Etiology-independent fibrosis severity scoring by quantitative digital pathology image analysis.

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INTRODUCTION

While fibrosis is the common end point of many chronic liver disease, little is known about possible histological differences between etiologies and the related performance of existing fibrosis staging system. Here, we used quantitative digital pathology image analysis to phenotype liver fibrosis using various histological traits that describe collagen content, collagen fiber morphometry and fibrosis architecture.

METHODS

Patients with chronic liver disease were included. Digital images of liver histology slides stained with Sirius red were categorised as mild (F0-2), moderate (F3-4) or severe (F5-6) fibrosis using the Ishak staging system. Disease etiology was classified as alcohol related liver disease (ARLD), non-alcoholic fatty liver disease (NAFLD), viral (chronic hepatitis B or C; CVH), or autoimmune (PBC, PSC or autoimmune hepatitis; AIH).

FibroNest™ detects collagen fibers in a stained digital image and analyses each collagen fibre to quantify histological traits such as fibre length, number of branches and homogeneity. These histological traits are then evaluated further to determine a variety of statistical features such as mean, median and standard deviation. These are outputted as continuous variables defined as quantitative fibrosis parameter trait (qFTs).

qFTs that showed significant variation (> 25%; $p < 0.05$) between mild and severe fibrosis in three or more etiological groups were used to calculate our severity scores.

RESULTS

We included 80 patients (60% male, mean age 59.0 years, mean BMI 28.8 kg/m^2). Disease aetiology was classified as NAFLD (n = 17), CVH (n = 20), AI (n = 18) or ARLD (n = 25). We staged biopsy images as mild (n = 28), moderate (n = 17), or severe (n = 35) fibrosis. There were no significant differences in mean CPA between etiological groups.

We calculated etiology-independent (aet-ind) severity scores (Figure 1) using the 78 qFTs which showed significant variation: Architecture Composite Scores (ACS, analogous to histological staging), Collagen Composite Scores (CCS, analogous to CPA), Morphometric Composite Scores (MCS, reflecting fibre morphology), and Phenotypic Fibrosis Composite Scores (PH-FCS, reflecting all histological features of fibrosis).

Figure 1 - Etiology-independent severity scores for each etiology group

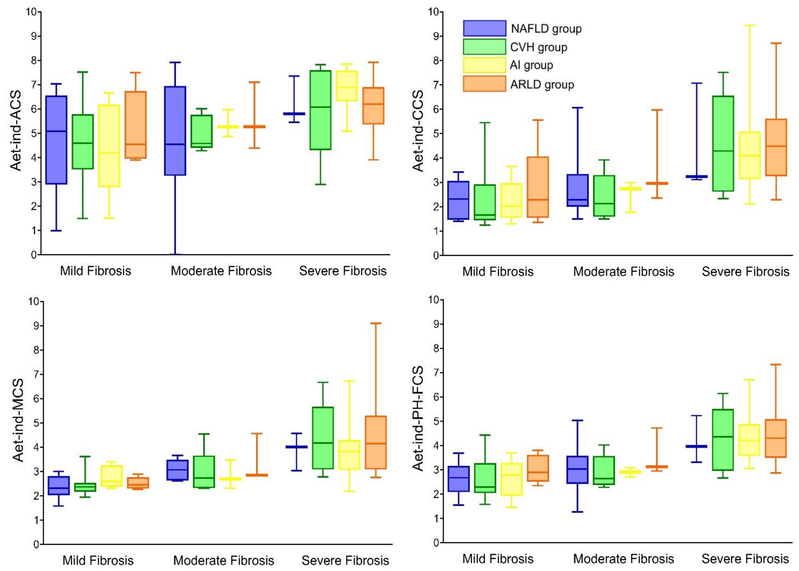
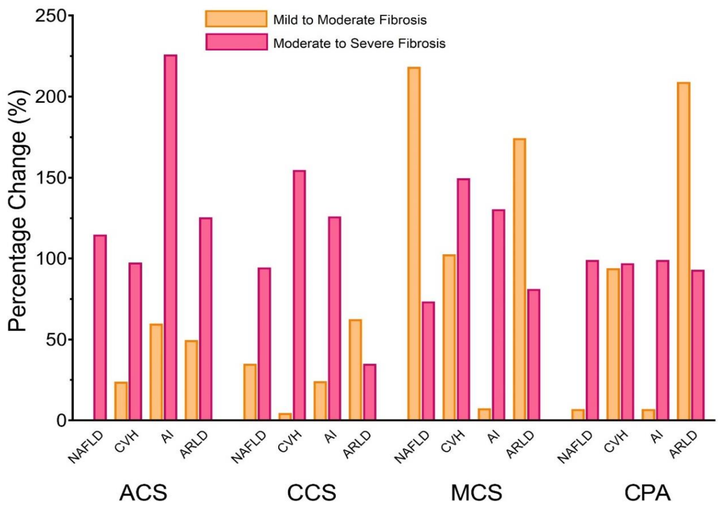


Figure 2 - Percentage changes in mean etiology-independent severity scores and CPA



We calculated the percentage change in mean unadjusted aetiology independent severity scores between each stage of fibrosis (Figure 2). For each aetiological group, aet-ind-ACS increased primarily between moderate and severe fibrosis: NAFLD (by 115%), CVH (98%), AI (226%), and ARLD (125%). Aet-ind-CCS also substantially increased between moderate and severe fibrosis for NAFLD (95%), CVH (155%) and AI (126%) groups; however, in the ARLD group the increase between mild and moderate fibrosis (63%) was greater than that between moderate and severe fibrosis (35%). In contrast, aet-ind-MCS primarily increased between mild and moderate fibrosis in the NAFLD (218%), CVH (103%) and ARLD (174%) group, except in the AI group where the increase was minimal (8%).

Mean collagen proportion area (CPA) increased between mild ($\bar{x}$ = 7.6%, SD 5.0) and moderate ($\bar{x}$ = 12.3%, SD 8.0, p = .04) fibrosis, and between moderate and severe ($\bar{x}$ = 27.0%, SD 11.8, $p < .001$) fibrosis.

CONCLUSIONS

We are the first to describe novel etiology-independent severity scores that individually quantify fibrosis architecture, collagen content and collagen fiber morphometry. This approach provides additional insight into how progression of architectural changes and accumulation of collagen may differ depending on underlying disease aetiology. Our observations suggest that disease progression in ARLD is dependent on the accumulation of collagen fibres with associated morphological changes, and that architectural changes are less predominant. Our data also suggests that fibrosis in autoimmune liver disease may be driven primarily by architectural changes without equally significant increases in the amount of collagen.

CONFLICTS OF INTEREST

LP and MP are employees of Pharmanest Inc, who analysed biopsy images for the University of Oxford as a contribution-in-kind.

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