Challenge Data 2025 : Overall Survival Prediction of Patients with Myeloid Leukemia

Winning solution

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`https://github.com/arthurdrk/QRT-Challenge-2025`

Context

This year's challenge was about a subtype of blood cancer called myeloid leukemia.

- Accumulation of abnormal immature myeloid cells
- The bone marrow produces dysfunctional blood cells

Goal of the Challenge : Predict risk disease

The risk is measured through the overall survival of patients, i.e., the duration of survival from the diagnosis of the blood cancer to the time of death or last follow-up.

Data Overview

Data is divided in two parts : **Clinical Data** and **Molecular Data**
Very large dataset :

- **3,323** patients in train set
- **1,193** patients in test set

	ID	CENTER	BM_BLAST	WBC	ANC	MONOCYTES	HB	PLT	CYTOGENETICS
0	P132697	MSK	14.0	2.8	0.2	0.7	7.6	119.0	46,xy,del(20)(q12)[2]/46,xy[18]
1	P132698	MSK	1.0	7.4	2.4	0.1	11.6	42.0	46,xx
2	P116889	MSK	15.0	3.7	2.1	0.1	14.2	81.0	46,xy,t(3;3)(q25;q27)[8]/46,xy[12]
3	P132699	MSK	1.0	3.9	1.9	0.1	8.9	77.0	46,xy,del(3)(q26q27)[15]/46,xy[5]
4	P132700	MSK	6.0	128.0	9.7	0.9	11.1	195.0	46,xx,t(3;9)(p13;q22)[10]/46,xx[10]

Figure 1 – Head of clinical train set

	ID	CHR	START	END	REF	ALT	GENE	PROTEIN_CHANGE	EFFECT	VAF	DEPTH
0	P100000	11	119149248.0	119149248.0	G	A	CBL	p.C419Y	non_synonymous_codon	0.0830	1308.0
1	P100000	5	131822301.0	131822301.0	G	T	IRF1	p.Y164*	stop_gained	0.0220	532.0
2	P100000	3	77694060.0	77694060.0	G	C	ROBO2	p.?	splice_site_variant	0.4100	876.0
3	P100000	4	106164917.0	106164917.0	G	T	TET2	p.R1262L	non_synonymous_codon	0.4300	826.0
4	P100000	2	25468147.0	25468163.0	ACGAAGAGGGGGTGTTC	A	DNMT3A	p.E505fs*141	frameshift_variant	0.0898	942.0

Figure 2 – Head of molecular train set

Clinical Data

Each patient is associated with a unique identifier and detailed clinical information :

- `ID` : unique identifier per patient
- `CENTER` : clinical center
- `BM_BLAST` : bone marrow blasts in % (blasts are abnormal blood cells)
- `WBC` : white blood cell count in Giga/L
- `ANC` : absolute Neutrophil count in Giga/L
- `MONOCYTES` : monocyte count in Giga/L
- `HB` : hemoglobin in g/dL
- `PLT` : platelet count in Giga/L
- `CYTOGENETICS` : description of the karyotype observed in blood cells, measured by a cytogeneticist

Molecular Data

One line per patient per somatic mutation :

- `ID` : Unique identifier per patient
- `CHR_START_END` : Position of the mutation on the human genome
- `REF_ALT` : Reference and alternate (mutant) nucleotide
- `GENE` : Affected gene
- `PROTEIN_CHANGE` : Consequence of the mutation on the protein expressed by the gene
- `EFFECT` : Broad categorization of the mutation consequence on the gene
- `VAF` : Variant Allele Fraction (proportion of cells carrying the deleterious mutation)
- `DEPTH` : Coverage (total number of reads at the locus)

Target & Metric

The goal of the challenge was to predict Overall Survival (OS).
Two outcomes : `OS_YEARS` (time) and `OS_STATUS` (event).

Metric : IPCW-Concordance Index

To take censoring into account, we use an *Inverse Probability of Censoring Weighted* (IPCW) version of the C-index, truncated at $\tau = 7$ years :

$$\hat{C}_\tau = \frac{\sum_{i=1}^{n}\sum_{j=1}^{n} \Delta_i \, \hat{G}(X_i)^{-2} \, \mathbf{1}\{X_i < X_j,\ X_i < \tau\} \, \mathbf{1}\{\hat{\beta}' Z_i > \hat{\beta}' Z_j\}}{\sum_{i=1}^{n}\sum_{j=1}^{n} \Delta_i \, \hat{G}(X_i)^{-2} \, \mathbf{1}\{X_i < X_j,\ X_i < \tau\}}$$

- X_i : follow-up time (`OS_YEARS`)
- Δ_i : event indicator (`OS_STATUS`)
- $\hat{G}(X_i)$: survival function of the censoring distribution
- $\hat{\beta}' Z_i$: predicted risk score
- $\tau = 7$ years : the loss is truncated at 7 years

Data vizualisation

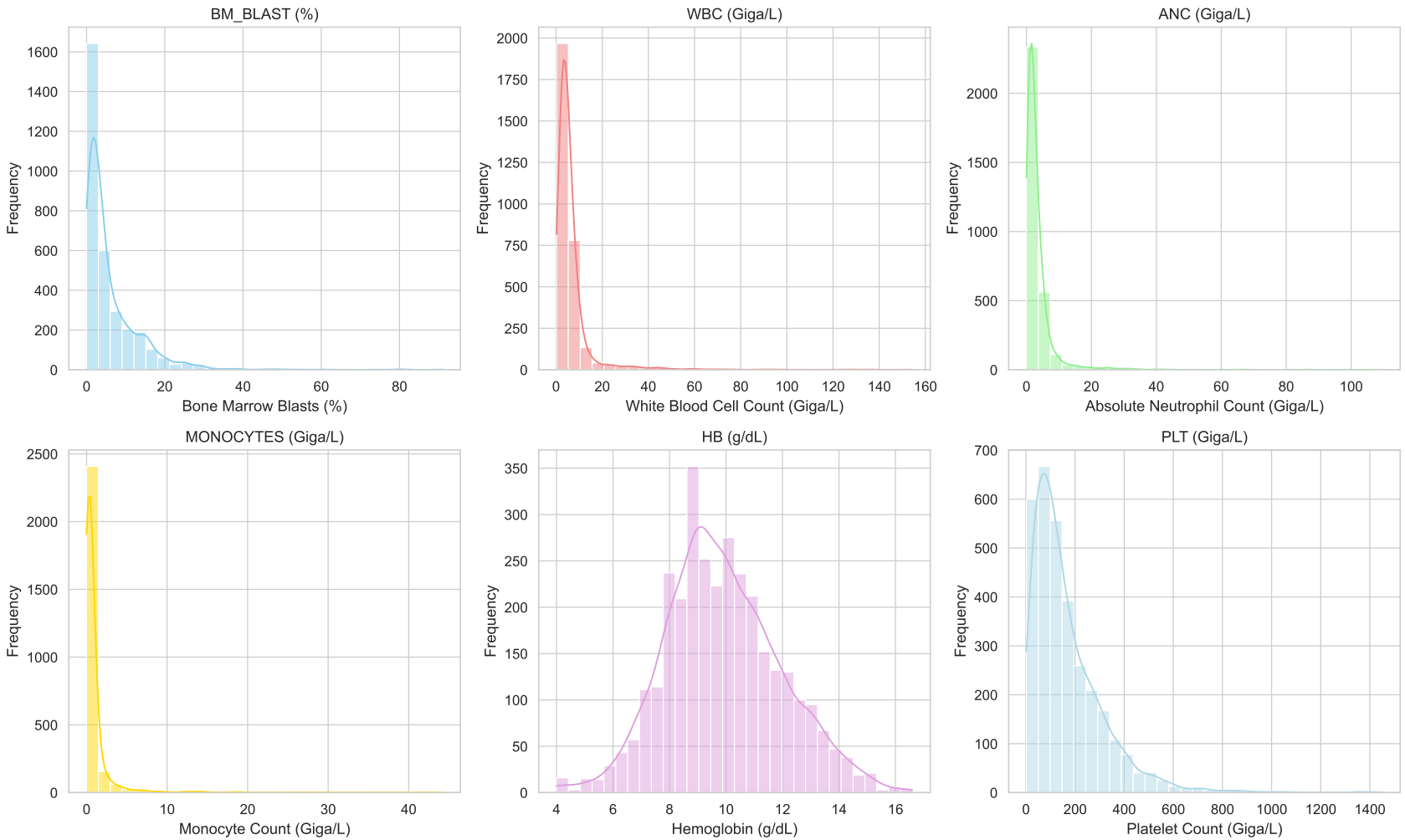


Figure 3 – Clinical variables distributions

Data vizualisation

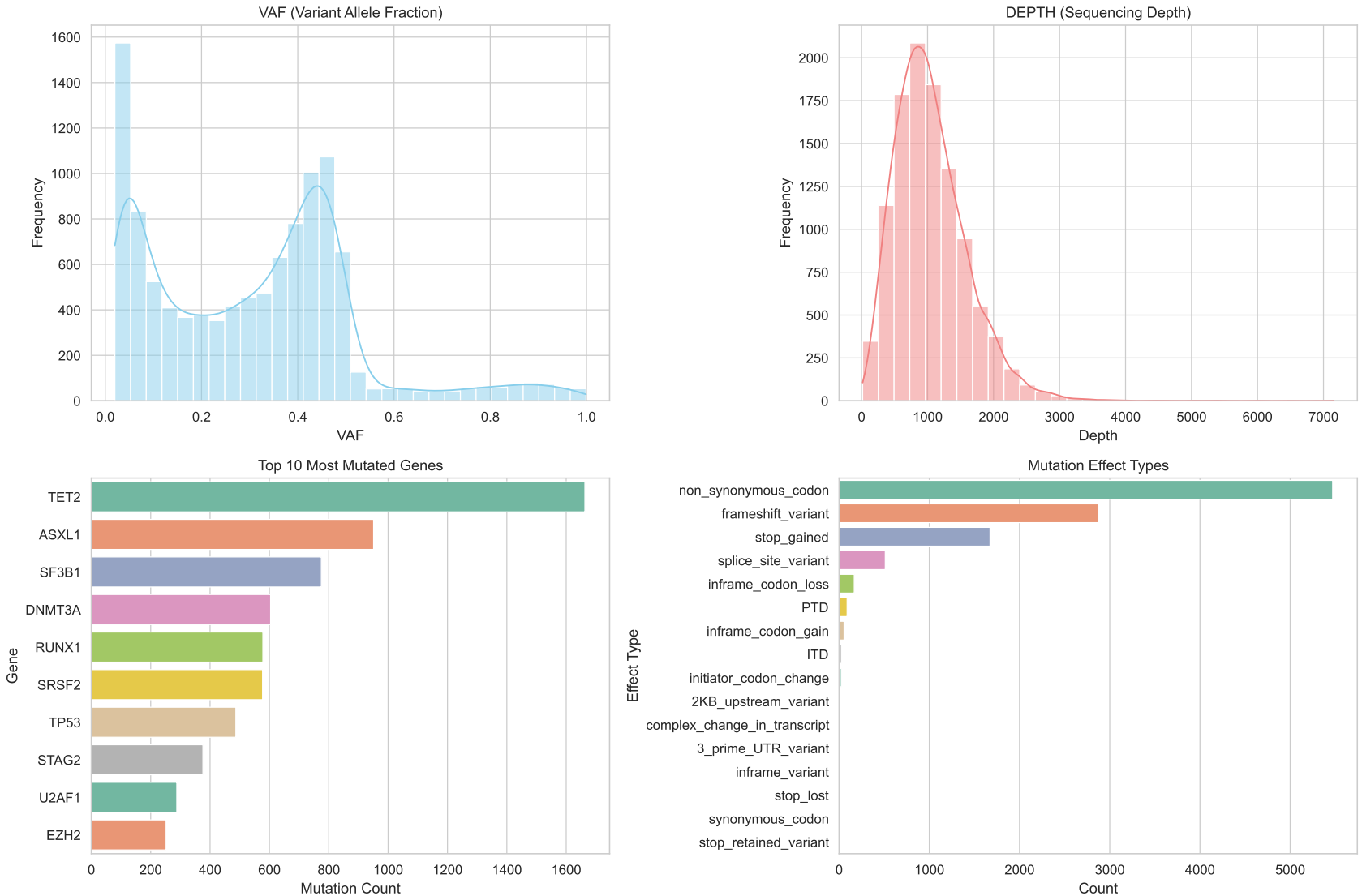


Figure 4 – Molecular variables distributions

Data Preprocessing

- Missing clinical values imputed using optimized XGBoost models (trained on the training set and applied to validation data)
- Continuous variables scaled using RobustScaler (median and IQR) to reduce the influence of outliers
- Log(`1+p`) transformation applied to highly skewed variables to stabilize variance and reduce asymmetry

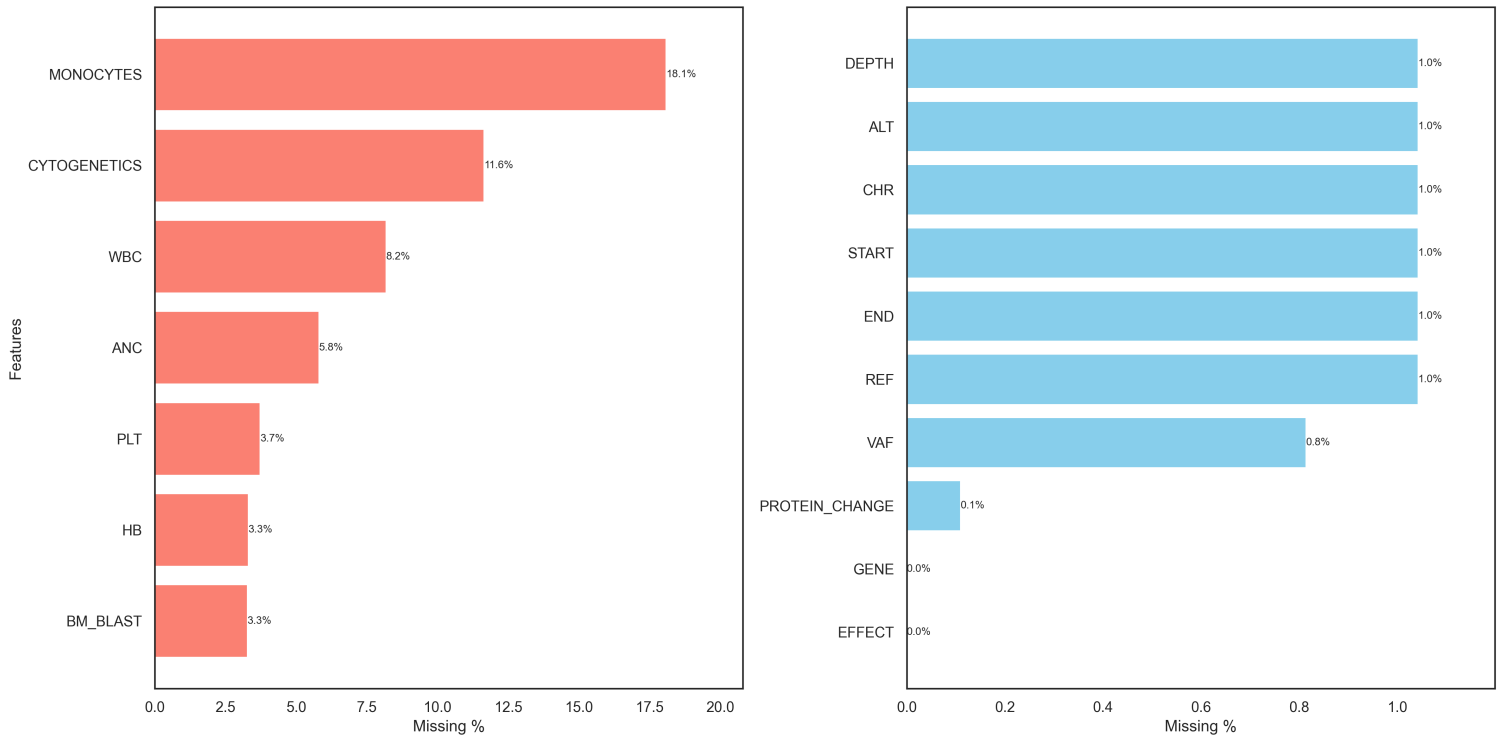


Figure 5 – Missing values in Clinical train and Molecular train

Prognostic Standard (ELN 2017)

Cytogenetic abnormalities and gene mutations are the primary determinants of prognosis in **Acute Myeloid Leukemia** (Döhner et al., 2017).

1. Cytogenetics (ISCN)

- **Normal :** *46,XX* (F) or *46,XY* (M). 23 standard pairs.
- **Abnormal :** Structural or numerical changes.
- *Example :* **-7** (Monosomy 7) indicates a high-risk profile.

46,XY,-7 = Male + Monosomy 7

2. Gene Mutations

- Comprehensive list of **mutated genes** per patient.
- Detailed descriptions of each mutation variant.
- Integrated with cytogenetics to define final ELN risk groups.

→ **Goal :** Transform these complex raw strings (ISCN/Mutations) into numerical features for XGBoost and Neural-MTLR.

Feature Engineering

ISCN mapping

1. Global Abnormality Load

- Any abnormal clone
- Total number of events
- Number of chromosomes affected
- Hypodiploidy / hyperdiploidy
- Baseline chromosome count

2. Clinically-Relevant Lesions

- -5, del(5q), -7, del(7q)
- $+8$
- CBF / APL rearrangements
- inv(3), t(6;9), t(9;22), 17p abnormalities

3. Risk Synthesis (ELN-like)

- Monosomal karyotype
- Complex karyotype
- ELN-like cytogenetic risk class
- Binary adverse / non-adverse flag

4. Clonality Structure

- Total metaphases analysed
- Largest clone size
- Proportion abnormal metaphases
- Severity of the worst clone

ISCN cytogenetic descriptions are mapped into a structured set of prognostic features for survival modelling.

Feature engineering

Added prognostic value of cytogenetics

Setup

- Models :
  1. Clinical + Molecular only
  2. Clinical + Molecular + Cytogenetics
- Cox elastic-net, fully nested CV (5-fold outer, 3-fold inner)

Performance (outer CV mean ± SD)

Metric	No cytogenetics	With cytogenetics
C-index	0.741 ± 0.004	0.742 ± 0.004
IBS	0.161 ± 0.009	0.161 ± 0.009
AUC (1 year)	0.795 ± 0.010	0.796 ± 0.010

Interpretation

- Cytogenetics provide a *small but consistent* improvement
- Gains are stable across folds (nested CV → low overfitting risk)
- Directionally aligned across all metrics (C-index, IBS, AUC)

Global statistics

- 124 genes analyzed
- 27 significant genes (FDR < 0.05)
- 21 significant genes (Bonferroni < 0.05)
- 26 higher–risk genes (HR > 1)
- 1 protective gene (HR < 1)

Gene	HR [95% CI]	FDR	Effect
TP53	2.74 [2.41–3.13]	4.91×10^{-49}	Higher risk
RUNX1	2.14 [1.89–2.43]	5.19×10^{-31}	Higher risk
ASXL1	1.67 [1.50–1.85]	2.18×10^{-20}	Higher risk
STAG2	1.96 [1.69–2.28]	2.33×10^{-17}	Higher risk
SF3B1	0.64 [0.56–0.72]	1.12×10^{-11}	Protective

Methods

- Log-Rank test (comparison of survival curves)
- Univariate Cox model (Hazard Ratios)
- Benjamini-Hochberg FDR correction
- Bootstrap (200 iterations) for stability assessment

Feature Engineering & Model Strategy

Extracting Signal from High-Dimensional Genomic Data

1. High-Dimensional Input & Filtering

Representing patient i as a binary sparse vector : $\mathbf{x}_i \in \{0,1\}^p$

- **Noise Reduction :** Retain genes with prevalence $\in [1\%, 99\%]$.
- **Rationale :** Eliminates "uninformative constants" to maximize the **signal-to-noise ratio**.

2. Survival Modeling : The Cox Framework

Modeling the **Hazard Rate** to quantify death risk over time.

- **Flexibility :** Semi-parametric (no baseline hazard assumption).
- **Censoring :** Robust handling of non-uniform follow-up periods.

Objective : Molecular Risk Score

Consolidate the sparse mutational landscape into a single, continuous metric to forecast survival and stratify risk.

The Predictive Engine : Cox Framework

Quantifying Mutational Impact on Survival

Model Specification

For patient i, the instantaneous risk of death (Hazard) is modeled as :

$$h(t \mid \mathbf{x}_i) = h_0(t) \exp(\mathbf{x}_i^\top \boldsymbol{\beta})$$

Core Assumption

- **Proportional Hazards :** The Risk Ratio between patients is **time-invariant**.
- **Flexibility :** $h_0(t)$ is unspecified, allowing focus on the **relative alpha** of mutations.

Interpretation

- $\beta > 0$: High-risk mutation.
- $\beta < 0$: Protective effect.
- **Censoring :** Naturally handles "survivors" or lost-to-follow-up data via partial likelihood.

Robust Estimation & Risk Scoring

Elastic Net Cox Model with Nested CV

Preprocessing

- Retain genes with prevalence $0.5\% \leq p_j \leq 99\%$
- Standardization within each training fold

Elastic Net-Penalized Cox Model

Estimate $\hat{\beta}$ by maximizing the penalized partial log-likelihood :

$$\ell_{\text{partial}}(\beta) - \lambda\big((1-\alpha)\|\beta\|_2^2 + \alpha\|\beta\|_1\big)$$

- `lifelines.CoxPHFitter` (`penalizer` $= \lambda$, `l1_ratio` $= \alpha$)
- **Nested CV** : 5 outer folds, 3 inner folds, 30 Optuna trials
- Hyperparameters selected by maximizing Harrell C-index
- Final $(\lambda^{,\alpha)}$ = median across outer folds, then refit on full data

Molecular Risk Score (MRS)

$$\text{MRS}_i = \mathbf{x}_i^\top \hat{\beta}$$

Higher MRS $\Rightarrow$ higher mortality risk (used for patient stratification).

- **Harrell's C-index (5-fold CV) :** 0.70
- **Bootstrap (1000 resamples) :** mean C-index = 0.700, 95% CI [0.686; 0.713]

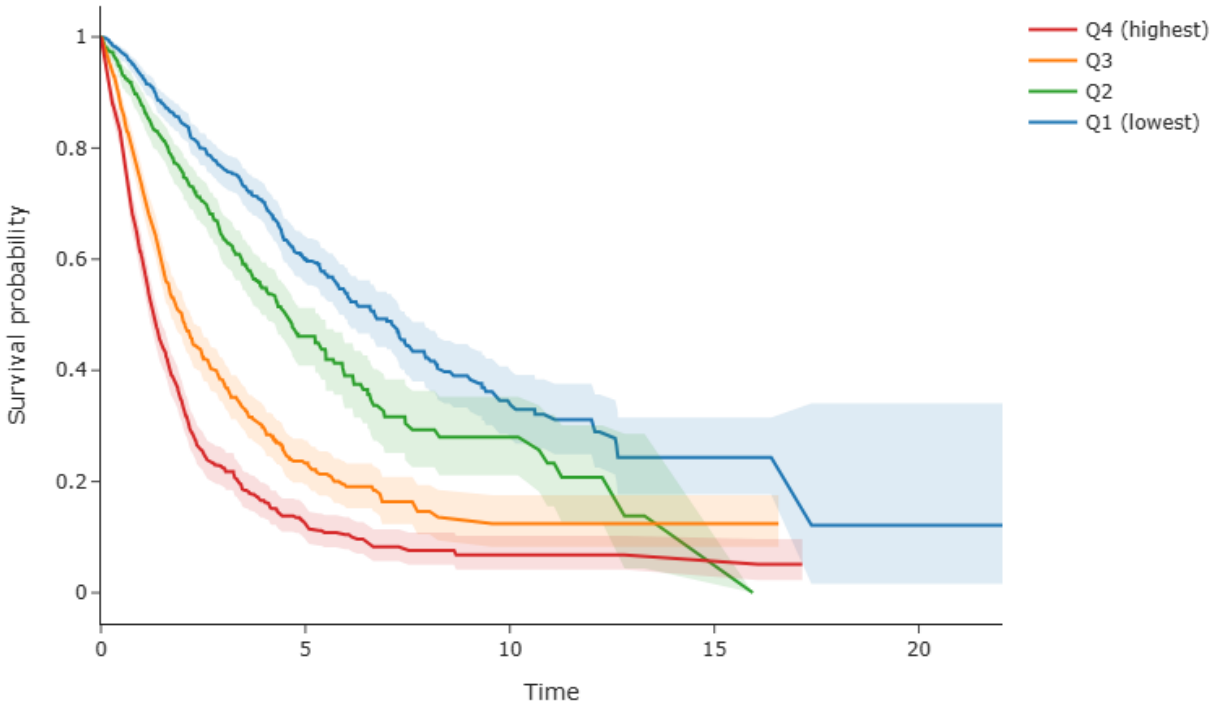
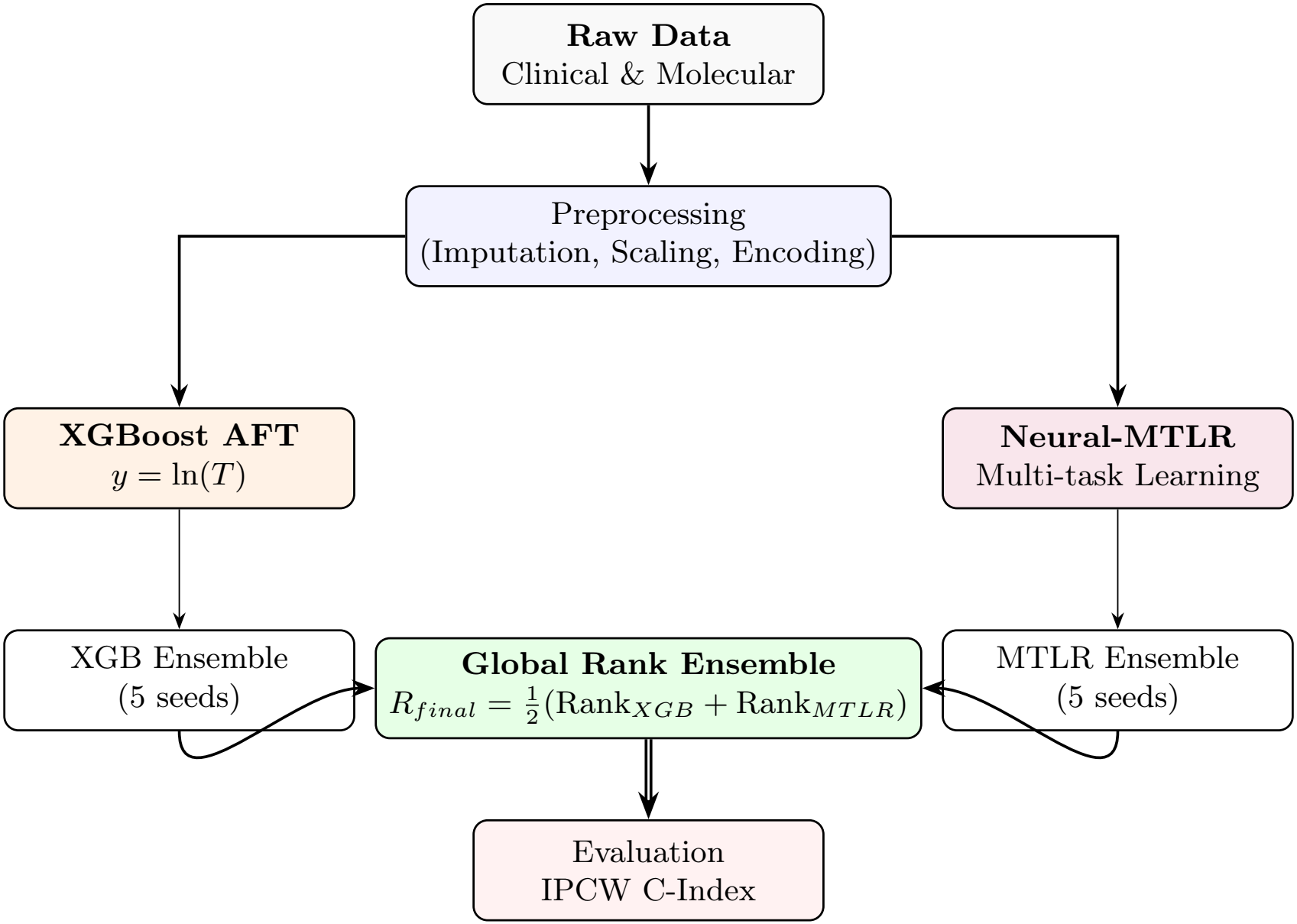


Figure 6 – **Kaplan–Meier** survival curves by molecular risk quartile

- Clear monotone pattern : higher risk quartiles are associated with poorer survival.

Model Architecture Overview



The **Accelerated Failure Time (AFT)** model is a robust alternative to Cox models, focusing on the survival time scale.

Acceleration Assumption

Covariates x act as a multiplicative factor $\exp(\eta(x))$ on survival time :

$$T = e^{\eta(x)} \cdot T_0 \quad \Longrightarrow \quad \ln(T) = \eta(x) + \ln(T_0)$$

- $\eta(x) > 0$: The event occurs **earlier** (accelerated time).
- $\eta(x) < 0$: The event is **delayed** (prolonged survival).

The XGBoost Advantage : Instead of a simple linear function, it learns a flexible $\eta(x)$ via tree boosting, capturing **non-linear effects** and complex genomic interactions.

Training is performed by minimizing the **Negative Log-Likelihood** to account for incomplete data.

Likelihood for Patient i

$$\mathcal{L}_i = \delta_i \underbrace{\ln f(z_i)}_{\text{Observed Event}} + (1-\delta_i) \underbrace{\ln S(z_i)}_{\text{Censoring}}$$

$$\text{where } z_i = \frac{\ln t_i - \eta_i}{\sigma}$$

- **Scale Parameter** σ : Controls log-survival dispersion (lower σ = higher confidence).
- **Numerical Stability** : Uses a second-order Taylor expansion ; gradients depend on the chosen distribution (Weibull, Log-Normal).

Multi-Task Logistic Regression (MTLR) treats survival as a sequence of dependent binary classification tasks.

- **Time Grid** : Defines k time points $\tau_1, \ldots, \tau_k$ (e.g., event quantiles) to partition the time axis.
- **Target Encoding** :
  - Pre-event : Vector of 1s (Survival).
  - Post-event : Vector of 0s (Event occurred).

Key Advantage

No Proportional Hazards Assumption : Allows the impact of a covariate to change or fluctuate over time.

Neural-MTLR

Architecture and Monotonicity

A neural network implemented via `nn.Sequential` extracts non-linear features prior to the MTLR layer.

From Features to Survival Curve

1. **Feature encoding :** Dense layers map clinical data into a latent representation.
2. **Piecewise linear scoring :** The MTLR layer outputs k scores $\{\phi_1, \ldots, \phi_k\}$.
3. **Global Softmax :** Ensures

$$\sum_j P(\text{death in interval } j) = 1.$$

Smoothing Regularization :

$$\text{Penalty} = \gamma \sum_{j=1}^{k-1} \|\theta_{j+1} - \theta_j\|_2^2$$

This yields a **monotone and stable** survival curve $S(t)$, avoiding unrealistic discontinuities.

Model Comparison and Ensemble Strategy

XGBoost AFT

Type : Parametric (Flexible η)
Assumption : Log-linearity in time
Strength : Robust to small samples
Output : Scalar log-time

Neural-MTLR

Type : Non-parametric
Assumption : No hazard structure
Strength : Captures non-PH effects
Output : Survival distribution

Rank-Based Ensemble Strategy

Combines complementary strengths by aggregating ranks :

$$\text{Score}_{\text{final}} = \text{mean}\left(\text{rank}(\hat{y}_{\text{AFT}}) + \text{rank}(P_{\text{MTLR}})\right)$$

Key Benefits :

Robust to scale differences • Reduced variance • Improved stability

Effect of Ensembling — XGBoost AFT

IPCW C-index (5-fold nested cross-validation)

Model	**Mean ± SD**	**95% CI**
Single model	0.7223 ± 0.0139	$[0.7050\,;\,0.7395]$
Ensemble (5 seeds, rank-avg.)	0.7243 ± 0.0131	$[0.7080\,;\,0.7406]$

Paired comparison (fold-wise) :

$$\Delta C = +0.0021, \quad t = 2.70, \quad p = 0.054$$

Interpretation

- Small but consistent improvement.
- Borderline statistical significance at the 5% level.
- Ensemble reduces variance and stabilises rankings.

Effect of Ensembling — Neural-MTLR

IPCW C-index (5-fold nested cross-validation)

Model	**Mean ± SD**	**95% CI**
Single model	0.6997 ± 0.0163	$[0.6795\,;\,0.7199]$
Ensemble (5 seeds, rank-avg.)	0.7102 ± 0.0151	$[0.6914\,;\,0.7290]$

Paired comparison (fold-wise) :

$$\Delta C = +0.0105, \quad t = 6.56, \quad p = 0.0028$$

Interpretation

- Clear and statistically significant improvement.
- Rank-based ensembling is particularly beneficial here.
- Suggests complementary inductive bias across random seeds.