Settima edizione di

AIEOP...
...in Lab

G.d.L. Biologia Cellulare Molecolare
AIEOP
ASSOCIAZIONE ITALIANA EMATOLOGIA ONCOLOGIA PEDIATRICA

clinTALL: classificazione multimodale dei sottotipi e predizione degli esiti terapeutici nella LLA-T pediatrica tramite machine learning

Stefano Rebellato, PhD

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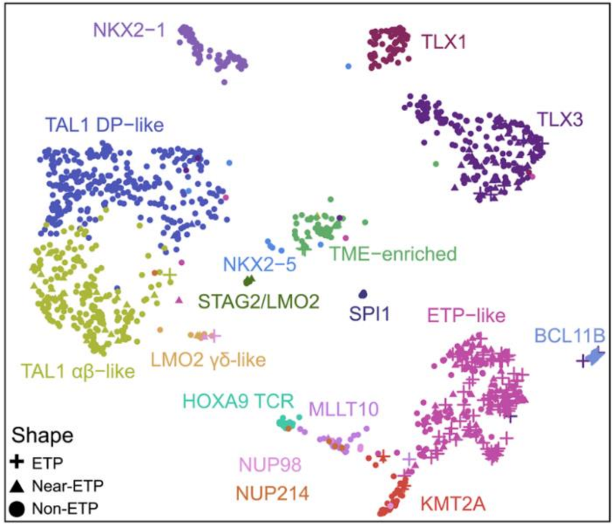
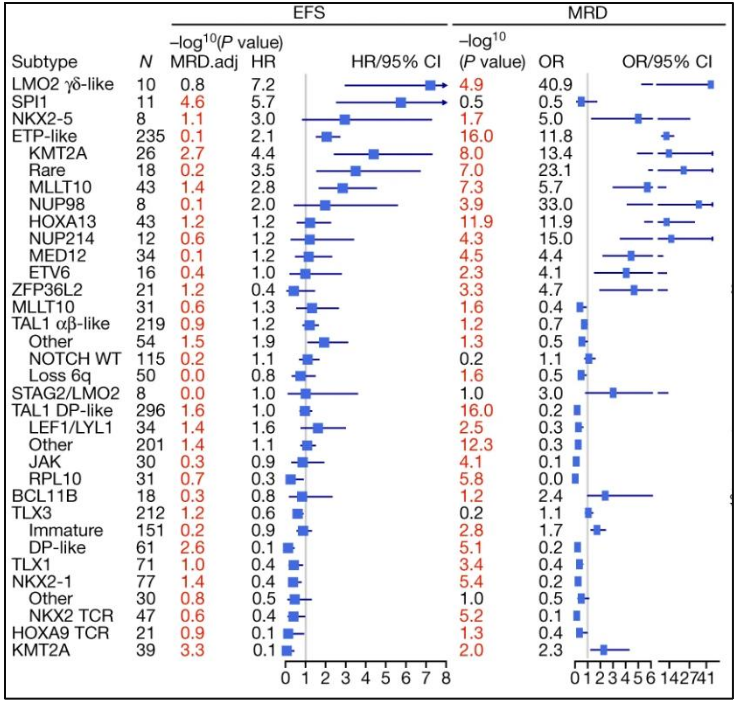
Nothing to disclose

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

T-cell acute lymphoblastic leukemia

- High-risk ALL subtype
- Poorly defined risk-stratification markers



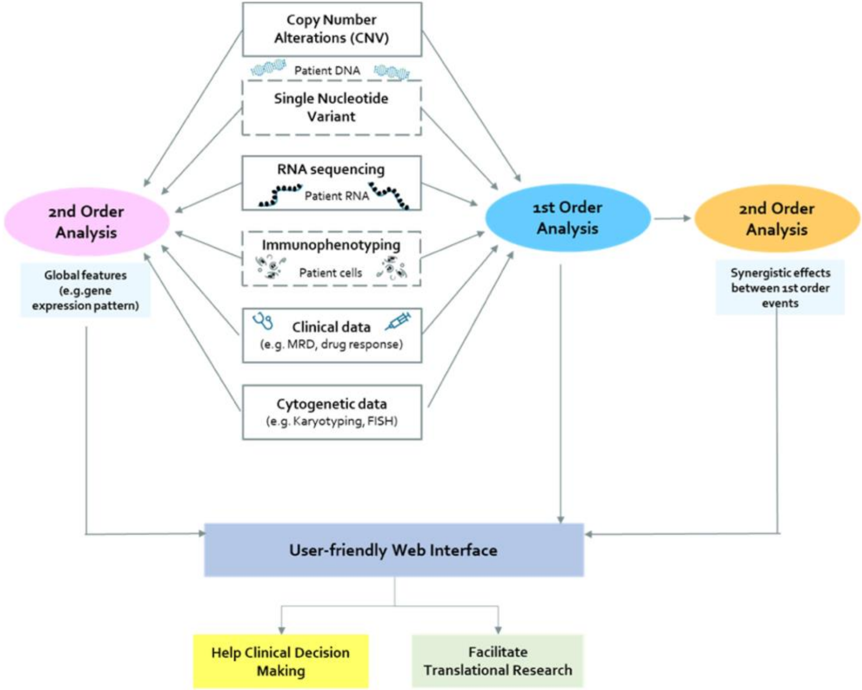


Subtype	*N*	EFS –log^{10}(*P* value) MRD.adj	EFS HR	MRD –log^{10} (*P* value)	MRD OR
LMO2 γδ-like	10	0.8	7.2	4.9	40.9
SPI1	11	4.6	5.7	0.5	0.5
NKX2-5	8	1.1	3.0	1.7	5.0
ETP-like	235	0.1	2.1	16.0	11.8
KMT2A	26	2.7	4.4	8.0	13.4
Rare	18	0.2	3.5	7.0	23.1
MLLT10	43	1.4	2.8	7.3	5.7
NUP98	8	0.1	2.0	3.9	33.0
HOXA13	43	1.2	1.2	11.9	11.9
NUP214	12	0.6	1.2	4.3	15.0
MED12	34	0.1	1.2	4.5	4.4
ETV6	16	0.4	1.0	2.3	4.1
ZFP36L2	21	1.2	0.4	3.3	4.7
MLLT10	31	0.6	1.3	1.6	0.4
TAL1 αβ-like	219	0.9	1.2	1.2	0.7
Other	54	1.5	1.9	1.3	0.5
NOTCH WT	115	0.2	1.1	0.2	1.1
Loss 6q	50	0.0	0.8	1.6	0.5
STAG2/LMO2	8	0.0	1.0	1.0	3.0
TAL1 DP-like	296	1.6	1.0	16.0	0.2
LEF1/LYL1	34	1.4	1.6	2.5	0.3
Other	201	1.4	1.1	12.3	0.3
JAK	30	0.3	0.9	4.1	0.1
RPL10	31	0.7	0.3	5.8	0.0
BCL11B	18	0.3	0.8	1.2	2.4
TLX3	212	1.2	0.6	0.2	1.1
Immature	151	0.2	0.9	2.8	1.7
DP-like	61	2.6	0.1	5.1	0.2
TLX1	71	1.0	0.4	3.4	0.4
NKX2-1	77	1.4	0.4	5.4	0.2
Other	30	0.8	0.5	1.0	0.5
NKX2 TCR	47	0.6	0.4	5.2	0.1
HOXA9 TCR	21	0.9	0.1	1.3	0.4
KMT2A	39	3.3	0.1	2.0	2.3

Pölönen et al., Nature, 2024.

clinALL

- An AI-assisted clinical framework that integrates both genomic and clinical data



Copy Number Alterations (CNV)

Patient DNA

Single Nucleotide Variant

RNA sequencing

Patient RNA

Immunophenotyping

Patient cells

Clinical data (e.g. MRD, drug response)

Cytogenetic data (e.g. Karyotyping, FISH)

2nd Order Analysis

Global features (e.g.gene expression pattern)

1st Order Analysis

2nd Order Analysis

Synergistic effects between 1st order events

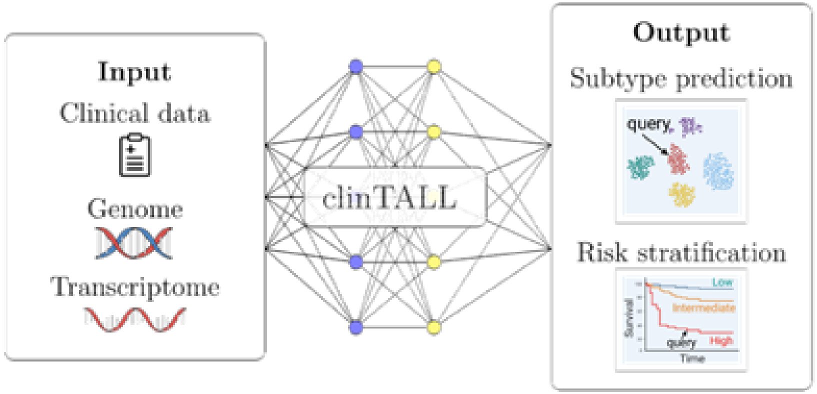
User-friendly Web Interface

Help Clinical Decision Making

Facilitate Translational Research

clinTALL

- Subtype classification and treatment outcome prediction in pediatric T-ALL
- ML-based framework



Input
Clinical data
Genome
Transcriptome

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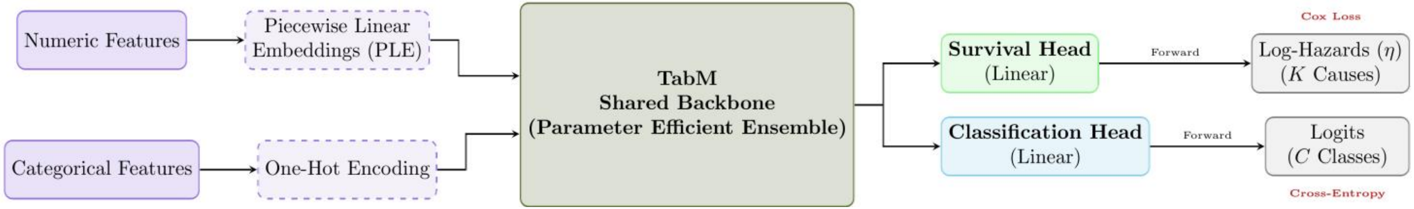
Output
Subtype prediction
Risk stratification



Numeric Features
Piecewise Linear Embeddings (PLE)
Categorical Features
One-Hot Encoding

TabM
Shared Backbone
(Parameter Efficient Ensemble)

Survival Head
(Linear)
Forward
Log-Hazards (η)
(K Causes)
Cox Loss

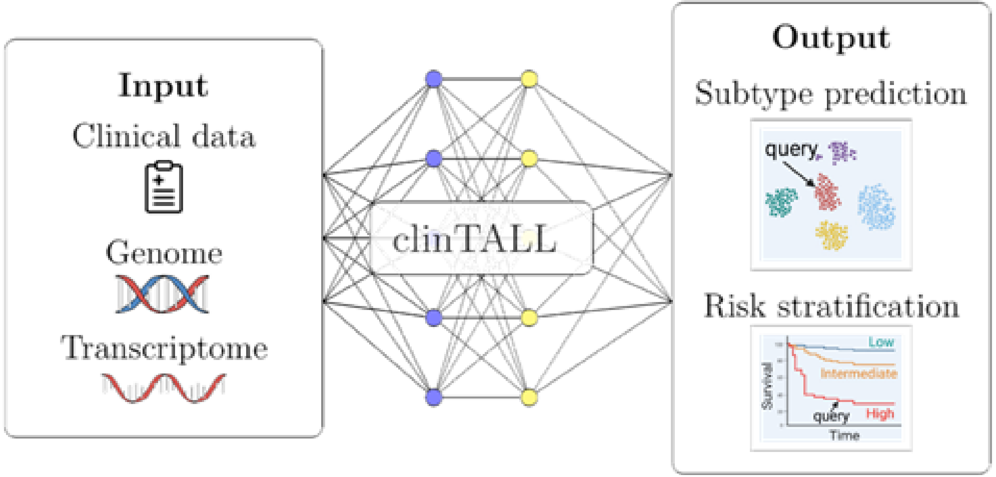
Classification Head
(Linear)
Forward
Logits
(C Classes)
Cross-Entropy

Stoiber et al., under revision

clinTALL

Training dataset

COG AALL0434
Pölönen et al.

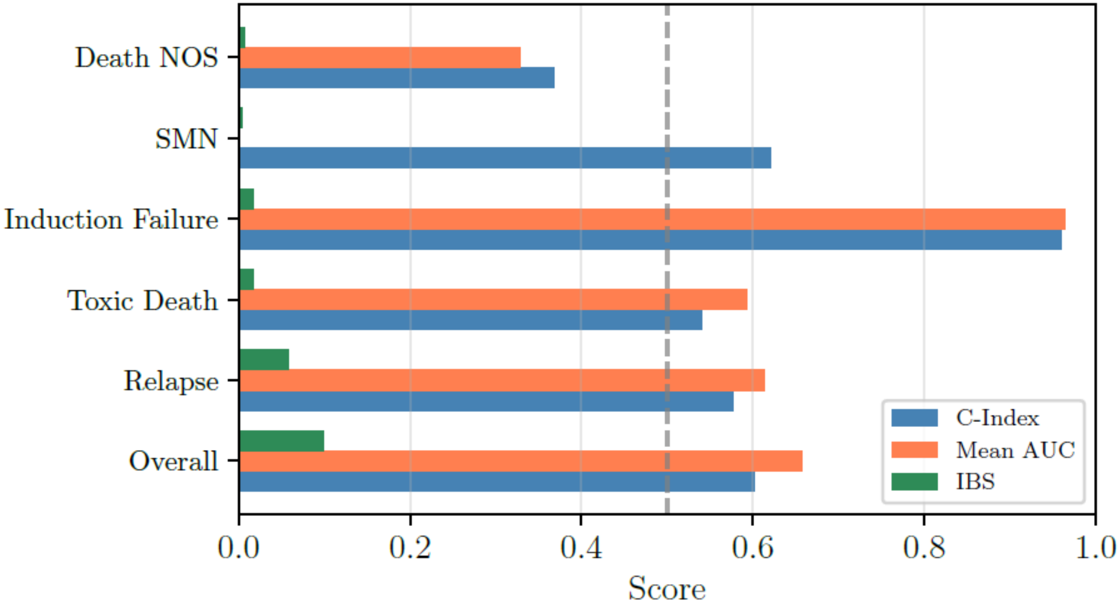


AIEOP-BFM 2017
-
NOPHO ALL2008
Hackenhaar et al.

Validation datasets

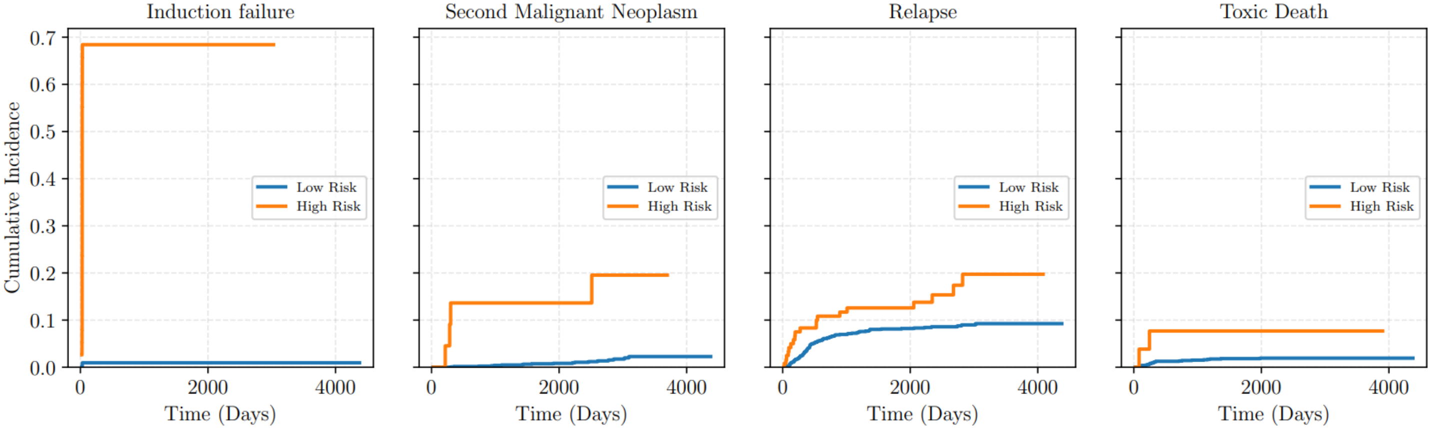
Outcomes and limitations of a single risk score

- Standard model successfully identifies patients with unfavorable outcome
- Can we move from a single „unfavorable“ outcome prediction model?



Cumulative incidence of events

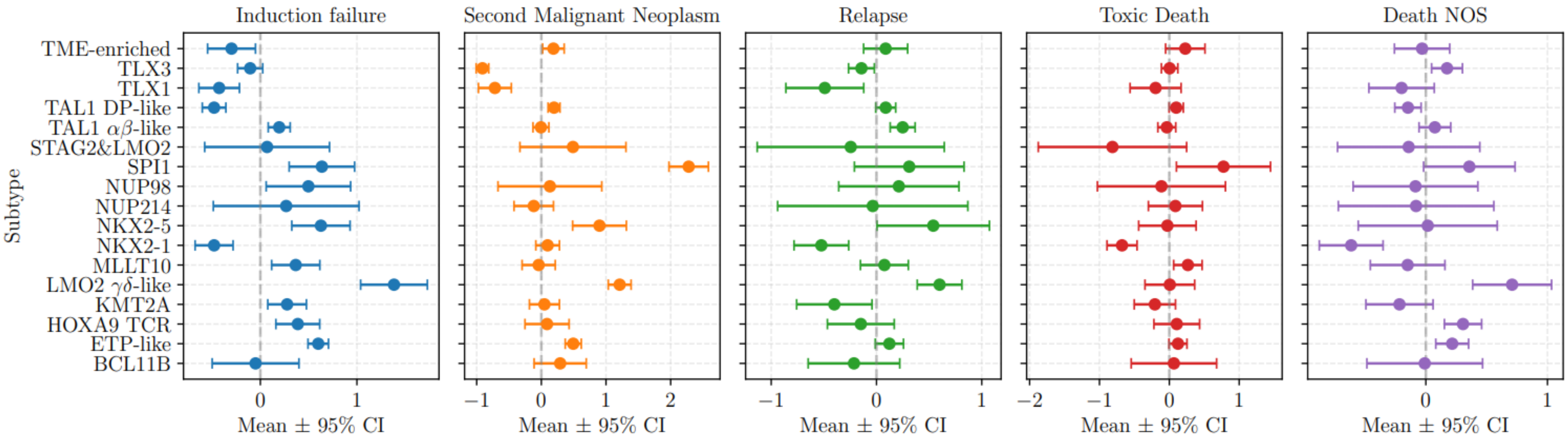
- Competing risk model
- Risk group stratification defined on the third percentile of the observed scores of each event



* Patients were classified as high-risk if their predicted cause-specific log-hazard was at or above the percentile threshold corresponding to the observed event rate for each specific event type

Cause-specific hazard coefficients per molecular subtype

- LMO2 γδ-like – induction failure and relapse
- SPI1 – second malignancy and toxic death



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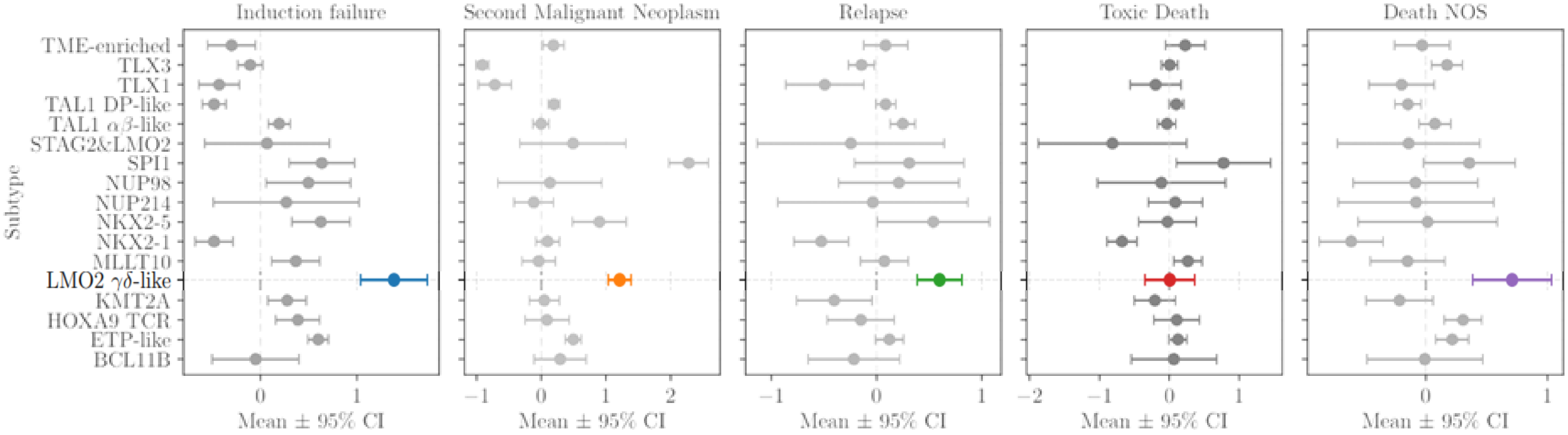

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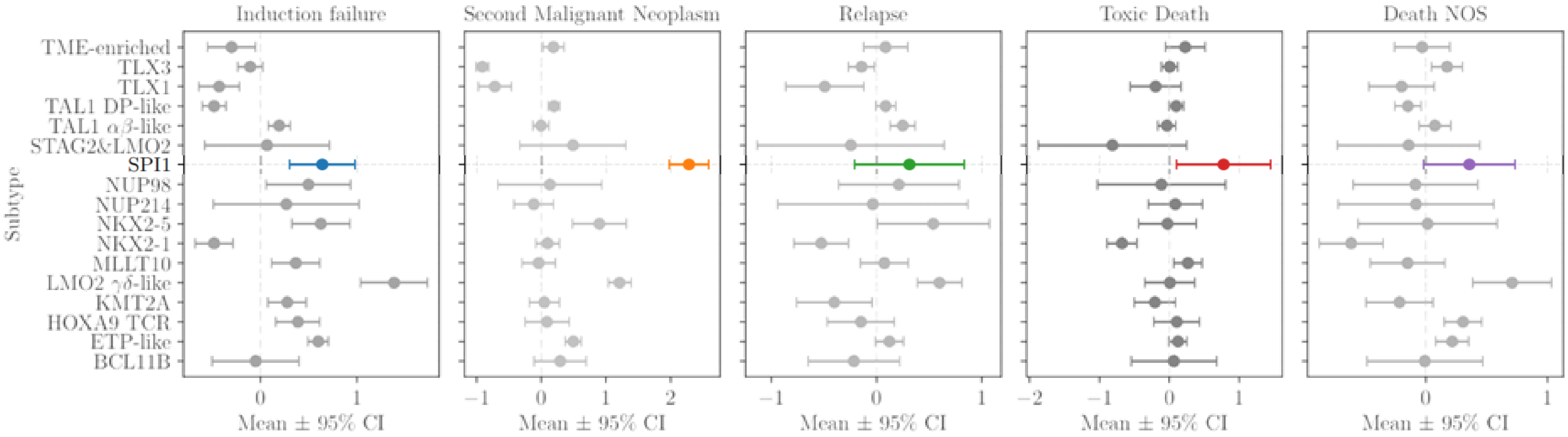
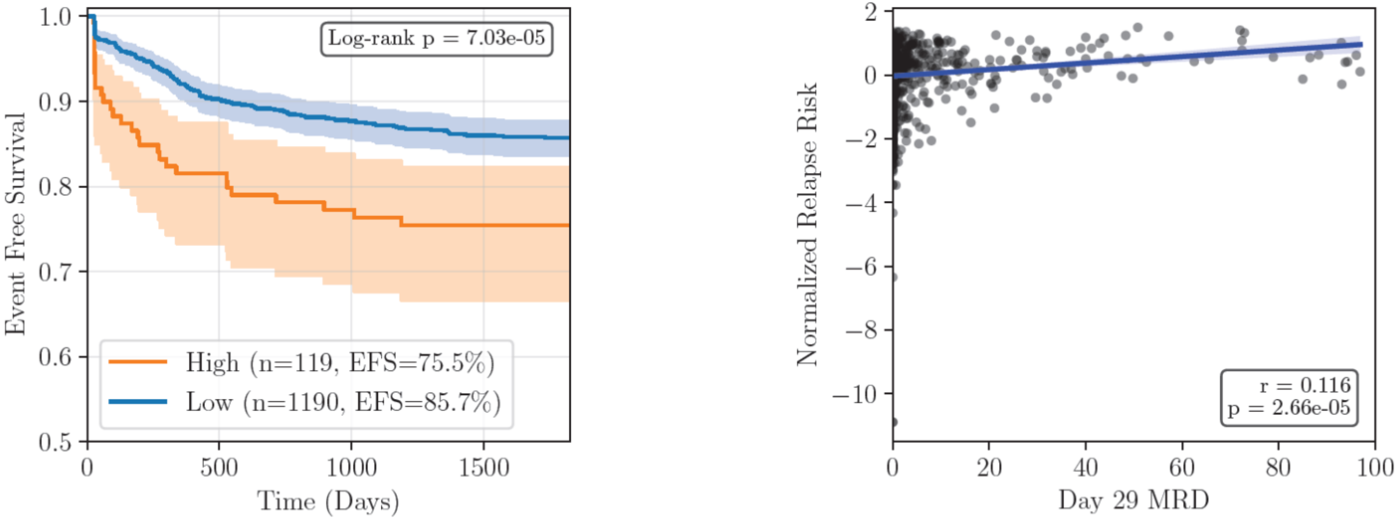


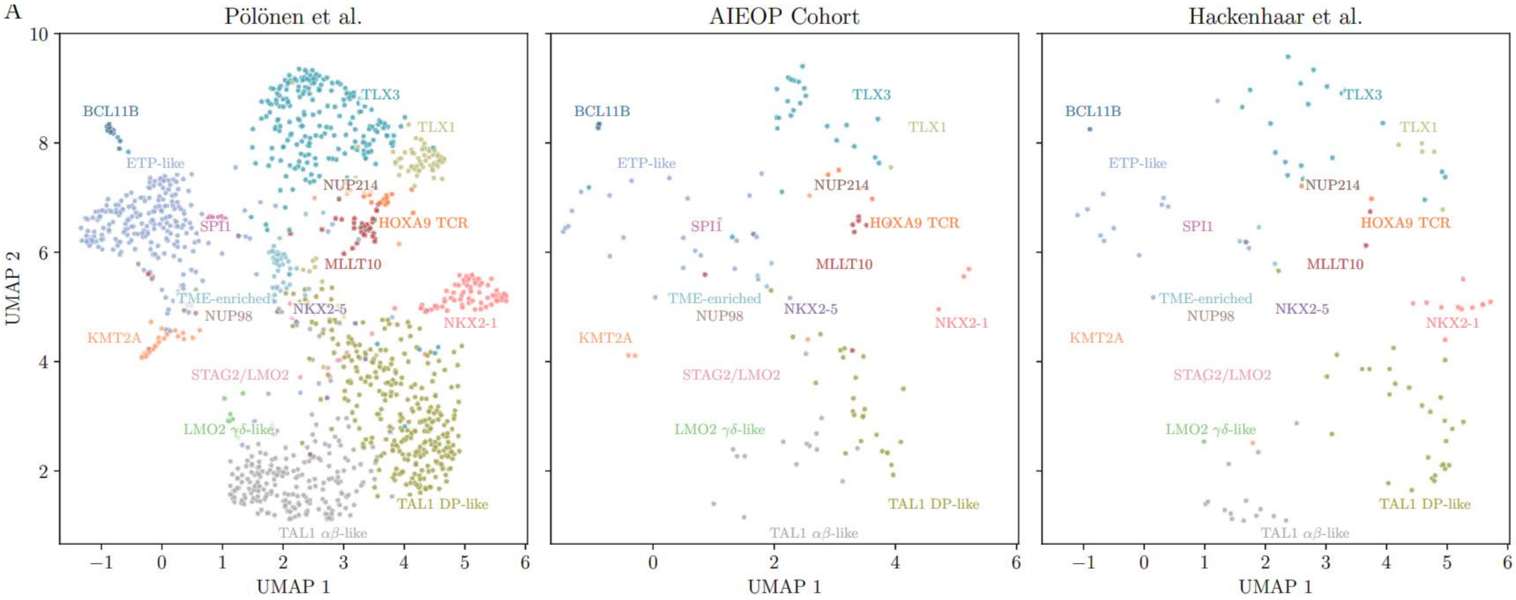
High-risk patients have lower 5-year EFS

- Relapse-specific risk score stratification
- Lower 5-year EFS in high-risk group
- Relapse risk score correlates with day 29 MRD



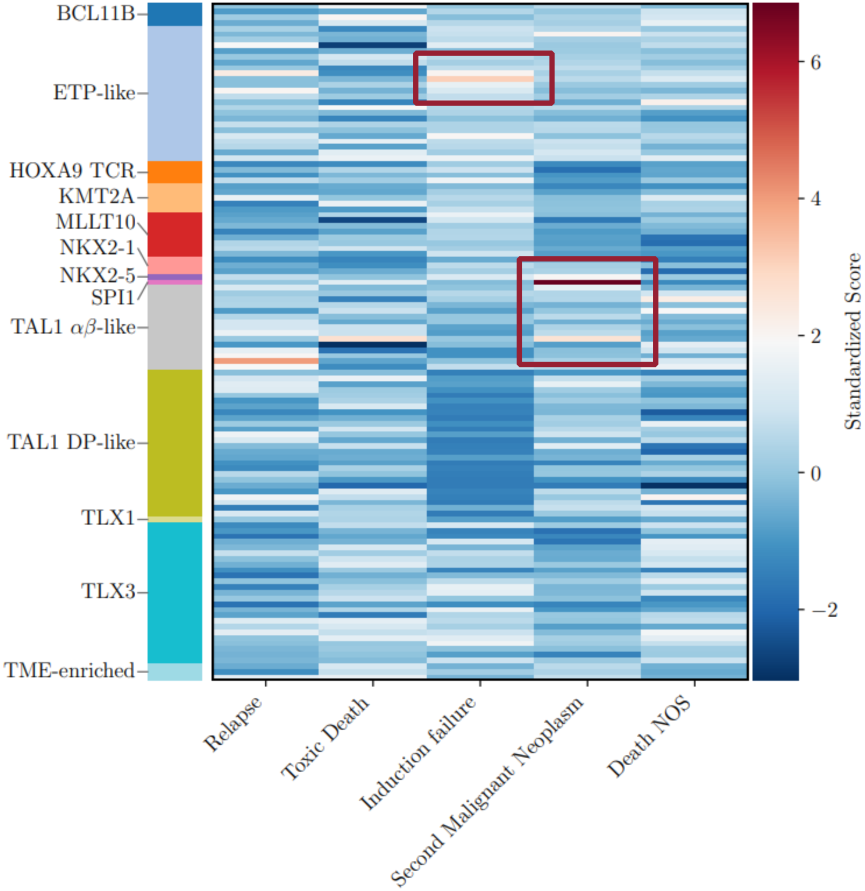
Performance in validation cohorts

- Correct assignment based on the subtypes
- Consistent molecular subtype distribution in two independent validation cohorts



AIEOP-BFM 2017

- In total 8 predicted events
  1) 5 relapses
  2) 2 SMN
  3) 1 induction failure
- Following treatment outcome assessment, predicted outcomes were confirmed in all patients



Conclusions and future directions

- clinTALL provides a unified multimodal, multitask framework
  1) molecular subtype
  2) outcome prediction
- Longitudinal data might be needed to improve prediction for later timepoints
- Exploratory studies in European cohorts
  1) Whole transcriptome sequencing of 172 T-ALL cases from German AIEOP-BFM 2009 study
  2) Additional 50 T-ALL cases from Italian AIEOP-BFM 2009 study
- Implementation of a Web-based interface

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