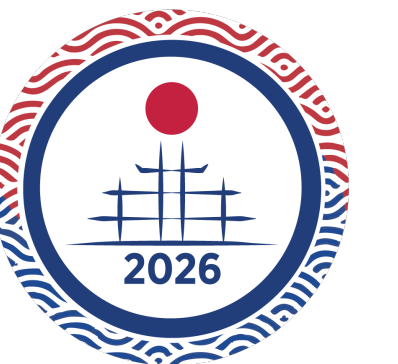




EP.06.17: Prediction of Tumor Hypoxia from H&E Histology in LUAD Using Deep Learning

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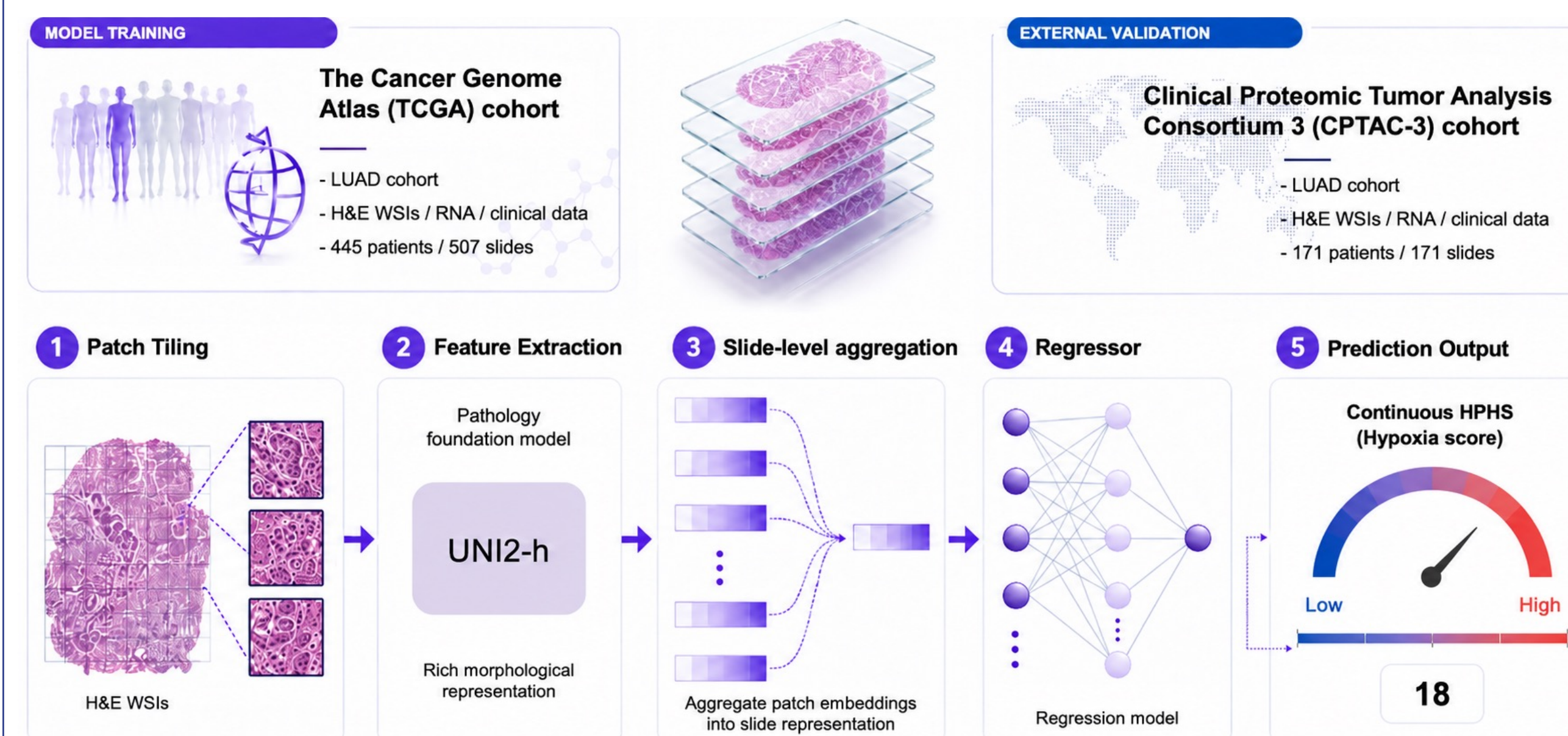
INTRODUCTION

Lung adenocarcinoma (LUAD), the most common subtype of non-small cell lung cancer (NSCLC), remains a major cause of cancer-related mortality. Tumor hypoxia is associated with metastasis, therapy resistance, and poor clinical outcomes. Hypoxia assessment can support patient stratification and treatment selection. In our TCGA-LUAD analysis, the BUFFA hypoxia score remained significantly associated with overall survival (OS), progression-free survival (PFS), and disease-specific survival (DSS) in multivariable Cox regression models, supporting its potential value as a clinically relevant prognostic biomarker.

However, conventional approaches for hypoxia assessment, including gene expression-based assays, require additional cost and laboratory resources. In contrast, hematoxylin and eosin (H&E)-stained whole-slide images (WSIs) are routinely available in clinical pathology and contain rich morphological information. Recent advances in computational pathology suggest that complex tumor microenvironments, including hypoxia-induced molecular alterations, may leave detectable morphological signatures in histology.

We hypothesized that hypoxia-associated molecular features are reflected in histomorphology and can be predicted from H&E-stained WSIs using deep learning.

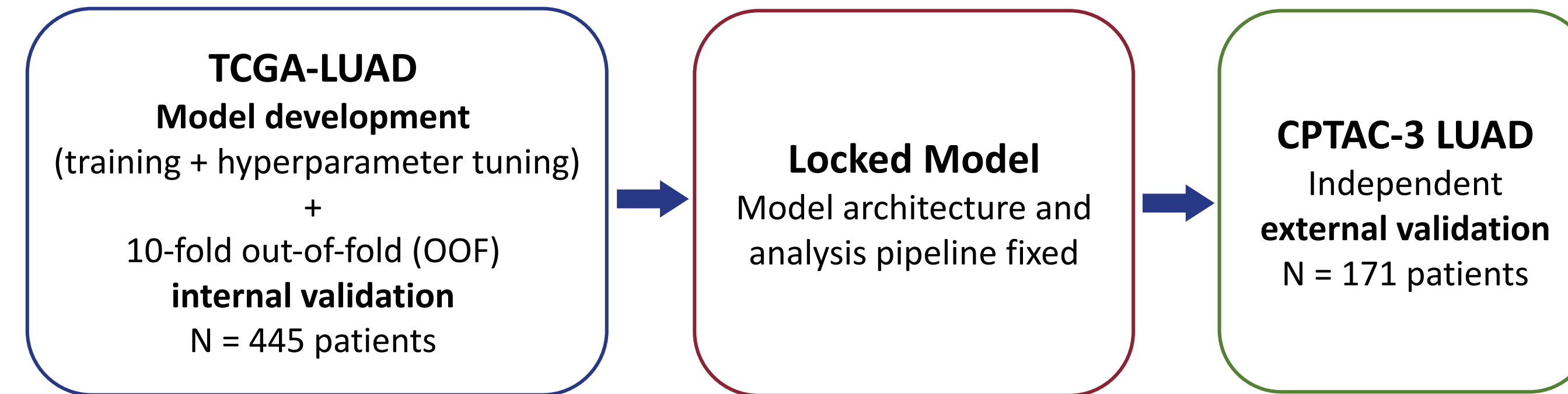
METHODS



- We used **BUFFA hypoxia scores** as an RNA-derived reference label.
- WSIs were tiled into patches and encoded using pathology foundation models; **UNI2-h** was selected as the final feature extractor based on validation performance.
- Patch embeddings were then aggregated via attention-based pooling within a multiple instance learning (MIL) framework to generate slide-level hypoxia predictions.
- Model performance was evaluated using **patient-level 10-fold cross-validation in TCGA-LUAD**.
- To assess discrimination of extreme hypoxia phenotypes, we calculated **ROC AUC (AUC25)** comparing patients at or below the 25th percentile with those at or above the 75th percentile of BUFFA hypoxia scores
- The **CPTAC-3 LUAD cohort** was used for independent external validation.

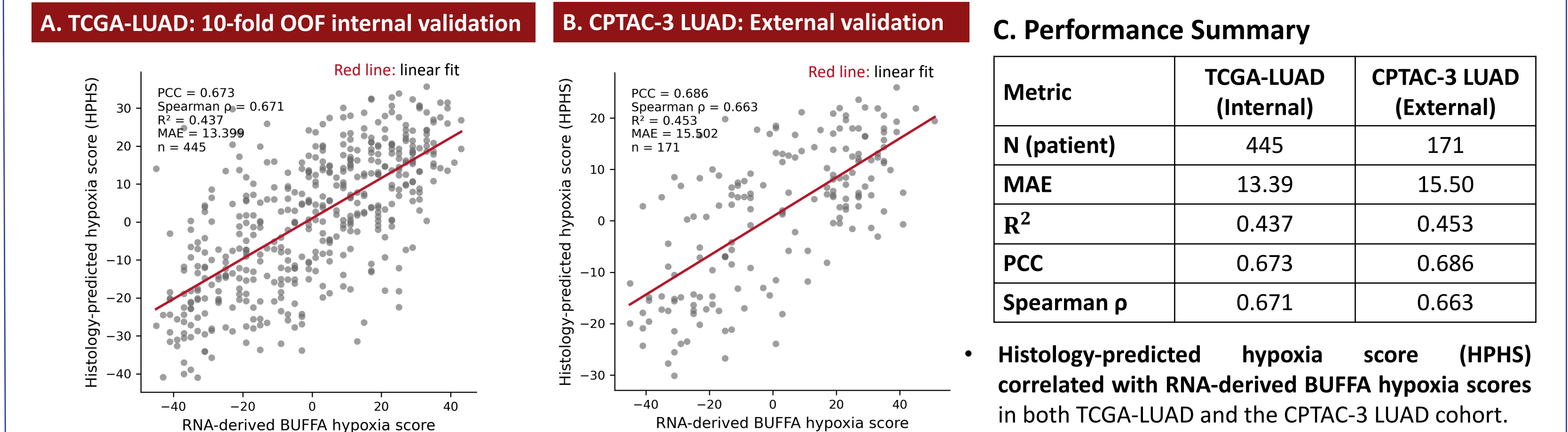
RESULTS

1. Study design



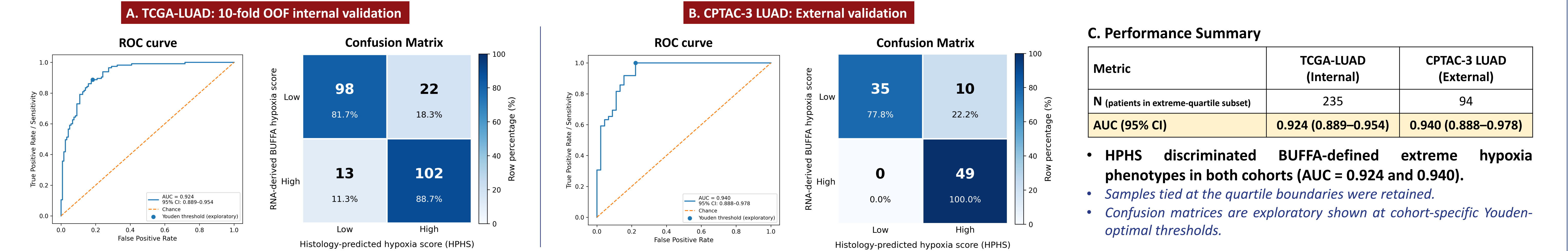
- RNA-derived BUFFA hypoxia scores were generated separately within each cohort using the same published scoring procedure and were used as cohort-specific reference labels.

2. Internal and External validation of continuous hypoxia score prediction



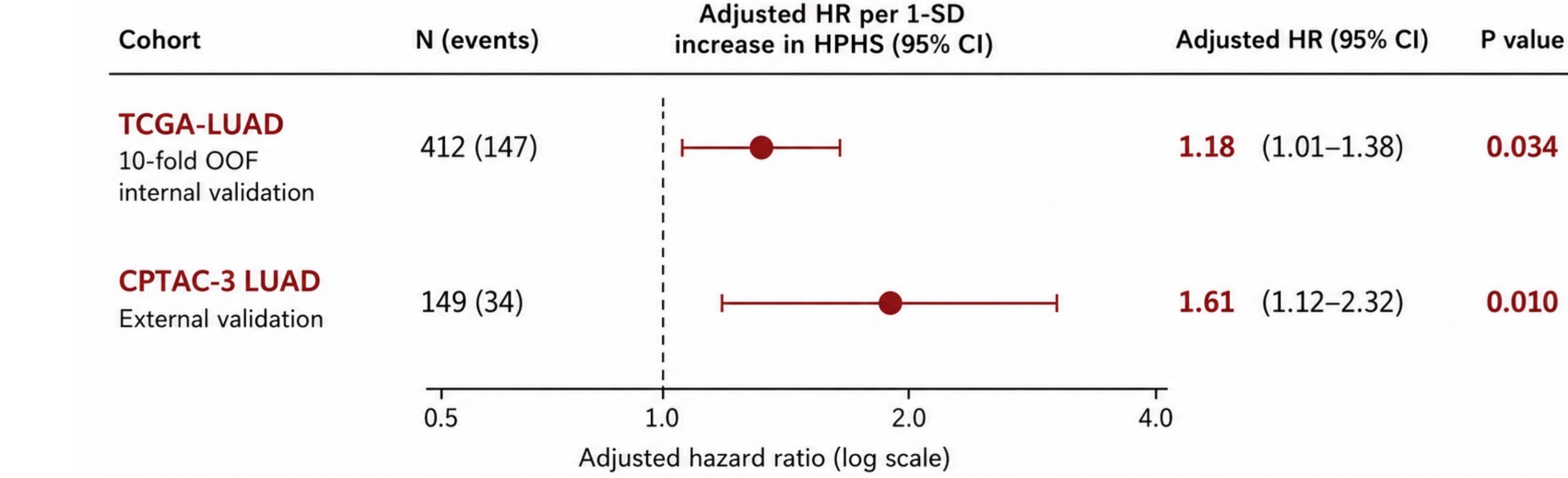
3. Exploratory analysis of extreme hypoxia phenotype discrimination

Extreme-quartile analysis based on the RNA-derived BUFFA reference label: BUFFA-low $\leq$ 25th percentile and BUFFA-high $\geq$ 75th percentile; patients between the quartile cutoffs were excluded.



4. Clinical relevance of histology-predicted hypoxia score (HP HS)

Adjusted association of HP HS with overall survival (OS)



- Higher HP HS was independently associated with worse OS in both TCGA-LUAD and CPTAC-3 LUAD after adjustment for clinical covariates.
- Multivariable Cox models were adjusted for age, sex, AJCC stage, and smoking status.
- HP HS was modeled as a continuous variable per 1-SD increase.

DISCUSSION AND CONCLUSION

- We developed an H&E-based deep learning model to predict tumor hypoxia in LUAD.
- The model showed comparable performance across TCGA-LUAD 10-fold out-of-fold internal validation and independent CPTAC-3 LUAD external validation, with moderate-to-good correlations with RNA-derived BUFFA hypoxia scores and strong discrimination of extreme hypoxia phenotypes.
- Higher HP HS was independently associated with worse OS after adjustment for clinical covariates in both cohorts.
- These findings support the potential of routine H&E histology as a scalable and cost-effective approach for tumor hypoxia assessment.
- Further external validation is planned in an independent University Hospital of Cologne cohort.
- Future work will include pathologist-guided validation and interpretation of patch-level attribution maps.

REFERENCES & ACKNOWLEDGEMENTS

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