HIGH RISK FIBROSIS SCORE PREDICTION USING COMPUTED TOMOGRAPHY IMAGING

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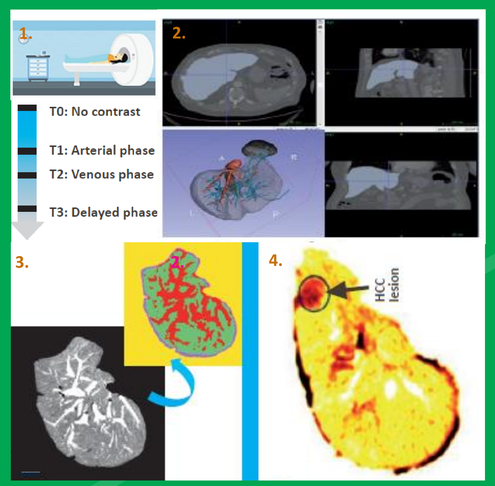
MAIN FINDINGS

FIBROSIS SCORING VALIDATED IN AN INDEPENDENT COHORT OF PATIENTS

RISK OF ADVANCED FIBROSIS IS CORRELATED TO LIKELIHOOD OF POOR OUTCOME (OS AND RFS)

RISK OF ADVANCED FIBROSIS IS CONFIRMED BY MOLECULAR MARKERS

NON-INVASIVE FIBROSIS SCORING STEPS



(1) CT scanning -> (2) Organ segmentation -> (3) Normalization -> (4) Multi-phase feature mapping

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1 INTRODUCTION

Hepatic fibrosis diagnosis is important for risk stratification, prognosis evaluation and monitoring of treatment response. We have previously [1] shown that computer tomography (CT) perfusion imaging and splenic radiomics can accurately assess and grade liver fibrosis.

2 AIM

Using this methodology, the objective of this study is to validate the use this non invasive fibrosis scoring method to identify patients whose tumors are at high risk of recurrence after hepatic resection.

3 METHOD

Patient cohorts: (Development) Ninety-four patients with focal liver lesions referred for liver resection underwent a pre-surgery standard triphasic contrast CT scan. The patients also had excised tissue samples graded for fibrosis by histopathology per the METAVIR scoring system (F0-F4). **(Repeatability Test)** For six patients with no apparent liver pathology CT scanning was repeated for five consecutive slice thickness and voltage parameters. **(Clinical Outcome Prediction)** The Cancer Genome Atlas Liver Hepatocellular Carcinoma (TCGA-LIHC) data collection (n=357) [2] is part of The Cancer Genome Atlas (TCGA). Clinical, genetic, and pathological data reside in the Genomic Data Commons (GDC) Data Portal while the radiological data is stored on The Cancer Imaging Archive (TCIA).

Imaging and omics integration: Development cohort was used to model relationship between imaging features and hepatic fibrotic histological stage. This model was then validated for clinical utility on the TCGA cohort where molecular data and detailed clinical follow up was available.

Model training: A logistic regression algorithm was used to model the relationship between hepatosplenic radiomics and fibrosis stages. The development cohort was split between a training (n=112) and a validation set (n=48) according to fibrosis stages. A logistic regression algorithm was used to model the relation between hepatosplenic imaging features and advanced fibrosis stages. Coefficient of variation (CoV) for each imaging feature used by the model and the output of the fibrosis model were reported as an average for each patient and for the cohort.

Model validation: The developed high-risk Fibrosis score is then correlated to recurrence free survival (RFS) (development and validation cohorts) and overall survival (OS) (validation) cohorts. Due to the low number of patient in the validation with both clinical and imaging data, a regression model was fitted on the survival data (RFS and OS) from all patients of the cohort (n=357) and event risk probability was inferred for patients with both imaging and clinical data.

5 REFERENCES

1. Rexhepaj et al,. Automated quantification of computed tomography hepatosplenic radiomics correlates with liver fibrosis. AASLD 2019.
2. Wheeler et al,. Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. Cell. 2017; 169(7): 1327–1341.e23.
3. Jiang et al,. Proteomics identifies new therapeutic targets of early-stage hepatocellular carcinoma. Nature. 2019; 567: 257–261.

6 CONTACT INFORMATION

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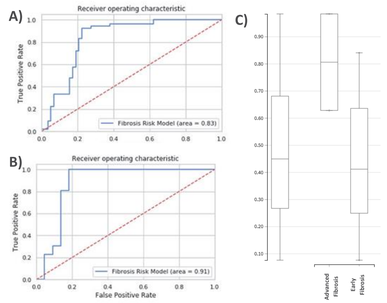
4 RESULTS

FIBROSIS SCORING MODEL TRAINING AND VALIDATION



COV OF MODEL PARAMETERS

Patient ID	Liver param 1	Spleen param 2	Spleen param 3	Spleen param 4	Spleen param 5
Normal Patient #1	7.65	5.09	3.36	1.34	9.18
Normal Patient #2	2.27	0.35	0.50	3.48	0.34
Normal Patient #3	2.02	1.01	0.40	1.32	0.36
Normal Patient #4	0.75	0.43	0.29	0.78	0.03
Normal Patient #5	0.93	0.68	0.91	0.60	0.48
Normal Patient #6	1.58	0.14	1.16	7.59	0.78
AVG	**2.53**	**1.28**	**1.10**	**2.52**	**1.86**

Table 1. CoV from the repeatability test of each imaging parameter used as input to the fibrosis model.

Figure 1. Receiver operator curves show the performances in the training (A) (AUC=0.83) and validation (B) dataset (AUC=0.91). Clinical prediction performances were comparable in the training (A) (Sensitivity=75%, Specificity=93%, NPV=93%, PPV=75%) in the validation (B) (Sensitivity=86%, Specificity=100%, NPV=82%, PPV=100%) dataset. C) The model was then applied to the TCGA validation cohort where distributions of advanced and early classification probabilities were different.

FIBROSIS SCORING OUTCOME PREDICTION

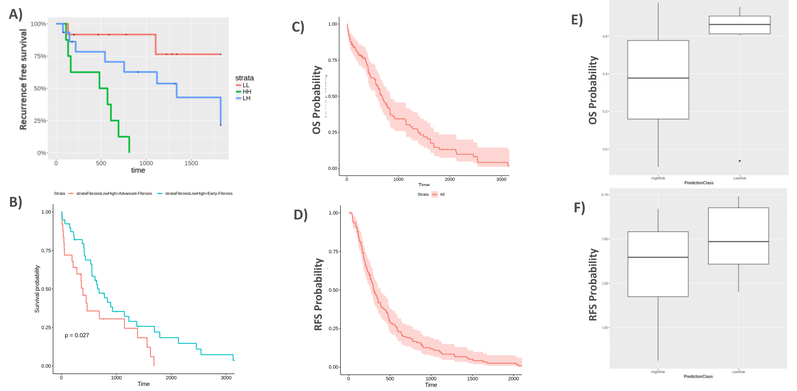


Figure 2. Survival analysis and correlation with clinical outcome risk. **A)** In the development cohort RFS analysis the development cohorts confirm poor and favorable outcome for patients where both invasive (histology) and non-invasive (CT imaging) confirmed (HH and LL groups). A third group of patients where both readings do not match shows a very clear different trend. **B)** In the validation cohort (TCGA) patient with advanced and early fibrosis shows significantly different survival trends. **C-D)** OS and RFS trend for the whole validation cohort (TCGA). **E-F)** For a subset of patients (n=22) we did have both clinical and imaging data to infer non-invasive fibrosis status (box-plot categories) and explore distributions of OS and RFS risk as defined by the global population trend **(C-D)**.

FIBROSIS SCORING CORRELATION WITH MOLECULAR MARKERS

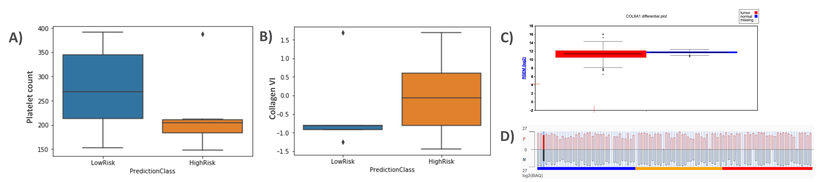


Figure 3. Given the issues related to the sampling and inter-observer variability of the histological assessment we verified also the correlation of non-invasive prediction of fibrosis with molecular markers. **A)** Distribution of platelet count for each fibrosis risk group as defined by our non-invasive test. **B)** Distribution of Collagen-VI for each fibrosis risk group as defined by our non-invasive test. Correlation of platelet count in the global population of TCGA (n=357) with proteomic assessment in plasma of Collagen-VI (Spearman Rho = 0.358). A similar trend was observed also for CollagenVI. **C)** Data from the recently published omics analysis of TCGA **(C)** and a Chinese cohort [3] **(D)** shows that there is no differences on a paired (tumour/non-tumour) tissue based omics analysis for CollagenVI (rnaseq:TCGA | proteome:CNHPP) indicating hence an unlikely bias on the expression due to a HCC lesion.