Deciphering the Prognostic Landscape of Regulated Cell Death in Colorectal Cancer using a Two-Step Machine Learning Framework

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भारतीय प्रौद्योगिकी संस्थान हैदराबाद
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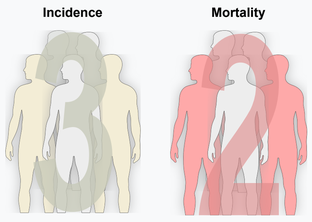
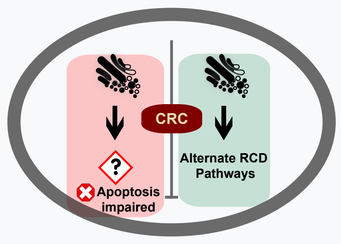
Briefings in Bioinformatics

INTRODUCTION

COLORECTAL CANCER GLOBAL BURDEN

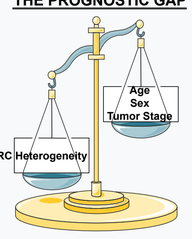


REGULATED CELL DEATH LOOPHOLE



Non-apoptotic Regulated Cell Death pathways:
New avenues of therapy

THE PROGNOSTIC GAP



Inaccurate prediction of CRC prognosis with traditional clinical factors: CRC Heterogeneity

THE INNOVATIVE OPPORTUNITY

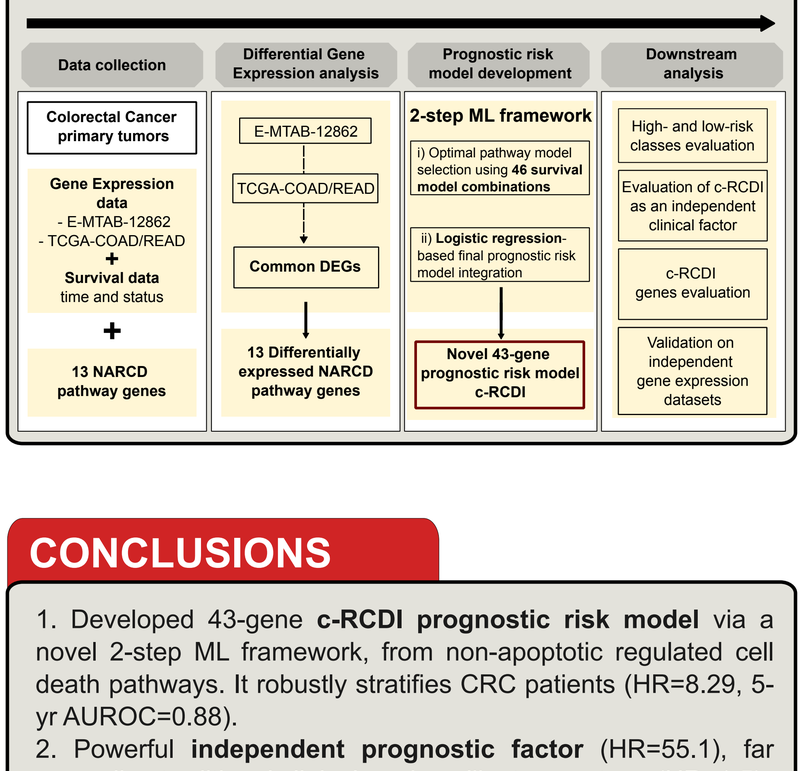
Exploring the symphony of NARCD pathways:
Precision Medicine/Therapy

OBJECTIVES

1. Develop a robust **c-RCDI risk model** from 13 NARCD pathways using a **novel two-step ML framework**.
2. Validate the c-RCDI as a powerful, **independent prognostic factor** against clinical benchmarks.
3. Uncover the **biological and immunological drivers** (oncogenic pathways, immune infiltration) of the high-risk class.
4. Test the c-RCDI's ability to **predict immunotherapy response** and identify **targeted drug sensitivities**.

METHODOLOGY

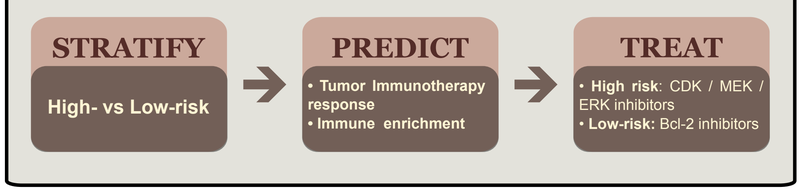
Fig. 1: Overall study design for the development of c-RCDI prognostic model.



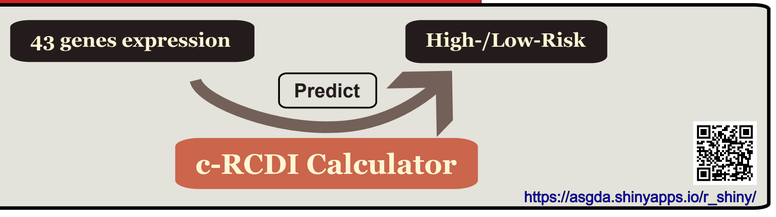
CONCLUSIONS

1. Developed 43-gene **c-RCDI prognostic risk model** via a novel 2-step ML framework, from non-apoptotic regulated cell death pathways. It robustly stratifies CRC patients (HR=8.29, 5-yr AUROC=0.88).
2. Powerful **independent prognostic factor** (HR=55.1), far exceeding traditional clinical markers like tumor stage (HR=1.5).
3. Biologically coherent: The model captures **core CRC oncogenic pathways** (*MYC*, EMT) and **immunosuppressive microenvironments.**
4. Identifies novel vulnerabilities by selecting **under-explored genes** (*ATP2B4*, *CHMP6*, *MAP1B*) involved in cellular homeostasis and metabolic resilience.
5. A dual-purpose clinical tool that predicts **immunotherapy failure (high TIDE score)** and guides **targeted therapies** (e.g., CDK/MEK inhibitors).

CLINICAL IMPACT



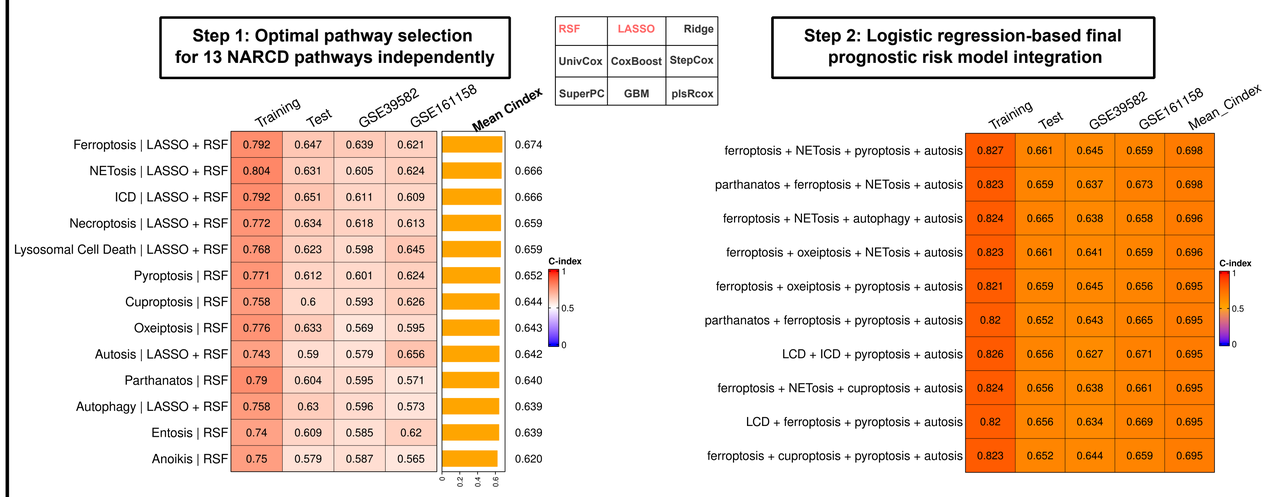
TOOL DEPLOYMENT



RESULTS

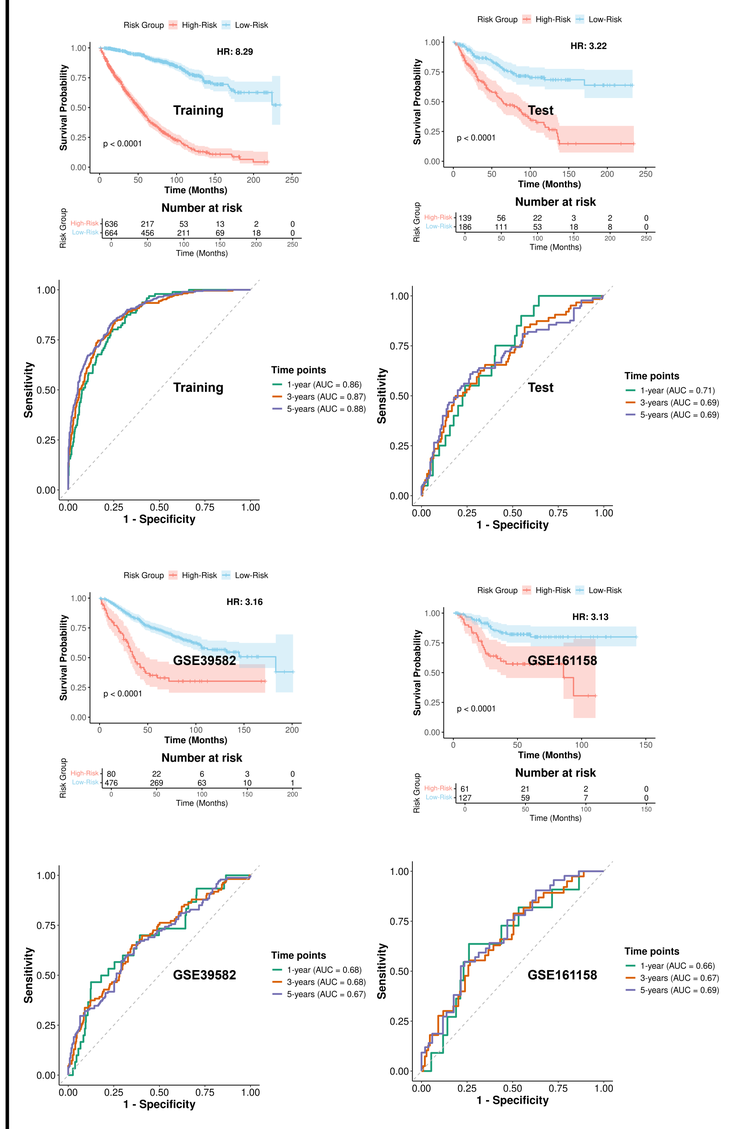
Novel two-step ML framework

Fig. 2: Heatmaps showing the best models from our step 1 and step 2 of the novel ML framework leading to the formation of c-RCDI.



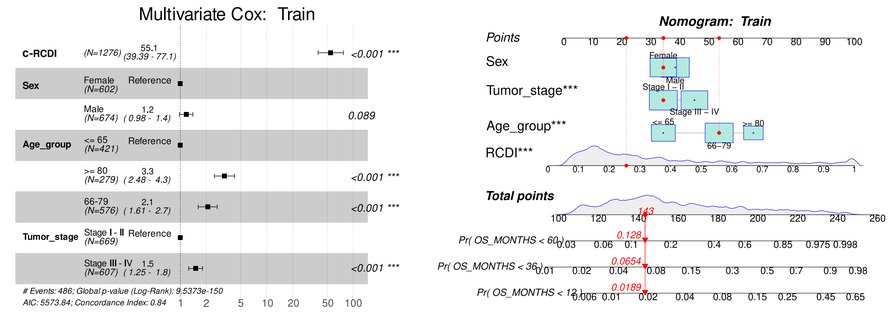
c-RCDI evaluation

Fig. 3: Constitution and performance of the c-RCDI prognostic risk model.



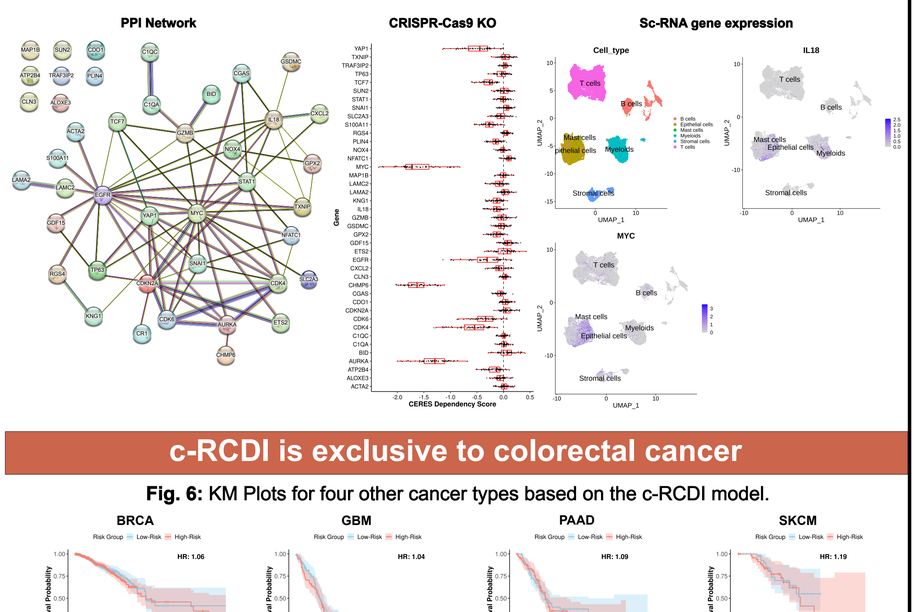
c-RCDI: an independent prognostic factor

Fig. 4: Multivariate Cox Regression and Nomogram analysis.



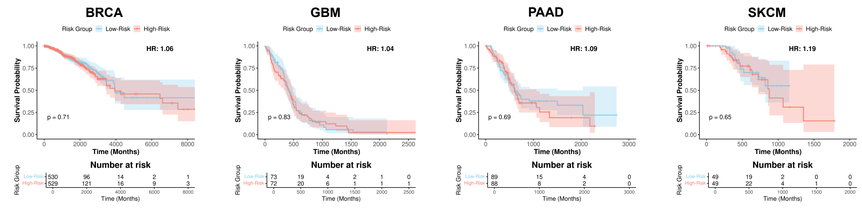
c-RCDI genes analysis

Fig. 5: PPI Network, CRISPR-Cas9 KO, and single cell gene analyses.



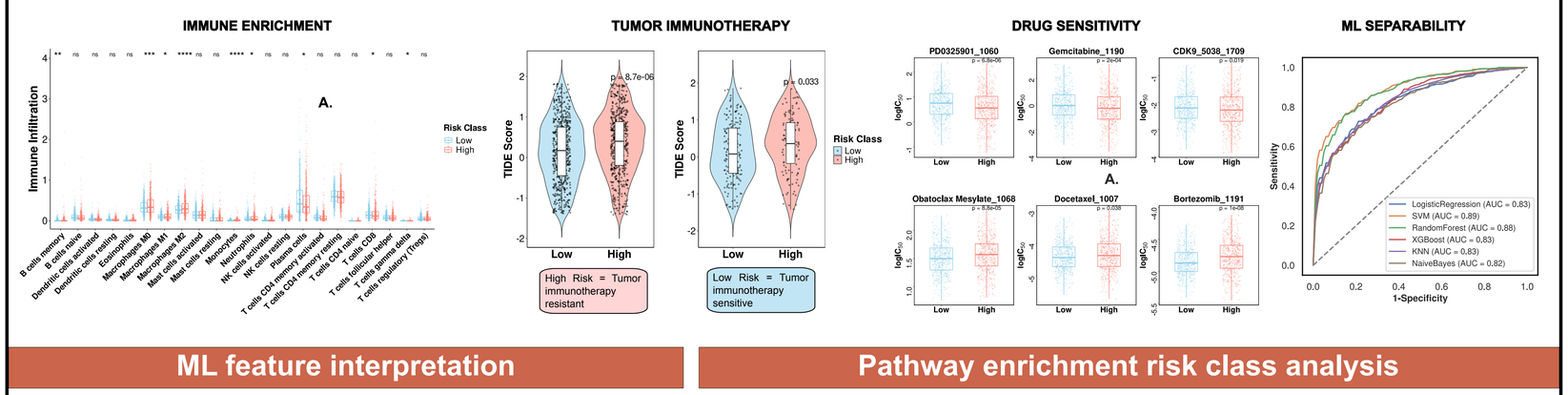
c-RCDI is exclusive to colorectal cancer

Fig. 6: KM Plots for four other cancer types based on the c-RCDI model.



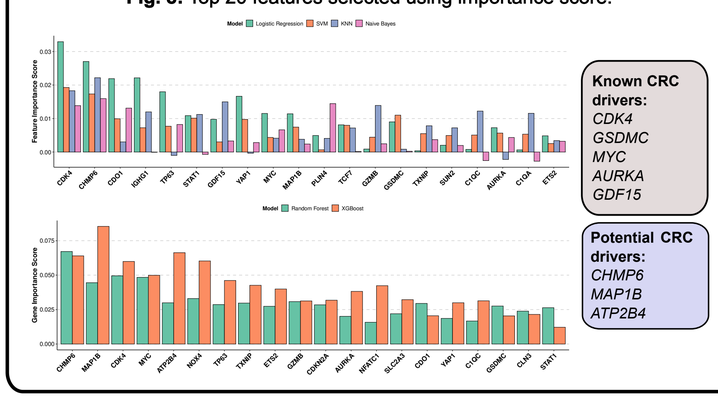
Clinical interpretation of c-RCDI

Fig. 7: Immune Enrichment, TIDE, Drug sensitivity and ML analysis for high- and low-risk classes.



ML feature interpretation

Fig. 8: Top 20 features selected using importance score.

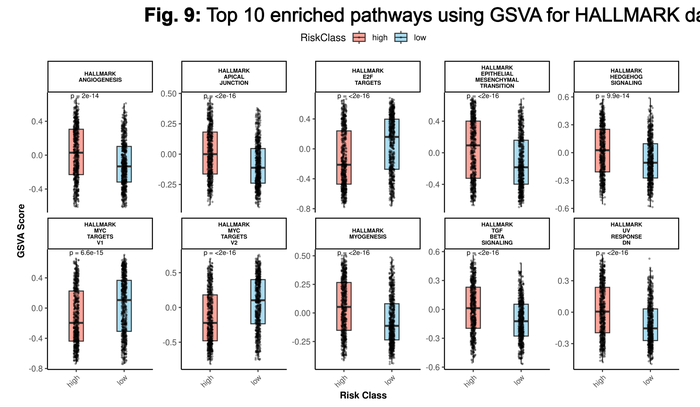


Known CRC drivers:
CDK4
GSDMC
MYC
AURKA
GDF15

Potential CRC drivers:
CHMP6
MAP1B
ATP2B4

Pathway enrichment risk class analysis

Fig. 9: Top 10 enriched pathways using GSVA for HALLMARK database.



Core CRC Pathways:
Angiogenesis
EMT
MYC Pathway
TGF-beta

High Risk = High oncogenic and immune suppressive pathways

ACKNOWLEDGEMENTS

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2. Cao K, Zhu J, Lu M, et al. Analysis of multiple programmed cell death-related prognostic genes and functional validations of necroptosis-associated genes in oesophageal squamous cell carcinoma. EBioMedicine 2024; 99:104920.