REDUCING SCREEN FAILURE RATES FOR NASH CLINICAL TRIALS USING BALLOONING AND FIBROSIS ASSESSMENT WITH SECOND HARMONIC GENERATION/TWO-PHOTON EXCITATION MICROSCOPY AND ARTIFICIAL INTELLIGENCE ANALYSIS: RESULTS FROM THE TANDEM TRIAL

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INTRODUCTION

- In NASH clinical trials, liver biopsy evaluations by pathologists based on NASH-CRN classification are used to determine trial inclusion and to measure treatment efficacy as the trial endpoint.
- NASH clinical trials are usually known to have high screening failure rates.
- Newer digital pathology platforms based on Second Harmonic Generation/Two Photon Excitation (SHG/TPE) imaging may be helpful in detecting fibrosis and ballooning and offer a fully-quantitative evaluation of liver histology.
- This study explores the potential of SHG/TPE microscopy with artificial intelligence (AI) analyses of liver biopsies for quantitative assessment of fibrosis and ballooning and its potential in aiding reduction of screening failure rates in NASH clinical trials.

MATERIALS AND METHODS

- Biopsies from 138 patients, who were not included (screening failures) in a NASH phase 2 clinical trial (NCT03517540), were evaluated for this study. The focus was on histological criteria of screening failure, specifically Fibrosis stage and Ballooning grade.
- The histological exclusion criteria evaluated in this study included Ballooning grade 0 and Fibrosis stage 0,1,or 4.
- Liver fibrosis and ballooning were quantitatively evaluated using SHG/TPE microscopy, providing continuous measurements (qFibrosis [qF] and qBallooning [qB]).
- The continuous qF and qB values were then categorized into stages using established cut-offs (qF0-qF4 and qB0-qB3).
- Comparisons were done between number of patients excluded by pathologist scoring versus SHG/TPE imaging-based scoring.

RESULTS

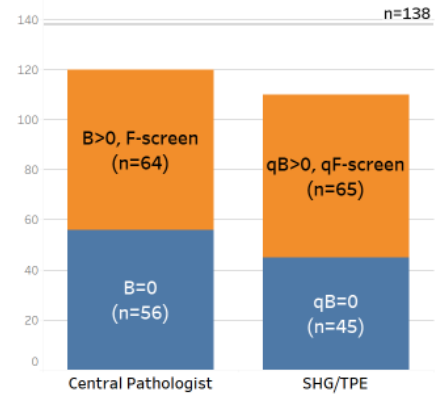

Figure 1. Comparison of number of screen failed patients determined by central pathologist versus SHG/TPE-based fibrosis and ballooning scores.

- Based on the central pathologist's scoring, 64 patients who had B>0 score were excluded due to the fibrosis stage being either F0, F1, or F4 (F-screen), compared to 65 patients potentially excluded by SHG/TPE microscopy who had qB>0 but qF stage was either qF0, qF1 or qF4 (qF-screen) [Figure 1].
- Similarly, based on the central pathologist's scoring, 56 patients who had the trial inclusion fibrosis stage (F2, F3) were excluded due to their ballooning score being 0 (B=0).
- However, when qB was used to score ballooning, only 45 patients with the trial inclusion fibrosis stage (qF2, qF3) were scored qB=0.
- The difference between patients excluded by screening criteria of B=0 (n=56) and qB=0 (n=45) is n=11, when the fibrosis stages were inclusionary.
- This suggests potential to reduce screen failure rates by incorporating SHG/TPE microscopy and AI analysis for ballooning assessment.
- Figure 2 illustrates the detection of a ballooned hepatocyte by SHG/TPE microscopy with AI analysis, which could have aided the pathologist in the overall evaluation of case otherwise scored as B = 0

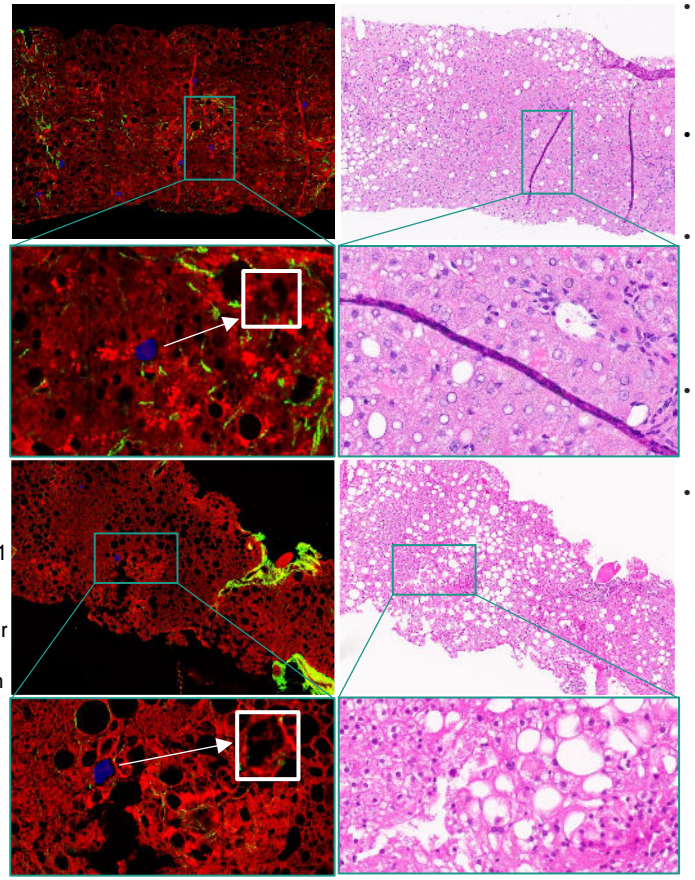

Figure 2. Comparisons between SHG/TPE images with qB>0 (balloon hepatocyte shaded in blue) and corresponding H&E-stained image. The balloon hepatocytes detected by algorithm and annotated in blue are further enlarged in the white box.

CONCLUSIONS

- Incorporating SHG/TPE with AI analyses for assessment, along with central pathologist evaluations, may be an effective means of reducing screening failure rates in NASH trials, especially in assessing ballooning.
- In this study, by using qB scores, it would have been possible to identify 11 additional patients to include in the NASH clinical trial: n=56 (B=0) vs. n=45 (qB=0).
- The inherent subjectivity of ballooning assessment (for instance, Kappa-value for overall interobserver agreement for presence/absence of ballooning was 0.197, Brunt et al [1]) could be improved upon using qBallooning.
- The qBallooning algorithm described in this study, although not fully-validated for aiding pathologists to reduce screen failure rates, is used here as an exploratory tool.
- The small sample size of this study may not allow for generalization of these results. Future studies on different cohorts with more patients may further help validate SHG/TPE based screening analysis.

REFERENCES

1. Brunt EM, Clouston AD, Goodman Z, et al. Complexity of ballooned hepatocyte feature recognition: Defining a training atlas for artificial intelligence-based imaging in NAFLD. J Hepatol. 2022 May;76(5):1030-1041.

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