Development of a polygenic risk score to predict recurrence and survival in patients with resected cholangiocarcinoma

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INTRODUCTION

- **Cholangiocarcinoma (CCA)** is a rare and aggressive malignancy originating in the bile ducts.
- Potentially curative interventions include surgical resection with negative margins (R0) and liver transplantation.
- However, the likelihood of **post-surgical recurrence remains high**, with 50–70% of patients experiencing recurrence within five years.
- There is an urgent need for reliable prognostic biomarkers to guide clinical decision-making and personalize postoperative care.
- Numerous tumor-derived prognostic biomarkers have been proposed, but none have reached clinical application due to limitations such as single-center study designs, small patient cohorts, and semi-quantitative methodologies.

AIM

To identify and validate robust quantitative prognostic biomarkers for CCA by analyzing tumor mRNA expression, integrating them using machine learning, and developing a web-based tool to predict tumor recurrence and overall survival.

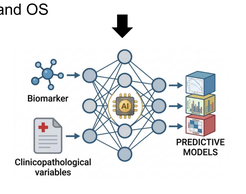
METHODS

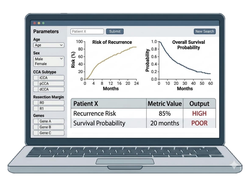
Literature Review → Identification of potential CCA tissue prognostic biomarkers through systematic literature review

Meta-Analysis → Selection of potential biomarkers through Cox PH overall survival (OS) analysis in five transcriptomic cohorts: E-MATB-6389, GSE89749, OEZ008243, GSE26566, EGA00001000950

- Collection of an international cohort including tumor tissue from 221 patients undergoing tumor resection
- Measurement of mRNA expression by high-throughput TaqMan OpenArray RT-qPCR
- Cox PH analyses on feature association with recurrence-free survival (RFS) and OS

Multicentre validation by OpenArray (PCR)





WEB-BASED CLINICAL CALCULATOR

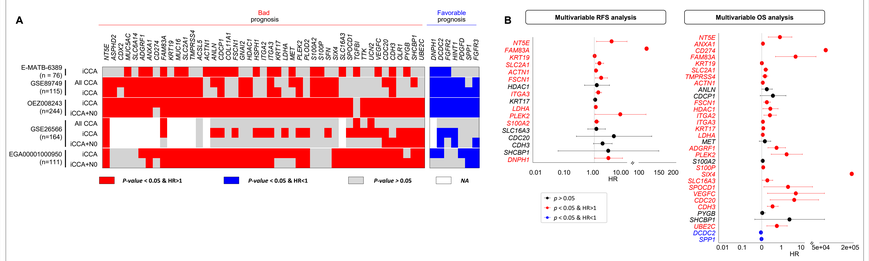
- Training and testing of machine learning (ML)–based models using nested cross-validation.
- Feature reduction and model optimization for prediction of RFS and OS.

CONCLUSIONS

- We identified and validated a robust panel of prognostic tissue biomarkers in patients with resected CCA.
- Integration of these biomarkers with clinical variables into ML-based prognostic models enabled accurate prediction of RFS and OS.
- The resulting web-based tool allows clinicians to input RT-qPCR results for the validated biomarkers and obtain precise, individualized prognostic predictions for postoperative recurrence and survival.

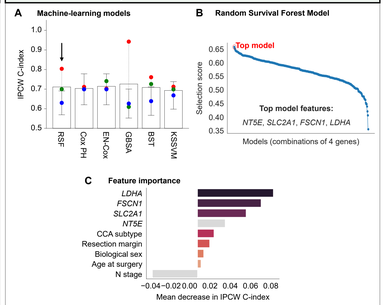
RESULTS

Figure 1. *Identification of prognostic tumor biomarkers by meta-analysis and validation in an international CCA cohort using OpenArray RT-qPCR*



(**A**) Heatmap summarizing 52 prognostic biomarkers across analysis groups: 45 associated with poor prognosis (red) and 7 with favorable prognosis (blue). Genes are classified according to hazard ratio direction (HR > 1, poor prognosis; HR < 1, favorable prognosis) and statistical significance ($p < 0.05$). (**B**) Forest plots of multivariable Cox proportional hazards analyses for the 17 genes identified as significantly associated with prognosis in univariable analyses for RFS (left) and OS (right). Models were adjusted for clinicopathological covariates, including resection margin status, lymph node involvement, T stage, CCA subtype, and center of origin. Eleven genes retained independent prognostic significance.

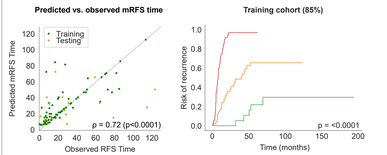
Figure 2. *Development and evaluation of ML–based predictive models for RFS*



(**A**) IPCW C-index of six ML-based RFS models under nested CV, training, and testing cohorts. (**B**) IPCW C-index–based selection of Random Survival Forest (RSF) models across all 4 gene-combinations selected from 11 RFS prognostic genes. (**C**) Feature importance of the final RSF model (NT5E, SLC2A1, FSCN1, LDHA + clinical variables).

Figure 3. *Performance of predictive models integrating three genes (LDHA, FSCN1, and SLC2A1) and four clinical variables (CCA subtype, resection margin, sex, and age at surgery) for RFS and OS*

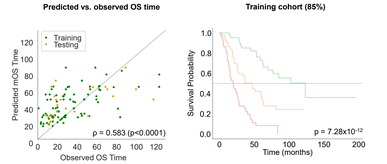
A Model performance for post-surgical **RFS**



	High-risk group	Moderate-risk group	Low-risk group
N° of patients	41	47	23
mRFS, *months* (95% CI)	5.98 (4.76 – 7.85)	17.48 (12.71 – 29.17)	– (69.55 -)
Log-rank Test	<0.0001 *(vs low)*	<0.0001 *(vs high)*	<0.001 *(vs moderate)*

	High-risk group	Moderate-risk group	Low-risk group
N° of patients	6	16	6
mRFS, *months* (95% CI)	18.13 (4.99 – 48.49)	19.09 (6.80 – 70.43)	– (10.55 -)
Log-rank Test	0.02 (vs low)	0.33 *(vs high)*	0.05 *(vs moderate)*

B Model performance for post-surgical **OS**

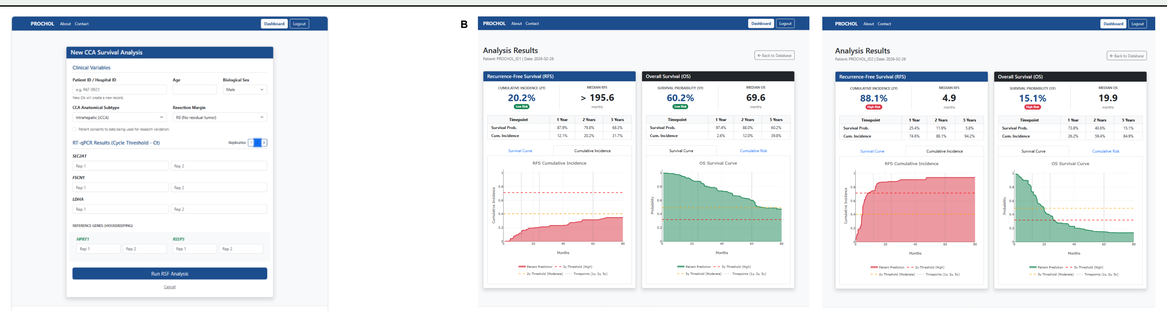


	High-risk group	Moderate-risk group	Low-risk group
N° of patients	44	44	44
mOS, *months* (95% CI)	19.78 (14.62 – 26.12)	36.73 (26.12 – 61.07)	123.09 (62.52 -)
Log-rank Test	<0.0001 *(vs low)*	<0.001 *(vs high)*	<0.001 *(vs moderate)*

	High-risk group	Moderate-risk group	Low-risk group
N° of patients	10	13	11
mOS, *months* (95% CI)	12.94 (8.54 – 21.08)	70.47 (19.28 – 99.57)	88.99 (13.83 – 88.99)
Log-rank Test	0.04 *(vs low)*	0.08 *(vs high)*	0.73 *(vs moderate)*

Model performance for post-surgical RFS (**A**) and OS (**B**) prediction.Median predicted versus observed survival time in uncensored patients (left panels).Cumulative incidence curves for recurrence (RFS) and survival (OS) stratified into high- (red), moderate- (yellow), and low-risk (green) groups in the training (middle panels) and testing (right panels) cohorts.

Figure 4. *Overview of the PROCHOL web-based clinical calculator for predicting RFS and OS after surgical resection*

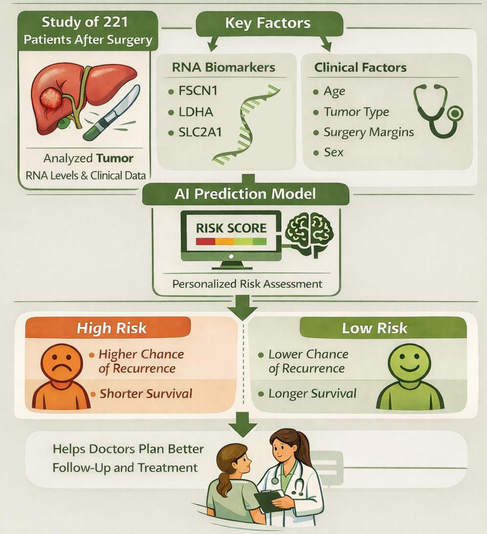


(**A**) Data entry interface for clinical variables—age, sex, CCA subtype, and resection margin—alongside RT-qPCR cycle threshold (Ct) values for the three-gene signature (SLC2A1, FSCN1, LDHA) and housekeeping reference genes (HPRT1, REEP5). (**B**) Examples of patient-level visual reports estimating individual recurrence risk and predicted survival.

PATIENT-FRIENDLY SUMMARY

*Predicting **Recurrence and Survival** in **Cholangio**carcinoma*

Researchers developed a new **genetic test** to help predict if bile duct cancer (*cholangiocarcinoma*) will come back after surgery and how long a patient might live.



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