Histological Correlation with Portal Pressures and Varices in NASH Cirrhosis using Quantitative Digital Pathology

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INTRODUCTION

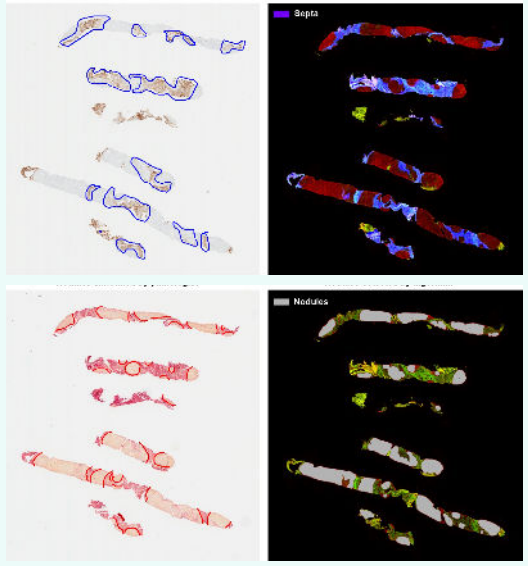
- Hepatic venous pressure gradient (HVPG) is commonly used as a primary efficacy endpoint in non-alcoholic steatohepatitis (NASH) cirrhotic studies.
- Previous studies have shown suboptimal correlations between HVPG and key histological features, including septa width, nodule size, and collagen proportionate area (CPA).
- This study aimed to determine the relationship between these specific features and HVPG in cirrhosis by using a quantitative digital pathology approach.

MATERIALS AND METHODS

- A second harmonic generation/two-photon excitation fluorescence (SHG/TPEF) imaging tool with image processing algorithms trained (n=25) and validated (n=10) by an expert liver pathologist, were able to detect fibrosis, septa, and nodules in NASH cirrhotic patients.
- In total, 457 features related to **s**epta, **no**dules, and **f**ibrosis were quantified by the algorithms, respectively (SNOF). **(Figure 2)**
- We compared the performances of single and composite parameters, and examined their correlation with HVPG, clinically significant portal hypertension (CSPH: HVPG ≥10 mm Hg) and the presence of varices (SNOF-V) by using data obtained from the Belapectin phase 2b trial (NCT02462967).

RESULTS

Figure 1. Examples of septa and nodules detection. Top row shows the septa (L) annotated by the pathologist, and (R) annotated by algorithm. Bottom row shows the nodules (L) annotated by the pathologist, and (R) annotated by the algorithm.



- 25 liver biopsies from 15 NASH patients with compensated cirrhosis were used.
- Digitized images stained with Sirius red and immunostain for smooth muscle actin were used by an expert pathologist to identify all septa and cirrhotic nodules.
- **Figure 1**: 91% and 95% accuracy was achieved for the agreement between pathologist's annotations versus algorithm detection for septa and nodule, respectively.

Figure 2. SHG/TPE image showing AI annotations of (A) Septa, (B) Nodules and (C) Fibrosis.

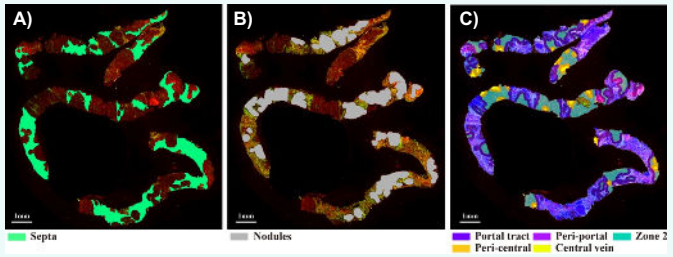


Table 1. Correlation between histological features and HVPG

Histological feature	Reported in literatures	SHG/TPEF
CPA	0.281 – 0.571 (p<0.001)	0.201 (p<0.001)
#Nodules	0.143 (p=0.367)	-0.211 (p<0.001)
Septa width	0.089 (p=0.577)	0.352 (p<0.001)
Nodule size	0.415 (p=0.006)	-0.096 (p=0.113)
Composite index	0.470 (p<0.001)	0.57 – 0.70 (p<0.001)

- **Table 1** shows moderate correlations between individual features detected by SHG/TPEF and HVPG [r value = 0.352, 0.201 and -0.211 for septa width, CPA and number of nodules, respectively (all p<0.001)].
- This is comparable with existing literature (*Sethasine et al., 2012; Bosch et al., 2021*) i.e., weak to moderate correlations observed between single features and HVPG (r = 0.09-0.57).
- However, the combination of these features into a composite SNOF index revealed improved correlations with HVPG with r = 0.57-0.60; regardless of whether the index was trained by the baseline or treatment cohorts.
- Similarly, combining features to develop separate indexes for predicting CSPH (AUROC=0.74) and the presence of varices (AUROC=0.73) were comparable with traditional method of using HVPG ≥10 (AUC 0.74) to predict varices. (*Data not shown here, manuscript in progress*)

CONCLUSION

- There is a need for a composite index by combining septa, nodules and fibrosis parameters, because of their accuracy at the individual level.
- The composite indexes not only predicted HVPG, but CSPH and the development of varices in patients with NASH cirrhosis.
- The application of composite indexes developed using digital quantitative approach has potential towards the assessment of the severity of cirrhosis in NASH cirrhosis.

DISCLOSURES

For presenting author:
Dr. Mazen Noureddin (MN) has been on the **advisory board** for 89BIO, Gilead, Intercept, Pfizer, Novo Nordisk, EchoSens, Fractyl, Terns, Siemens and Roche diagnostic; MN has **received research support** from Allergan, BMS, Gilead, Galmed, Galectin, Genfit, Conatus, Enanta, Madrigal, Novartis, Pfizer, Shire, Viking and Zydus; MN is a **minor shareholder** or has stocks in Anaetos, Rivus Pharma and Viking.

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