Predict Early Recurrence of Hepatocellular Carcinoma Using Multi-dimensional Artificial Intelligence Analysis of Liver Fibrosis

I-Ting Liu[1,2], Chia-Sheng Yen[3], Wen-lung Wang[2], Hung-Wen Tsai[4], Chang-Yao Chu[4], Ming-Yu Chang[2] , Ya-Fu Hou [2] , Chia-Jui Yen [2]

[1] Institute of Clinical Medicine, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [2] Department of Oncology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan, [3] Division of General Surgery, Department of Surgery, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan, [3] Department of Pathology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan

1. Purpose

- Hepatocellular carcinoma (HCC) is the third commonly diagnosed cancer and takes the second place in cause of cancer death in Taiwan for years.
- Surgical resection is the commonly used curative management of early stage disease. However, the recurrence rate is high after resection.
- Liver fibrosis has been thought to increase the risk of recurrence. However, conventional histological staging of fibrosis is highly subjective to observer variations.
- To overcome this limitation, we aimed to combine a fully quantitative fibrosis assessment tool, **qFibrosis** (utilising second harmonic generation and two photon excitation fluorescence microscopy), with multi-dimensional artificial intelligence analysis to establish a fully-quantitative, accurate fibrotic score to predict early recurrence of HCC after curative intent resection.

2. Materials & Methods

- We used qFibrosis to evaluate the fibrotic status of the hepatic tissue from total 81 patients who received curative hepatectomy for HCC in National Cheng Kung University Hospital and Chi Mei Hospital.
- Firstly, 100 morphological collagen features were obtained from portal, septal, fibrillar and overlap regions of non-tumor hepatic tissues for 64 patients without nonalcoholic steatohepatitis (NASH). Another 76 relativistic features were constructed based on the morphological features.
- Secondly, the morphological and relativistic collagen features with significant difference between patients with early (< 1 year) and late recurrence were selected, based on two-tailed Wilcoxon rank-sum test ($p < 0.05$).
- Thirdly, the significant features were used to build a recurrence prediction model, which generated a single index (combined index) to indicate the early recurrence using linear regression method (Fig. 1).

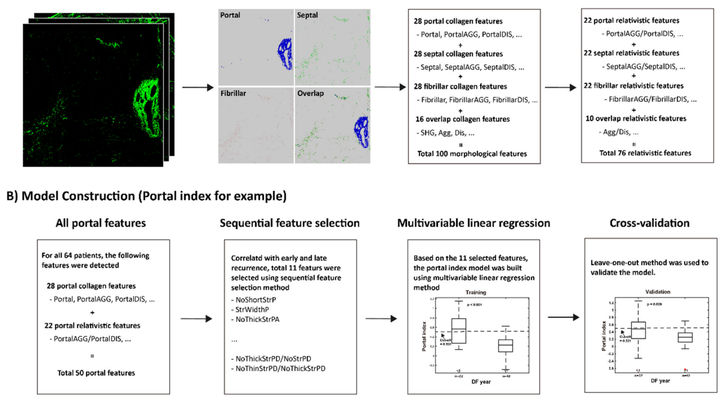

Figure 1. Flowchart of model construction.

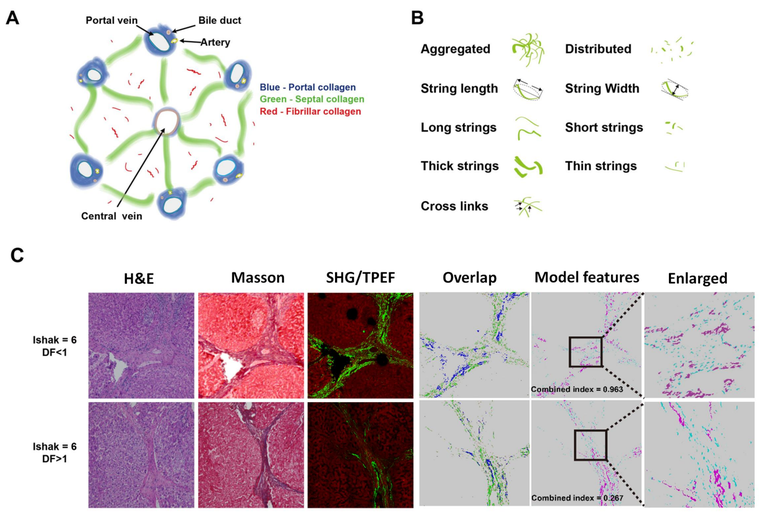

Figure 2. Schematic illustration of the studied collagen features for the prediction of early recurrence.

3. Results

- Figure 2 illustrates the studied collagen features by qFibrosis.
- A combined index cut-off value of 0.501 being useful to differentiate early (< 1 year; combined index > 0.501) from late recurrence (≧ 1 year; combined index ≦ 0.501) (Fig. 3A).
- The ROC curves for the prediction of early recurrence versus late or no recurrence was 0.917 (AUC) (Fig. 3B).
- Disease free probability was lower in high-risk group than low risk group (Fig. 4).
- Using a Cox proportional hazards analysis, higher "combined index" is also a poor prognostic factor of disease-free survival and overall survival. (Table 1).
- Fibrotic features in different regions of non-tumor hepatic tissue showed different level of correlation. Overall, combined index still has the best correlation (Fig. 5).

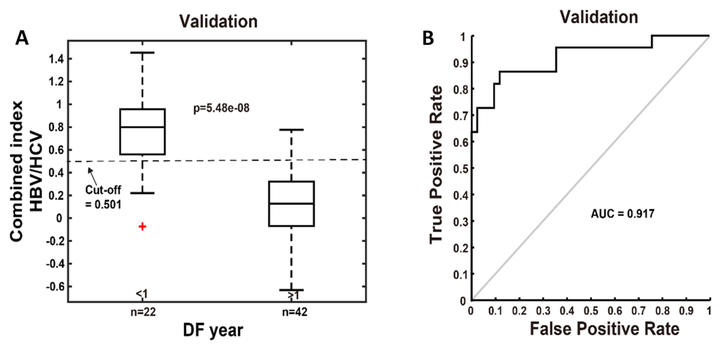

Figure 3. ROC curves for the prediction of early recurrence versus late recurrence. (A) A combined-index cut-off value of 0.501 for differentiating between early and late recurrence. (B) ROC curve for combined-index, AUC = 0.917.

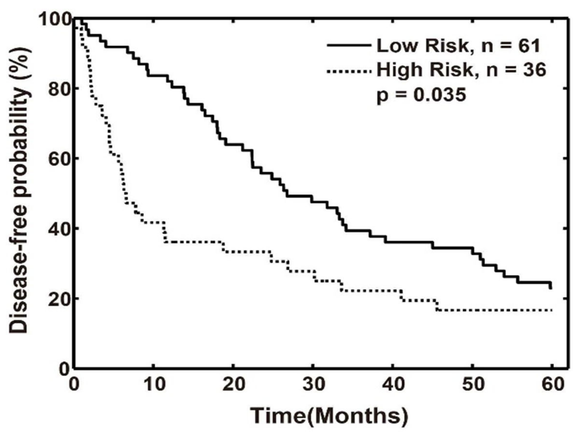

Figure 4. Disease free probability analysis for HCC patients as high risk group (combined-index > 0.501) and low risk group (combined-index ≦ 0.501) (n = ?? and ??, p = 0.???).

Table 2. Univariate analysis of variables for prediction of recurrence in HCC.

Variable	Number of patients	Recurrence		*p*-value
		Number	Percent	
Gender				0.169
Male	71	44	62.0	
Female	26	20	76.9	
Groups				0.331
HBV+cirrhosis	27	18	66.7	
HBV	40	26	65.0	
HCV+cirrhosis	14	12	85.7	
HCV	5	3	60.0	
Non-B, Non-C	11	5	45.5	
Liver cirrhosis				0.322
No	55	34	61.8	
Yes	42	30	71.4	
Histologic grade				0.246
Well	10	7	70.0	
Moderate	75	46	61.3	
Poor	9	8	88.9	
Vascular invasion				0.281
No	65	45	69.2	
Yes	31	18	58.1	
Tumor size (cm)				0.538
≦5	57	36	63.2	
> 5	39	27	69.2	
AFP (ng/ml)				0.192
≦20	44	26	59.1	
> 20	53	38	71.7	
Pathological Stage				0.202
Stage I, II	81	51	63.0	
Stage III, IV	15	12	80.0	
Clinical Stage				0.336
Stage I, II	74	47	63.5	
Stage III, IV	20	15	75.0	
Combined Index				0.001*
≦3.6	60	32	53.3	
>3.6	37	32	86.5	

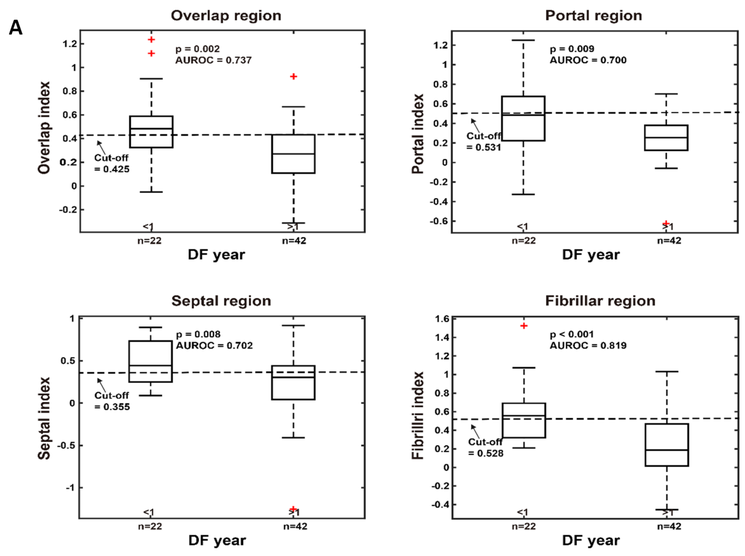

Figure 5. The prediction of early recurrence versus late recurrence using features in overlap, portal, septal and fibrillary regions of non-tumor liver, respectively. (A) box plots. (B) Disease free probability analysis

4. Conclusion

- By integrating multi-dimensional artificial intelligence and qFibrosis, we may locate patients with a higher risk of recurrence, follow these patients more carefully, and do further management if needed.