various methods

Classification	Models	Proportional hazards Assumption	Interpretability	Parameter tuning
Traditional statistical method	CoxPH model	Yes	High	No
	Stepwise CoxPH	Yes	High	No
	CoxEN	Yes	High	No
Ensemble machine learning	RSF	No	Moderate	Yes
	GBM	No	Moderate	Yes
Interpretability machine learning	AutoScore-Survival	Yes	High	Yes
Feedforward deep neural network	DeepSurv	Yes	Low	Yes
	CoxTime	No	Low	Yes
	DeepHit	No	Low	Yes

AutoScore: An Interpretable Machine Learning-Based Automatic Clinical Score Generator

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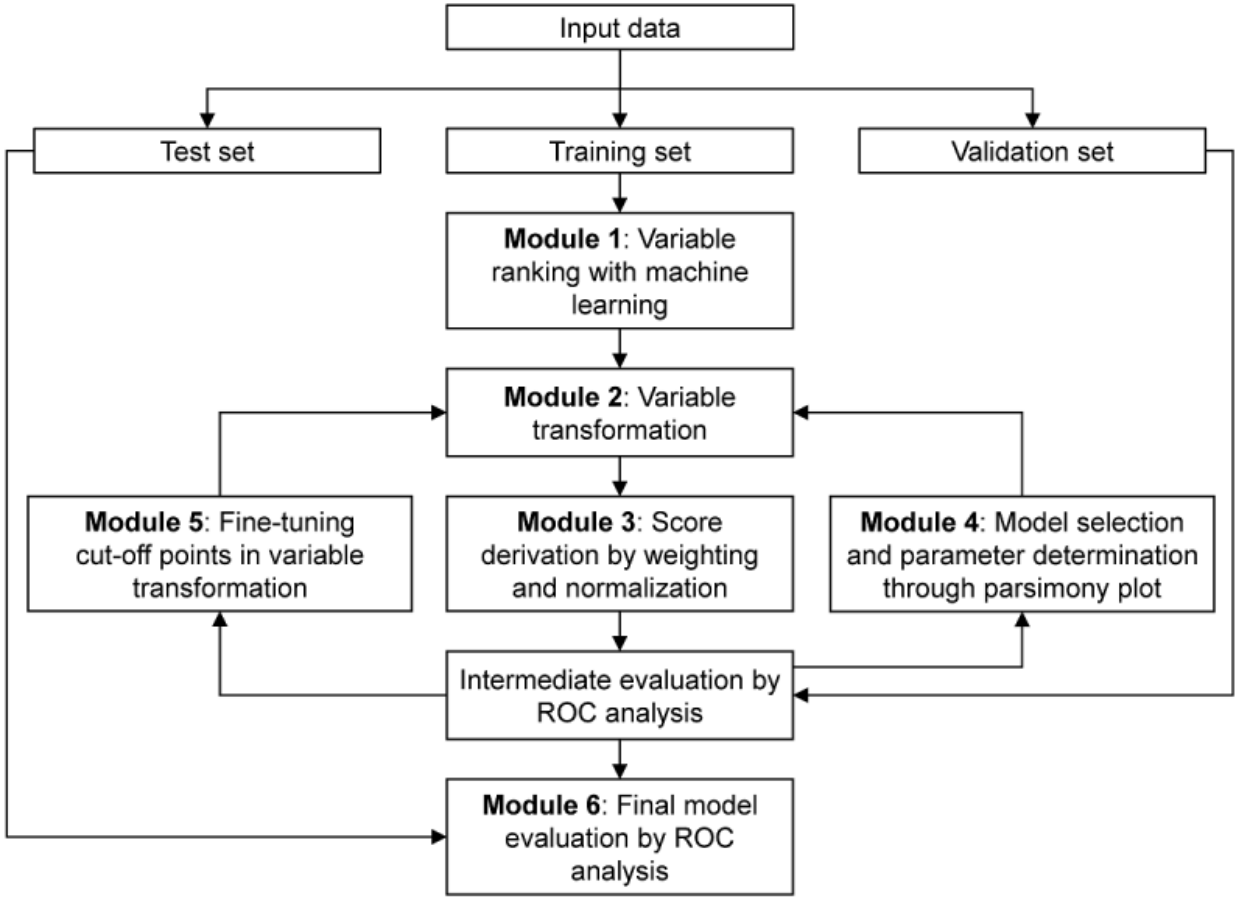
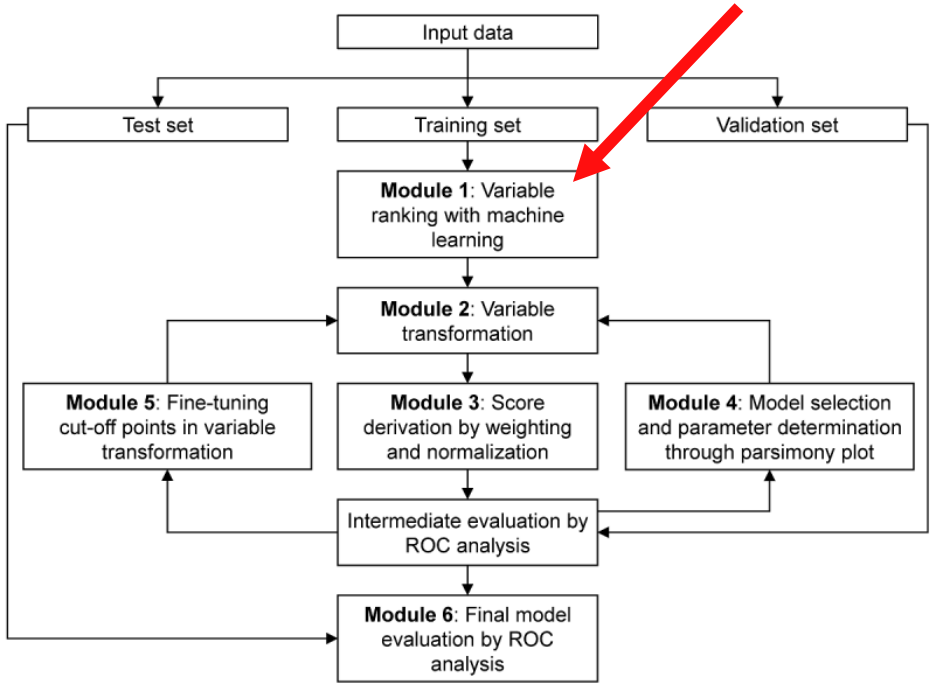
AutoScore

- A machine learning framework to automate development of clinical scoring models.



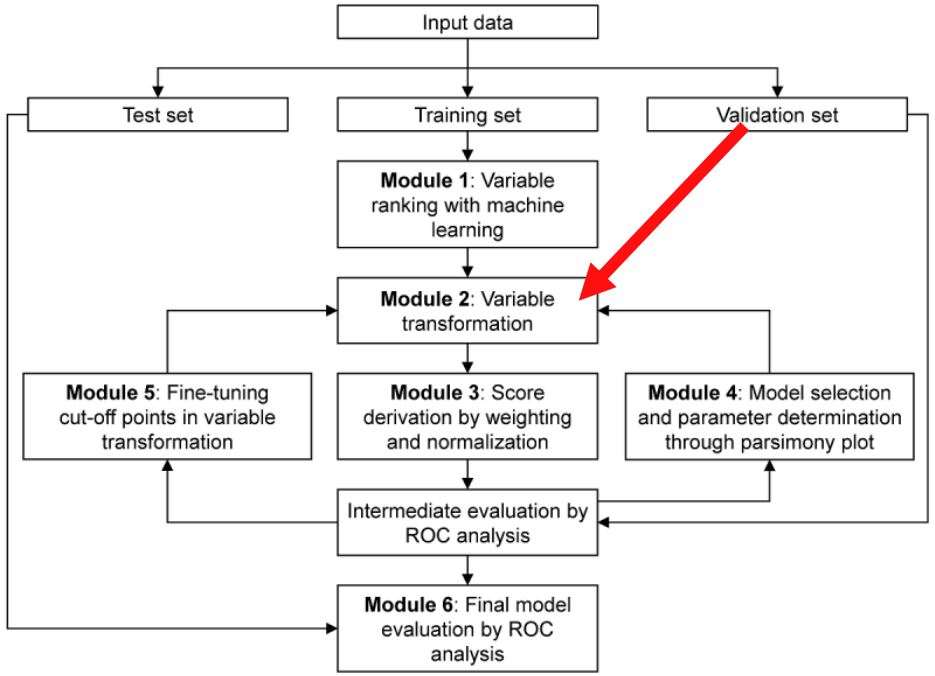
AutoScore



Module 1: **Variable ranking**

- Use random forest to rank variable importance.

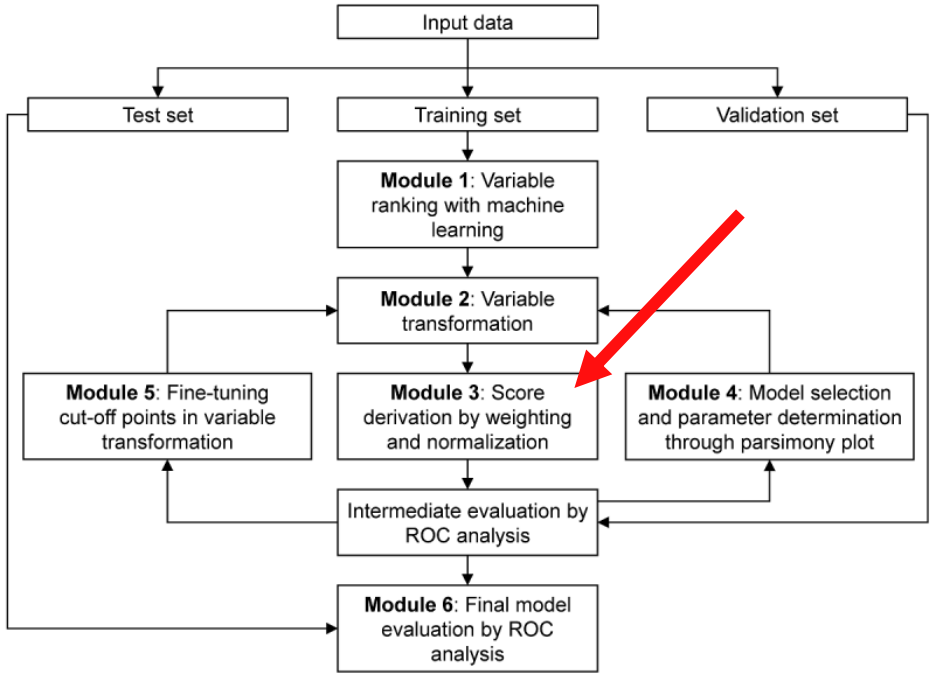
AutoScore



Module 2: Variable transformation

- Continuous variables are converted into categorical variables
  - Stratified by specific quantiles into *K* categories to develop a point-based score.
- The maximum categories (eg, *K*=5) for each variable is predefined.

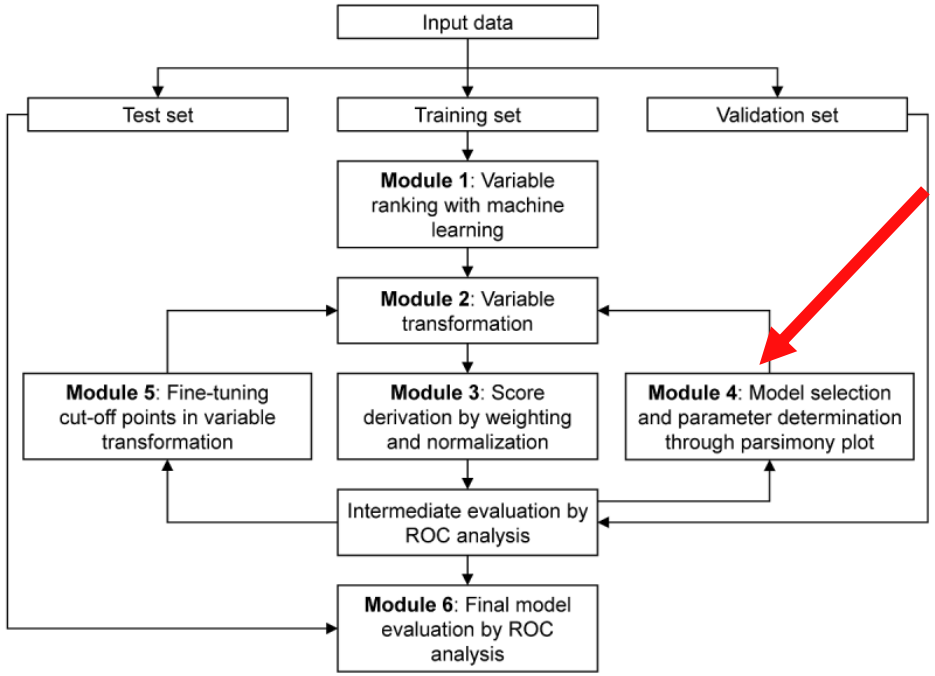
AutoScore



Module 3: Score Derivation by Weighting and Normalization

- **1st logistic regression**
  - obtain coefficient
- **2nd logistic regression**
  - use the category with lowest coefficient form 1st round and set as reference (ensure coefficient is not negative)
- Use coefficient from 2nd round and ensure that all coefficients are larger than 1
  - $\beta_{new} = \beta/\beta_{lowest}$
- Finally, round all coefficient
  - $\beta_{score} = round(\beta_{new})$
- In this step, we obtain scoring rules.

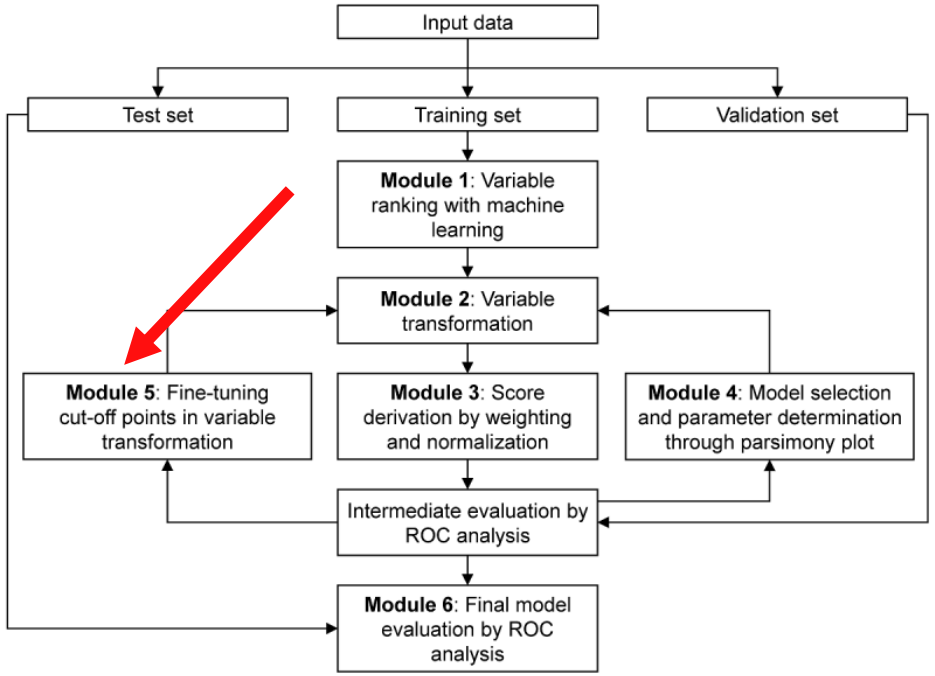
AutoScore



Module 4: Model Selection and Parameter Determination

- Determine the optimal number of variable (m) by evaluation of performance on validation set
- Best m = when *m* continues to increment and the prediction performance is no longer improving significantly.
- Then, do module 2 and 3 again.

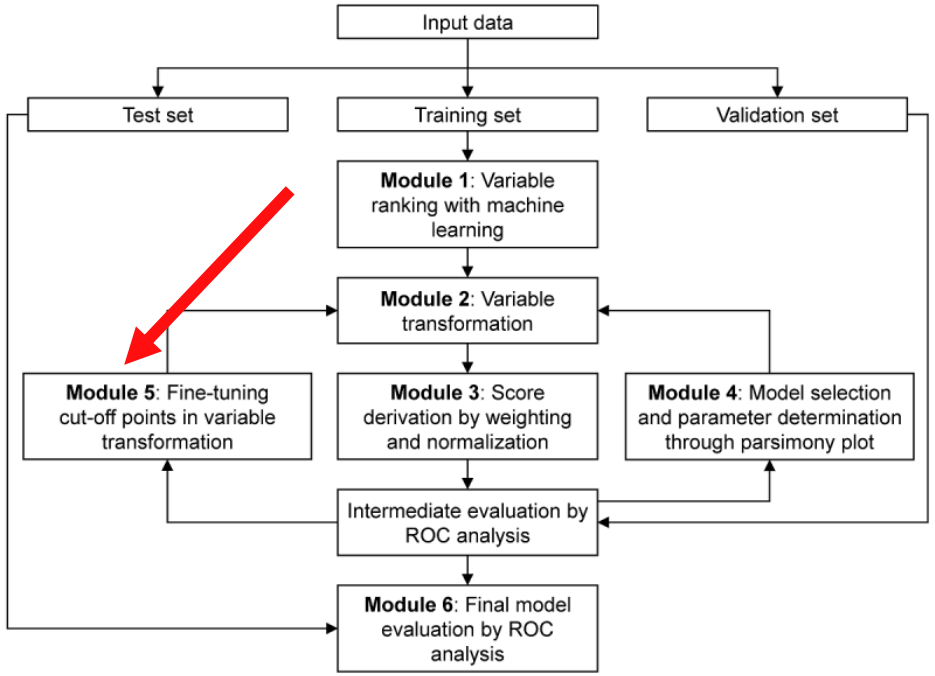
AutoScore



Module 5: **Fine-Tuning Cutoff Points in the Variable Transformation**

- Manually select cut-off for continuous variable and do module 2 and 3 again.

AutoScore



Module 6: **Final model evaluation**

- Evaluate final model on the test set using various metrics.

Models

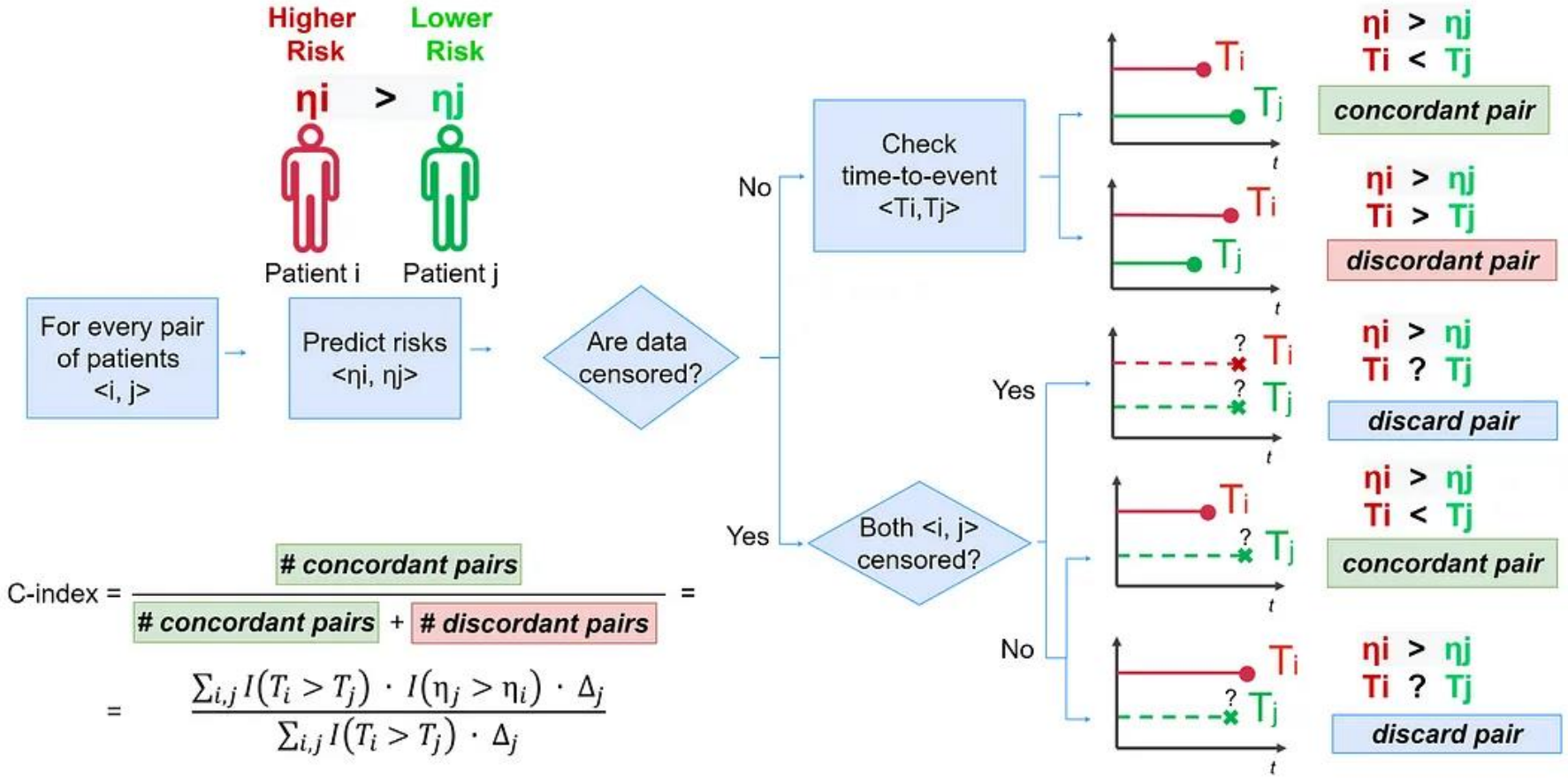
- **Traditional statistic:**
  - CoxPH
  - Step-wise CoxPH
  - Elastic net penalty Cox model
- **Machine learning:**
  - AutoScore-Survival
  - Random survival forest
  - Gradient boosting
- **Deep learning:**
  - DeepSurv
  - CoxTime
  - DeepHit

Method

- **Feature selection:**
  - **Traditional statistical model:**
    - Step-wise CoxPH
      - Forward selection based on Alkaine Information Criterion (AIC)
    - CoxEN
      - Tuning alpha through cross validation for Elastic Net penalty
  - **ML model:**
    - RSF, GBM
      - Full variable
      - Chosen based on variable importance
  - **Deep learning:**
    - Use all variables

Metrics

- **C-index** – Measure of discriminative performance



$$\text{C-index} = \frac{\#\text{ concordant pairs}}{\#\text{ concordant pairs} + \#\text{ discordant pairs}} = \frac{\sum_{i,j} I(T_i > T_j) \cdot I(\eta_j > \eta_i) \cdot \Delta_j}{\sum_{i,j} I(T_i > T_j) \cdot \Delta_j}$$

https://towardsdatascience.com/how-to-evaluate-survival-analysis-models-dd67bc10caae

Metrics

- **Integrated Brier Score** – Combined measure of discrimination, calibration

$$\text{Brier score} = \frac{1}{n}\sum_{i=1}^{n}(p_i - 0_i)^2$$

  - n = the number of subjects
  - p_i = the probability of event predicted by the model for the *i* subject
  - o_i = the observed outcome in the *i* subject
  - Brier score is calculated separately for each time point.
  - Integrate all Brier score at all time point to obtain overall performance measure for all times.

Table 3: Performance of different methods with/without variable selection mechanisms.

Methods	No. of Variables	Evaluation Criteria	
		C-index	CI (95%)
CoxPH	60	0.879 (0.0031)	0.873 – 0.885
CoxEN	26	0.875 (0.0035)	0.868 – 0.882
Stepwise CoxPH	50	0.879 (0.0033)	0.872 – 0.886
AutoScore-Survival	16	0.867 (0.0031)	0.861 – 0.873
RSF	16	0.876 (0.0032)	0.871 – 0.882
RSF	60	0.889 (0.0028)	0.883 – 0.895
GBM	16	0.880 (0.0028)	0.874 – 0.885
GBM	60	0.891 (0.0034)	0.884 – 0.898
DeepSurv	60	0.893 (0.0032)	0.886 – 0.899
CoxTime	60	0.891 (0.0027)	0.886 – 0.896
DeepHit	60	0.892 (0.0031)	0.886 – 0.898
	No. of Variables	IBS	CI (95%)
CoxPH	60	0.0428 (0.0008)	0.0414 – 0.0443
CoxEN	26	0.0445 (0.0010)	0.0426 – 0.0467
Stepwise CoxPH	50	0.0436 (0.0009)	0.0416 – 0.0457
AutoScore-Survival	16	0.0439 (0.0008)	0.0425 – 0.0456
RSF	16	0.0425 (0.0008)	0.0411 – 0.0440
RSF	60	0.0418 (0.0008)	0.0405 – 0.0434
GBM	16	0.0445 (0.0008)	0.0427 – 0.0459
GBM	60	0.0421 (0.0010)	0.0406 – 0.0442
DeepSurv	60	0.0406 (0.0009)	0.0390 – 0.0423
CoxTime	60	0.0429 (0.0008)	0.0412 – 0.0443
DeepHit	60	0.0489 (0.0010)	0.0470 – 0.0511

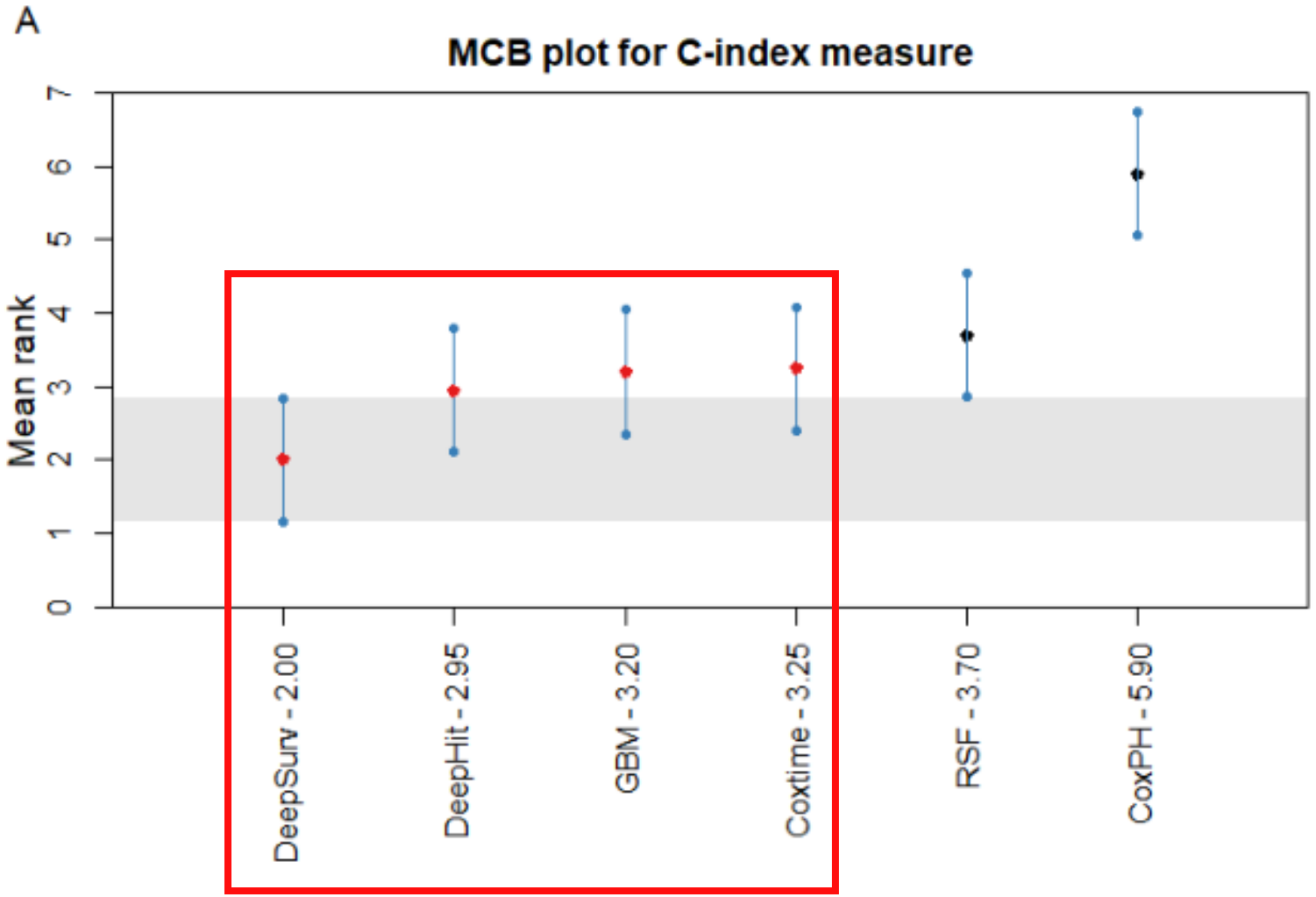
C-Index

Top-3 60 variables model:
DeepSurv
DeepHit
CoxTime, GBM

Multiple Comparisons with the Best (MCB) test with simulated 20 simulations

Red dot = insignificant difference from the best

60-variable model



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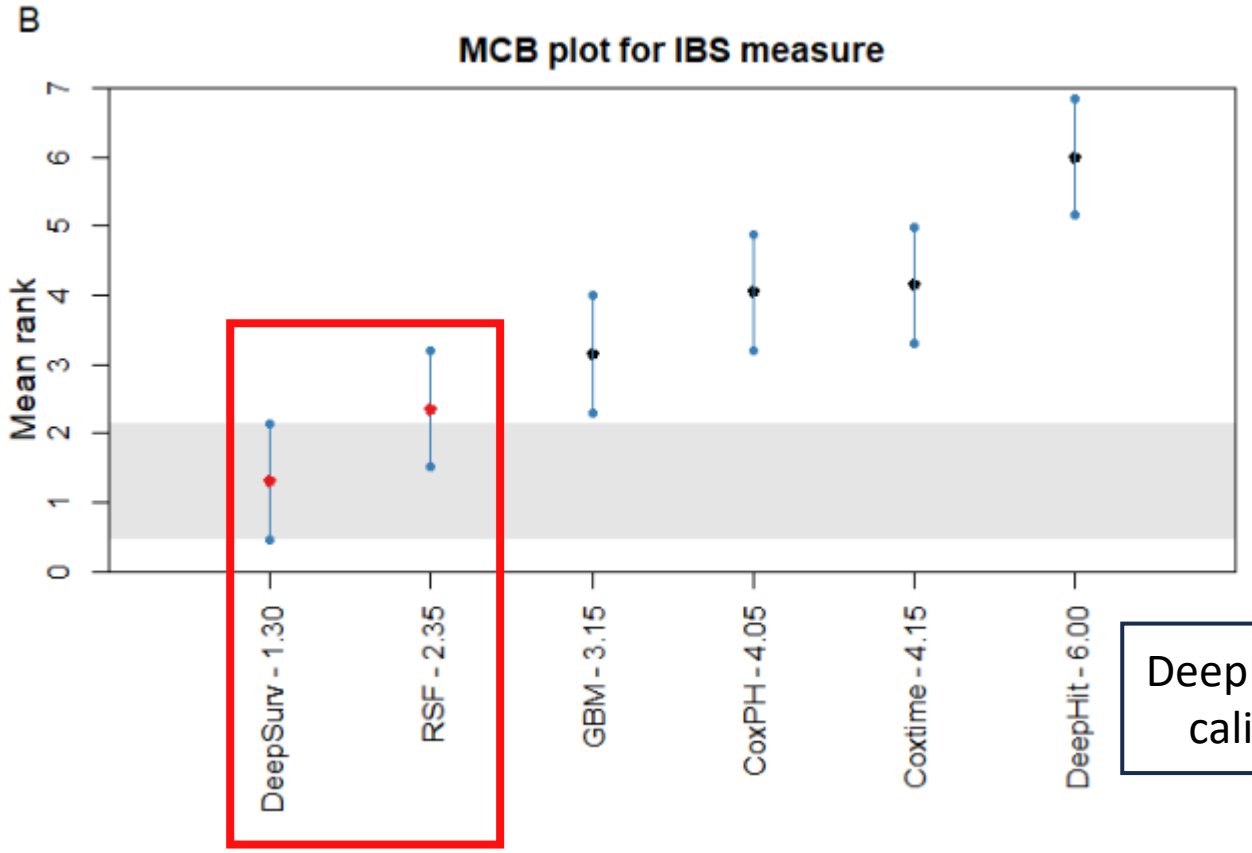

DeepHit suffer from calibration a lot

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C-Index

Top 3 models with feature selection:
GBM
Stepwise CoxPH
CoxEN

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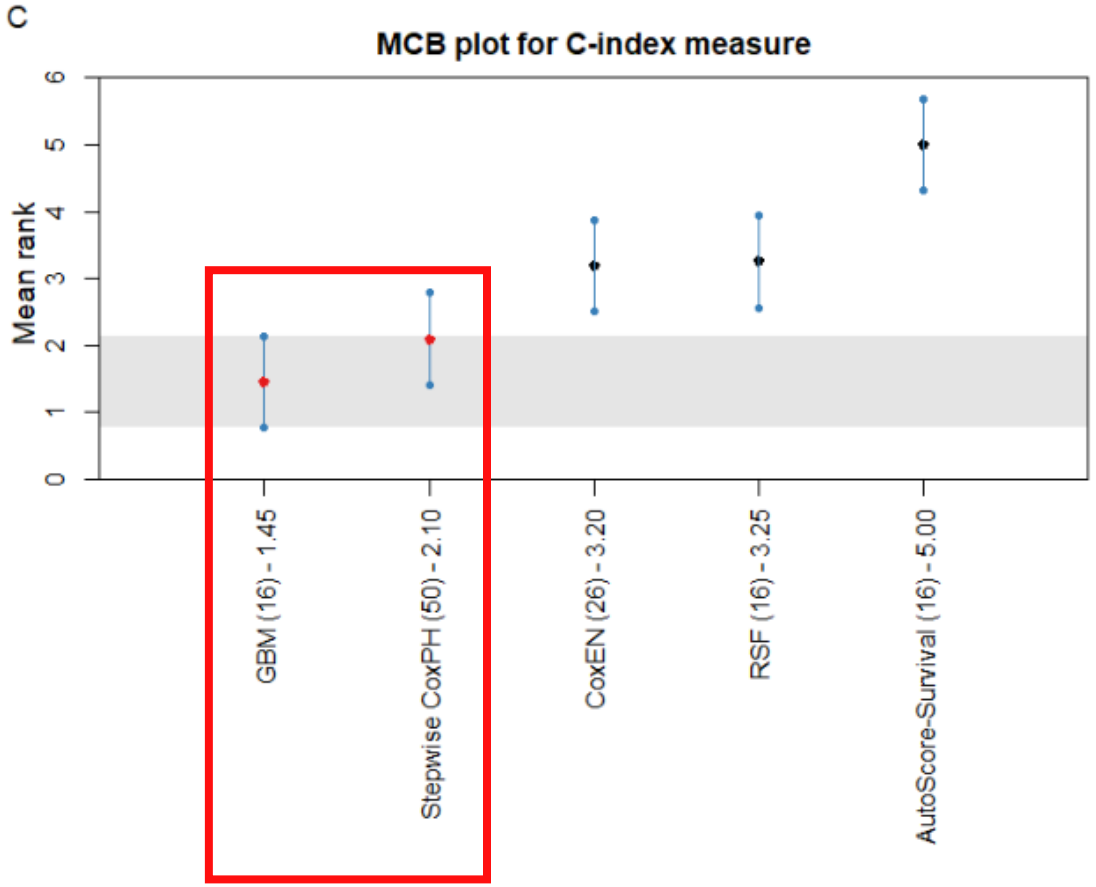
Model with feature selection



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GBM	16	0.0445 (0.0008)	0.0427 – 0.0459
GBM	60	0.0421 (0.0010)	0.0406 – 0.0442
DeepSurv	60	0.0406 (0.0009)	0.0390 – 0.0423
CoxTime	60	0.0429 (0.0008)	0.0412 – 0.0443
DeepHit	60	0.0489 (0.0010)	0.0470 – 0.0511

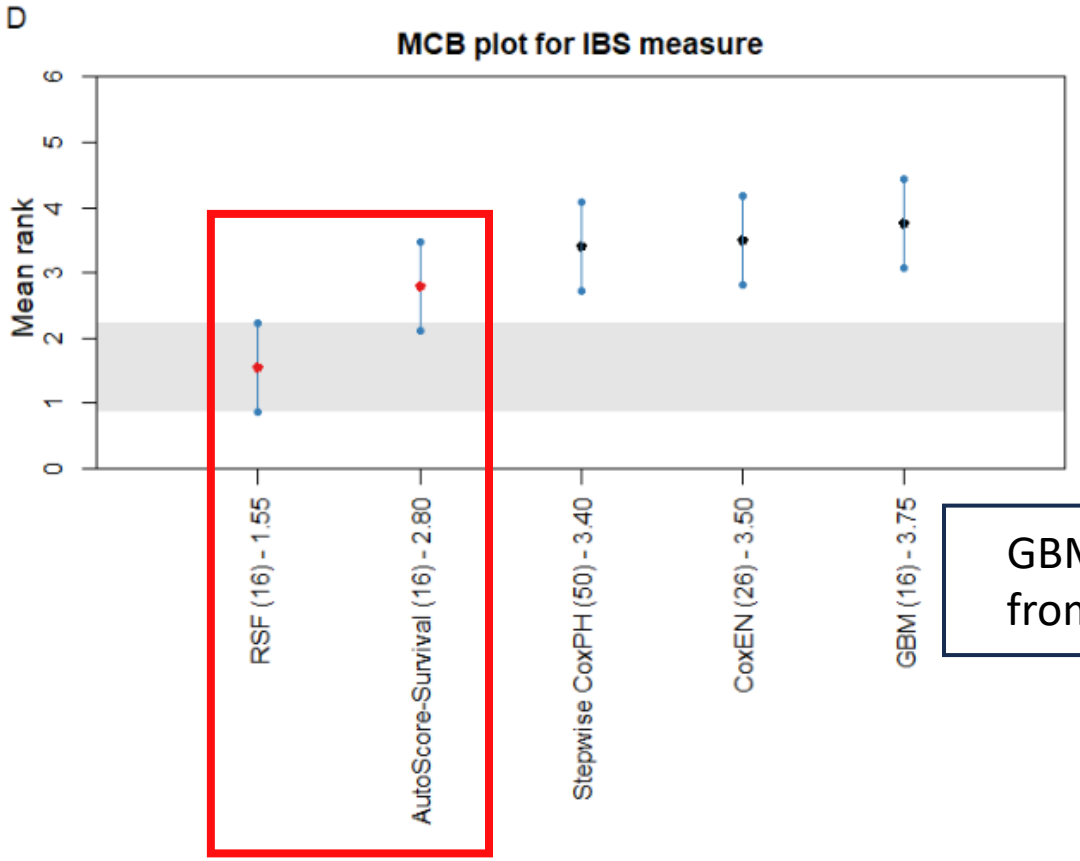
IBS

Top 3 models with feature selection:
RSF
AutoScore-Survival
CoxEN, GBM

Multiple Comparisons with the Best (MCB) test with simulated 20 simulations

Red dot = insignificant difference from the best

Model with feature selection

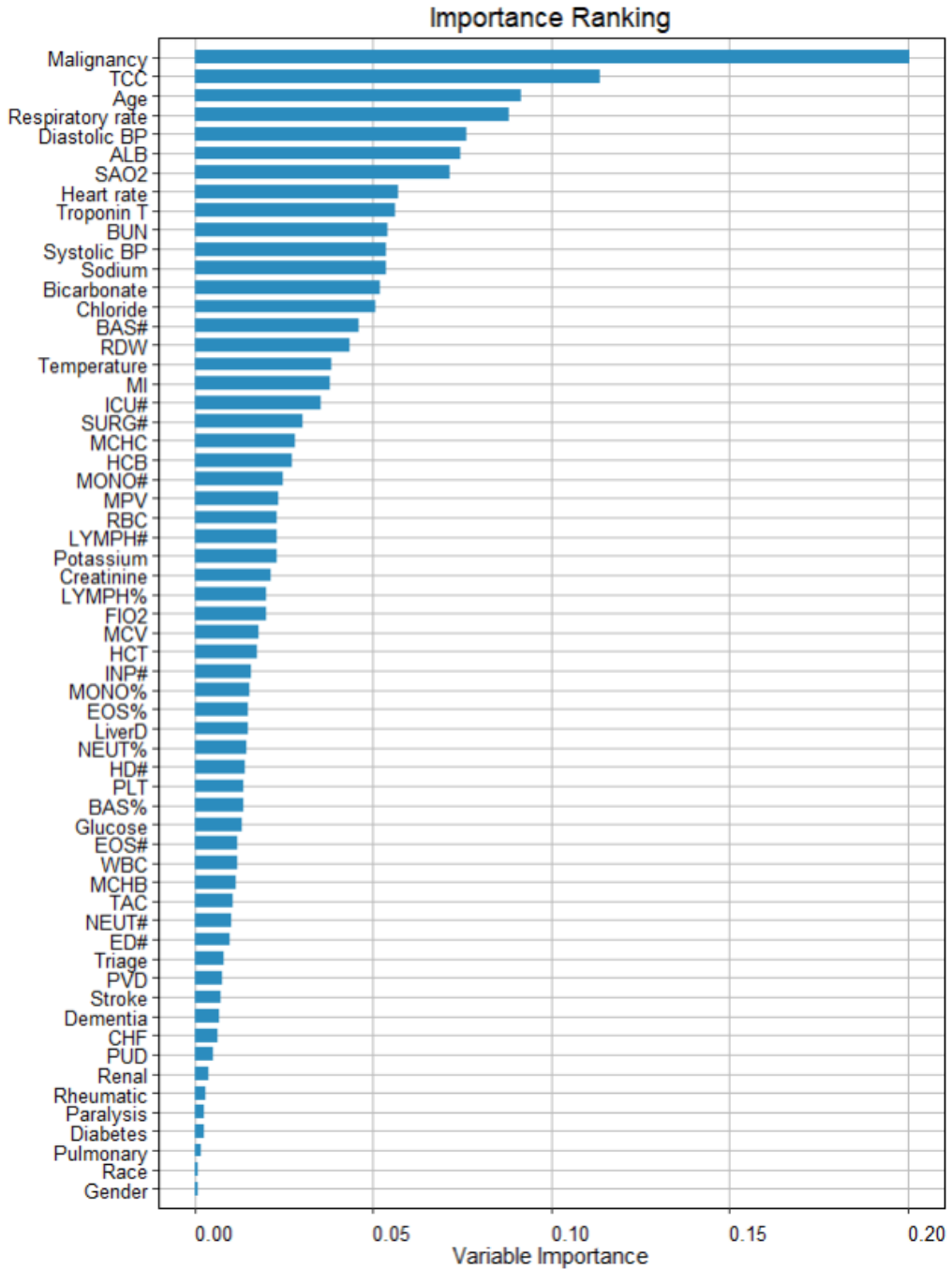


GBM also suffer from calibration

Selected features

- **Random forest**
  - Malignancy
  - Total cell count
  - Age
  - Respiratory rate

Figure S5. Variable importance based on RSF.



Selected features

- **AutoScore-Survival**
  - Malignancy
  - Total cell count
  - Age
  - Respiratory rate

Figure S1. Parsimony plot on the validation cohort based on AutoScore-Survival.

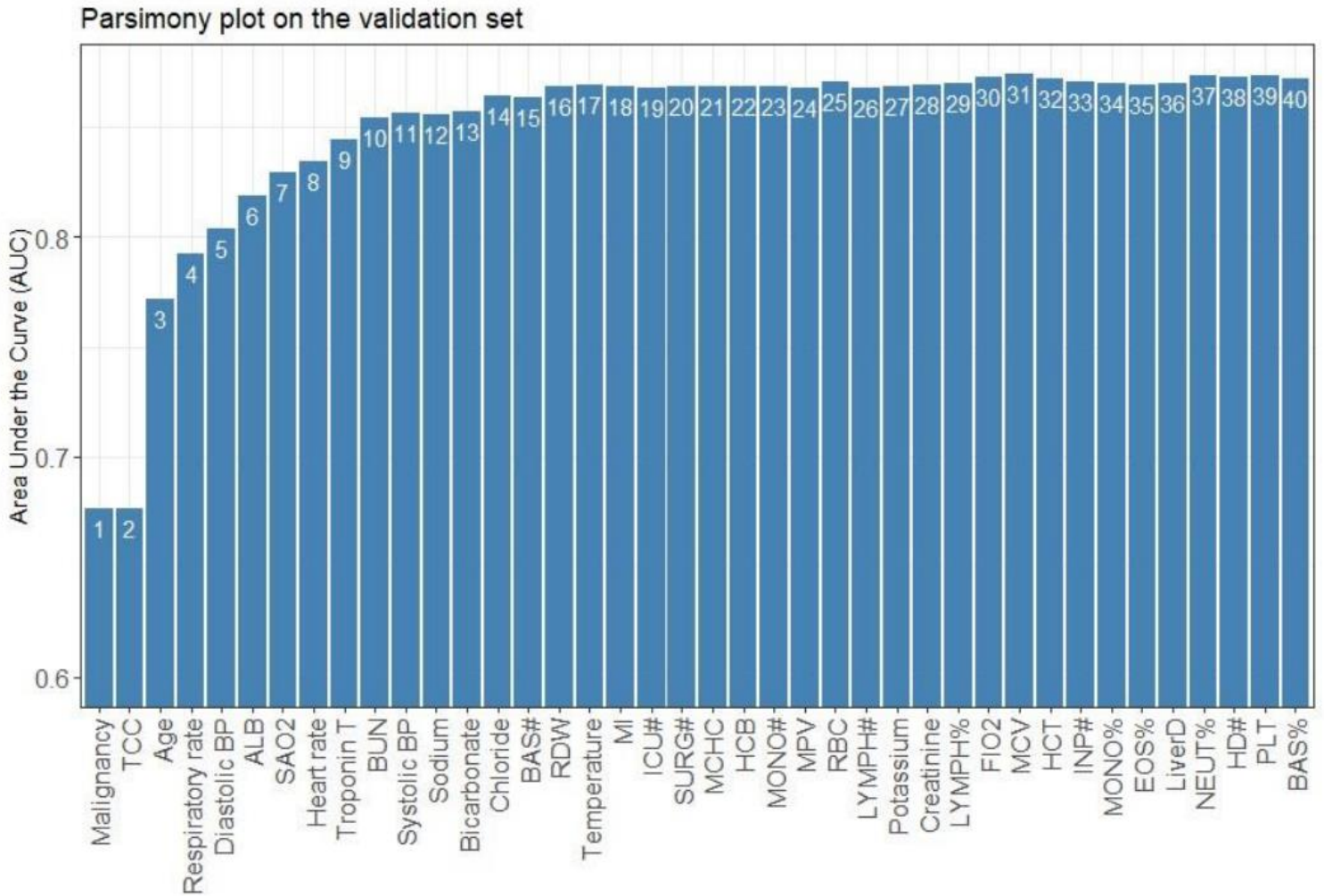


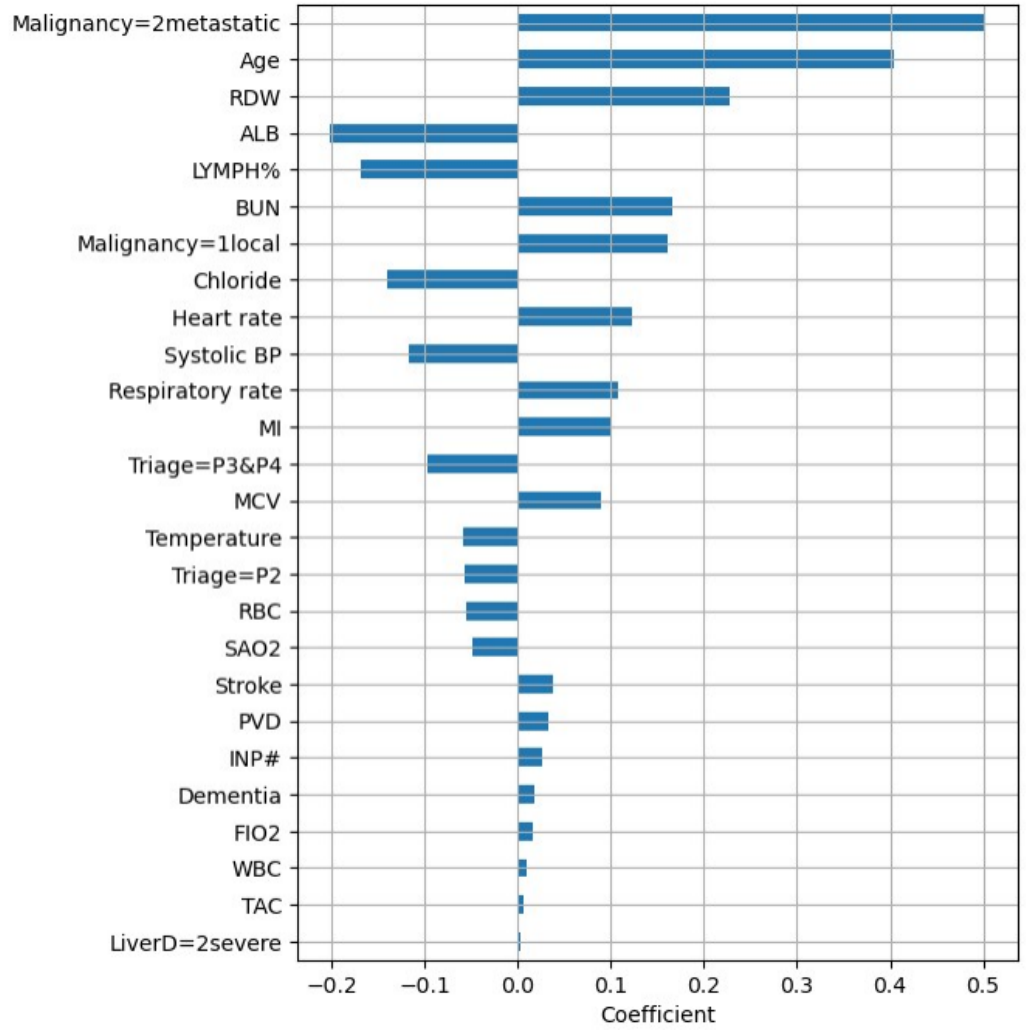
Table S5. Sixteen-variable score for all-cause mortality for the inpatient dataset.

Variables	Interval	Point
Malignancy	NA	**0**
	1local	**7**
	2metastatic	**15**
Total cell count (TCC)	< 100	**0**
	≥ 100	**6**
Age	[21, 41)	**0**
	[41, 58)	**7**
	[58, 76)	**10**
	[76, 85)	**13**
	≥ 85	**17**
Respiratory rate	<16	**2**
	[16, 17)	**0**
	[17, 18)	**1**
	[18, 20)	**1**
	≥ 20	**3**
Diastolic BP	< 79	**0**
	[79, 91)	**1**
	≥ 91	**2**
Blood albumin (ALB)	< 34	**10**
	[34, 39)	**5**
	[39, 41)	**6**
	≥ 41	**0**
SAO2	< 95	**4**
	[95, 97)	**1**
	≥ 97	**0**
Heart rate	< 75	**0**
	[75, 94)	**1**
	[94, 109)	**2**
	≥ 109	**4**
Troponin T Quantitative	< 13	**2**
	[13, 36)	**0**
	≥ 36	**4**
Blood urea nitrogen (BUN)	< 4.7	**0**
	[4.7, 8)	**2**
	[8, 16.4)	**4**
	≥ 16.4	**6**
Systolic BP	< 105	**6**
	[105, 121)	**5**
	[121, 148)	**4**
	[148, 174)	**2**
	≥ 174	**0**
Sodium	< 95	**8**
	[95, 100)	**5**
	[100, 104)	**3**
	[104, 107)	**0**
	≥ 107	**1**
Bicarbonate	< 18.8	**3**
	[18.8, 27.2)	**0**
	≥ 27.2	**2**
Chloride	<95	**8**
	[95, 100)	**5**
	[100, 104)	**3**
	[104, 107)	**0**
	≥ 107	**1**
BAS#	< 0.02	**2**
	[0.02, 0.03)	**1**
	[0.03, 0.05)	**1**
	[0.05, 0.07)	**0**
	≥ 0.07	**1**
RDW	< 12.3	**0**
	[12.3, 13.1)	**1**
	[13.1, 14.6)	**4**
	[14.6, 17.2)	**7**
	≥ 17.2	**10**

Selected features

- **CoxEN**
  - Malignancy
  - Age
  - Red cell distribution width
  - ALB

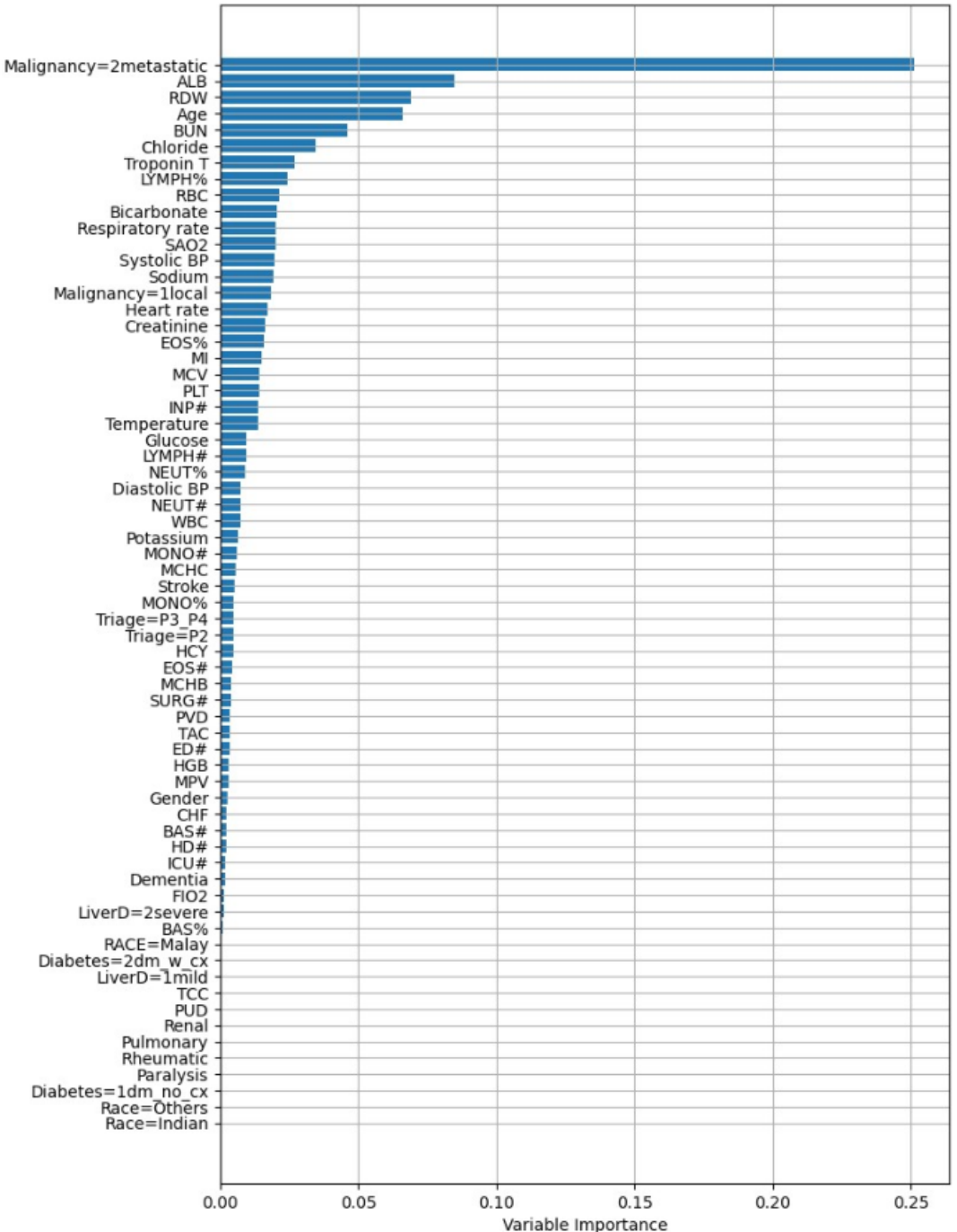
Figure S3. Variable importance on the validation cohort based on the CoxEN model.



Selected features

- **Gradient boosting**
  - Malignancy
  - ALB
  - Red cell distribution width
  - Age

Figure S6. Variable importance based on GBM.



Discussion

- **Traditional statistical methods** tend to have better interpretability.
- **Machine learning** and **deep learning** algorithms have superior discrimination.
- **Deep learning** can have challenges in calibration.
- **AutoScore-Survival** is the most easily interpretable model and has competitive calibration performance.

predict
breast cancer

Home | About Predict | Predict Tool | Contact | Legal | Change Language

We recommend that patients use this tool in consultation with their doctor, and read About Predict before starting.

Settings

Reset

Predict is not designed to be used in all cases. Click here for more details.
If you are unsure of any inputs or outputs, click on the buttons for more information.

A clinician would usually fill this in. If you are a patient and don't know these inputs, ask your team to go through this tool with you. You can go change inputs at any time - even after results are displayed.

DCIS only or LCIS only? Yes | No

Age at diagnosis – | +
Age must be between 25 and 85

Smoker? Yes | Never or Ex

Post Menopausal? Yes | No | Unknown

ER status Positive | Negative

Progesterone Status Positive | Negative | Unknown

Invasive tumour size (mm) – | +
If there was more than one tumour, enter the size of the largest tumour. If neo-adjuvant therapy was undertaken, enter the size before neo-adjuvant therapy.

Tumour grade 1 | 2 | 3

Detected by Screening | Symptoms | Unknown

Positive nodes – | +

Micrometastases only Yes | No | Unknown
Enabled when positive nodes is 1.

https://breast.v3.predict.cam/tool

Treatment Options

Try different combinations of treatments to find out which has the best overall effect

Radiotherapy

No | Yes

The main reason for having radiotherapy is to stop cancer cells regrowing after surgery (local recurrence). Its effect on how long patients might live is therefore not its only benefit.

Mean heart dose in Grays

– 5 +

Heart dose must be between 0 and 20.
If you are unsure, use 0 for cancer on the right hand side and 2 for cancer on the left hand side.

Hormone Therapy

No | 5 Years | 10 Years

Hormone (endocrine) therapy
Available when ER-status is positive

Chemotherapy

None
Standard-dose, anthracycline-based
High-dose, anthracycline- or taxane-based

Trastuzumab

No | Yes

Available when HER2/ERRB2 status is positive

Bisphosphonates

No | Yes

Available for post-menopausal women

When you add or remove a treatment, the results of some other treatments sometimes change. This text explains why.

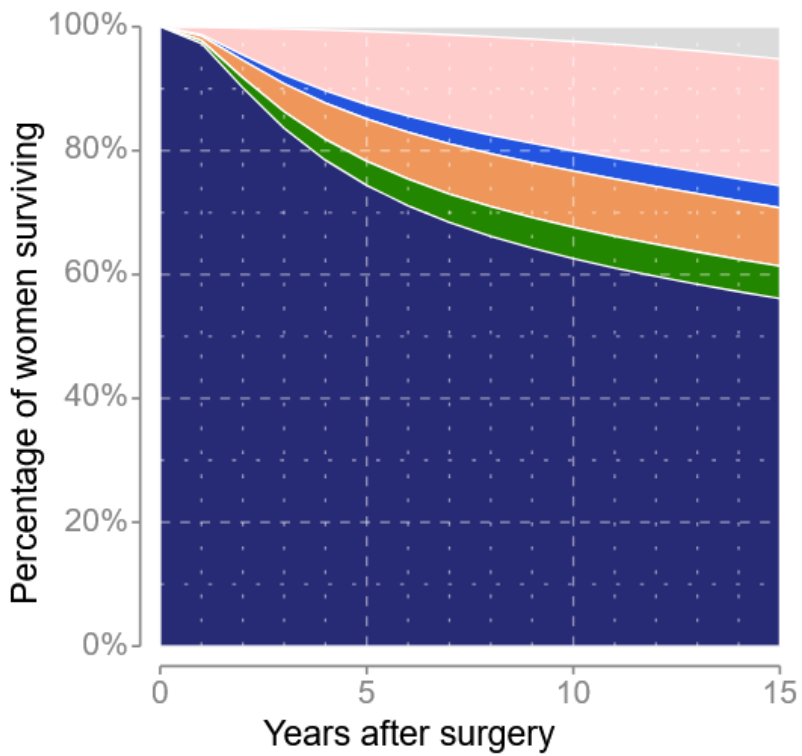
Results

All treatments have side effects. Weigh up the benefits shown with the side effects in this website.

When you click each of these buttons it will show the same information but in a different way. Choose whichever you are most comfortable with. You do not need to read them all.

Table | Icons | **Curves** | Chart | Texts

This display shows what we would expect to happen to women who had surgery and then took the combination of treatments you have selected over the first 15 years.



- Deaths due to other causes
- Deaths related to breast cancer
- Additional benefit of bisphosphonates
- Additional benefit of chemotherapy
- Additional benefit of radiotherapy
- Surgery only

To understand these results fully, read How Predict Works

⚠ WARNING!
Some treatments are likely to cause more deaths in the long term than lives saved for patients like this. Please check survival 15 years after surgery.

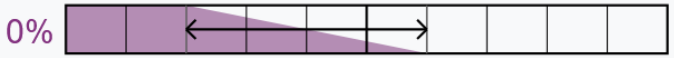
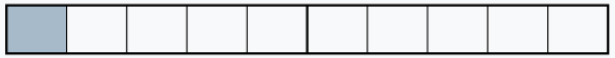
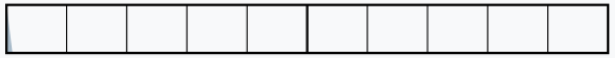
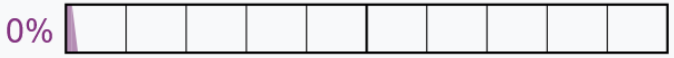
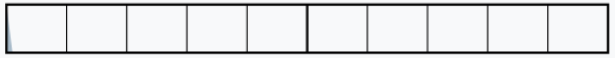
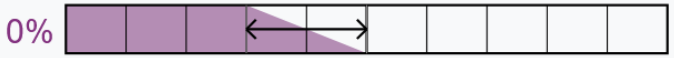
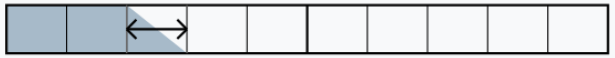
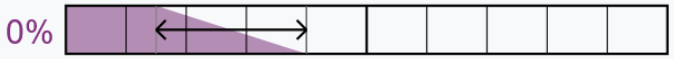
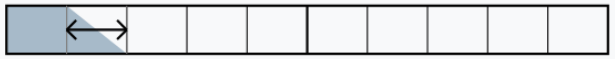
This display shows what we would expect to happen to women who had surgery and then took the combination of treatments you have selected, at 5 **10** 15 years.

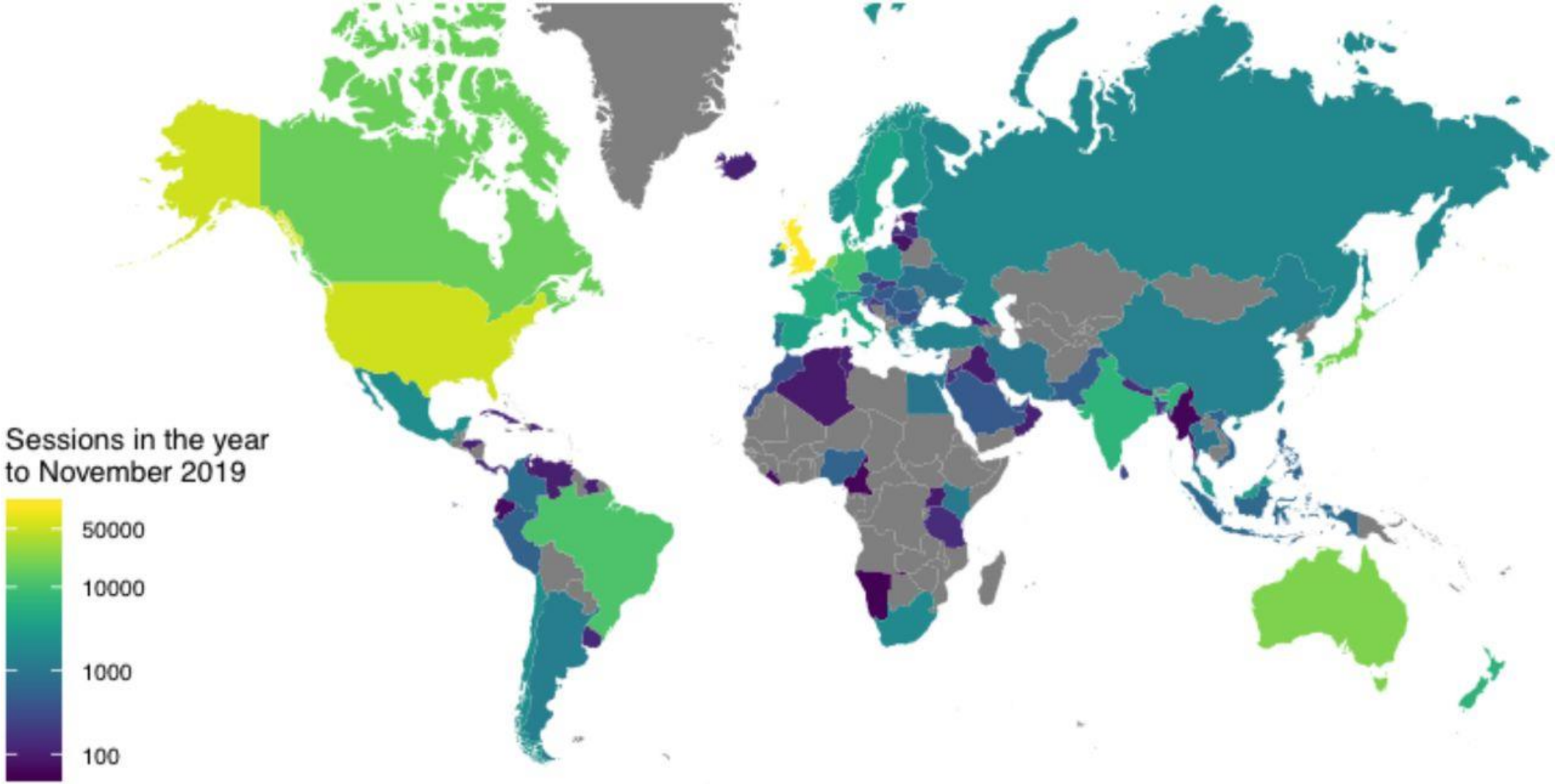
Removing one treatment from this treatment combination may have a larger or smaller effect on overall survival than shown below. This text explains more. Try removing treatments to see the effect it has on survival.

Important: if you are a clinician considering the benefits of chemotherapy, read this.

Treatment	Additional benefit as part of treatment combination	% survival for those taking treatment combination
Surgery only	-	49%
+ Radiotherapy	+0.3% (-0.8% – 1.2%)	49%
+ Hormone therapy	+3.8% (2.5% – 4.9%)	53%
+ Chemotherapy	-2.1% (-2.8% – -1.4%)	51%
+ Trastuzumab	+1.6% (1.0% – 2.1%)	52%
+ Bisphosphonates	+0.7% (0.2% – 1.0%)	53%

Side effects you might have during treatment or shortly after. These tend to be at their worst the week or two after you finish your whole course of treatment.

Possible side effect	How many patients have this side effect:	
	On radiotherapy	NOT on radiotherapy (but having other treatments for breast cancer)
+ Fatigue	 0% 100% About 90% have this — About 10% don't	 0% 100% About 60% have this — About 40% don't
+ Skin changes (including soreness, changing colour, dryness, and itching) and loss of hair over the affected skin	 0% 100% 20% - 60% have this — 40% - 80% don't	 0% 100% About 10% have this — About 90% don't
+ Skin ulceration	 0% 100% About 10% have this — About 90% don't	 0% 100% Less than 1% have this — 99% - 100% don't
+ Slight breathlessness	 0% 100% 1% - 2% have this — 98% - 99% don't	 0% 100% Less than 1% have this — 99% - 100% don't
+ Pain/stiffness in the arm and shoulder	 0% 100% 30% - 50% have this — 50% - 70% don't	 0% 100% 20% - 30% have this — 70% - 80% don't
+ Problems with the breast reconstruction	 0% 100% 15% - 40% have this — 60% - 85% don't	 0% 100% 10% - 20% have this — 80% - 90% don't



https://www.medrxiv.org/content/10.1101/2020.11.16.20232348v1.full-text