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INTRODUCTION

- Resmetirom, an oral, liver-targeted thyroid hormone receptor- β selective agonist, has been shown to achieve NASH resolution and fibrosis reduction endpoints on liver biopsy at 52 weeks in an ongoing Phase 3 registrational non-cirrhotic NASH trial.
- A previous exploratory analysis of qSteatosis and qFibrosis in the phase 2 36-Week study of resmetirom in patients with NASH demonstrated that reduction of collagen near steatosis associates with steatosis improvement in Zone 2.
- The aim of this analysis was to study the association between ballooning reduction and steatosis reduction in the resmetirom versus placebo group using second harmonic generation (SHG)/two-photon excited fluorescence (TPEF) microscopy imaging of paired biopsy samples with artificial intelligence (AI)-based algorithms. The interaction between steatosis and concomitant fibrosis reduction will also be shown.

METHODS

- 103 paired biopsy samples from a 36-week, randomized, double-blind, placebo-controlled Phase 2 study with resmetirom (NCT02912260) were imaged using SHG/TPEF.
- Ballooning and steatosis were estimated as a continuous variable using an AI-based algorithm as previously described.¹
- Resmetirom-mediated changes of ballooning in relation to steatosis reduction were evaluated by simultaneous measurement of ballooning and hepatic fat in selected areas around the fat vacuoles in liver regions: portal tract (Zone 1), central vein (Zone 3), and transitional (Zone 2).

RESULTS

Figure 1. Co-localisation analysis of qSteatosis and qFibrosis.

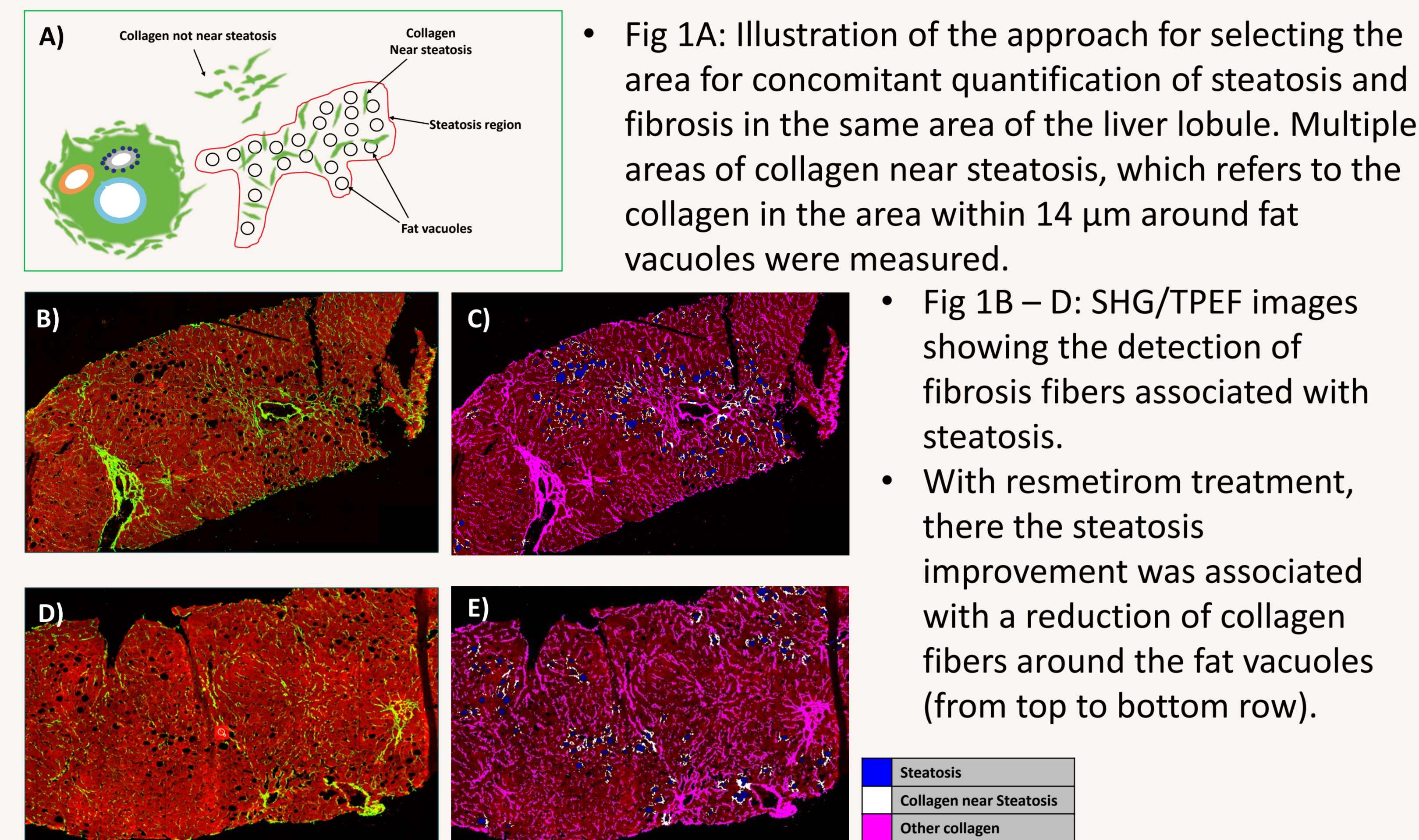


Figure 2. Co-localisation analysis of qFibrosis and steatotic changes based on pathologist's reads.

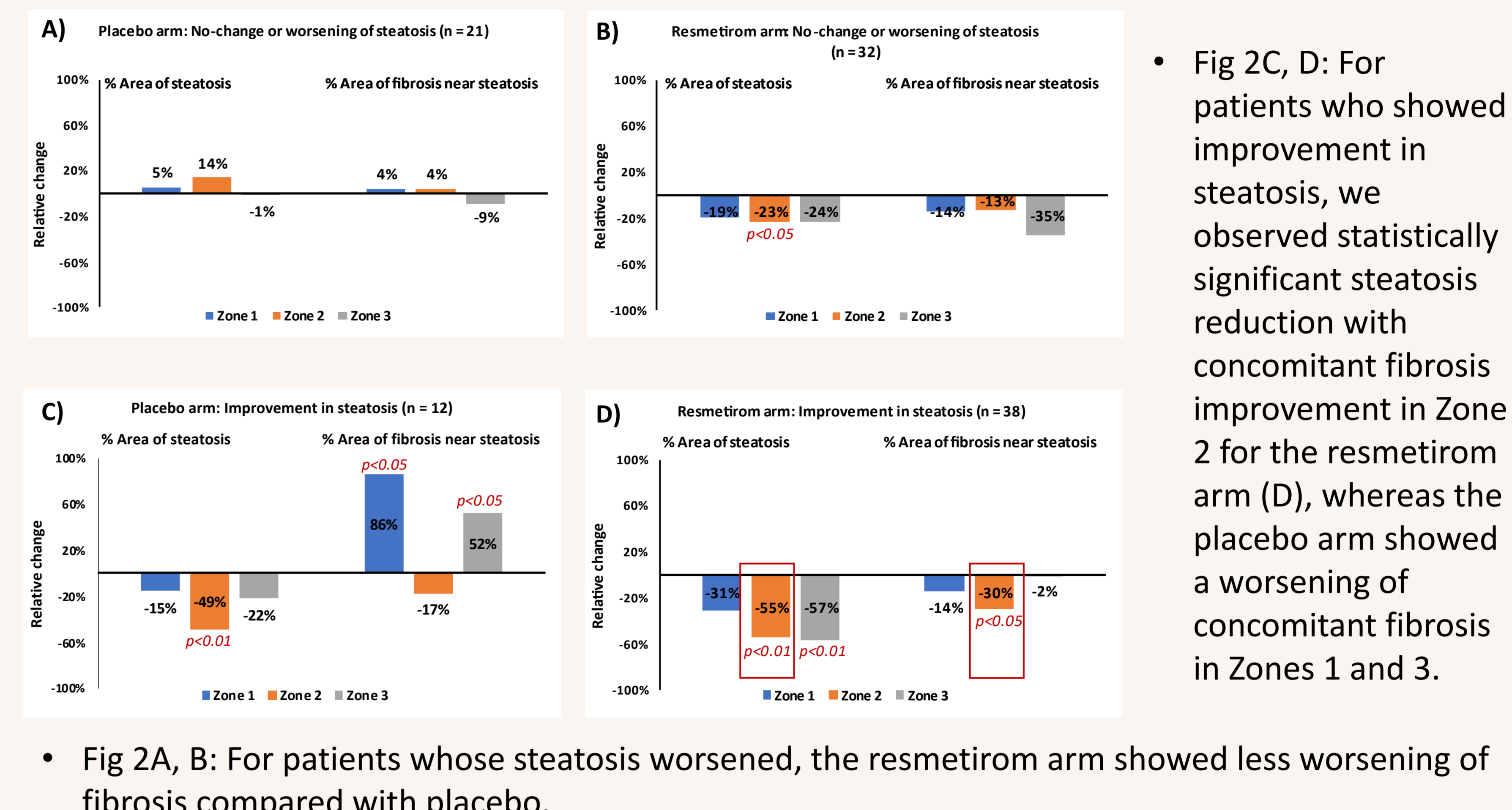


Figure 3. Co-localisation analysis of qSteatosis and qBallooning.

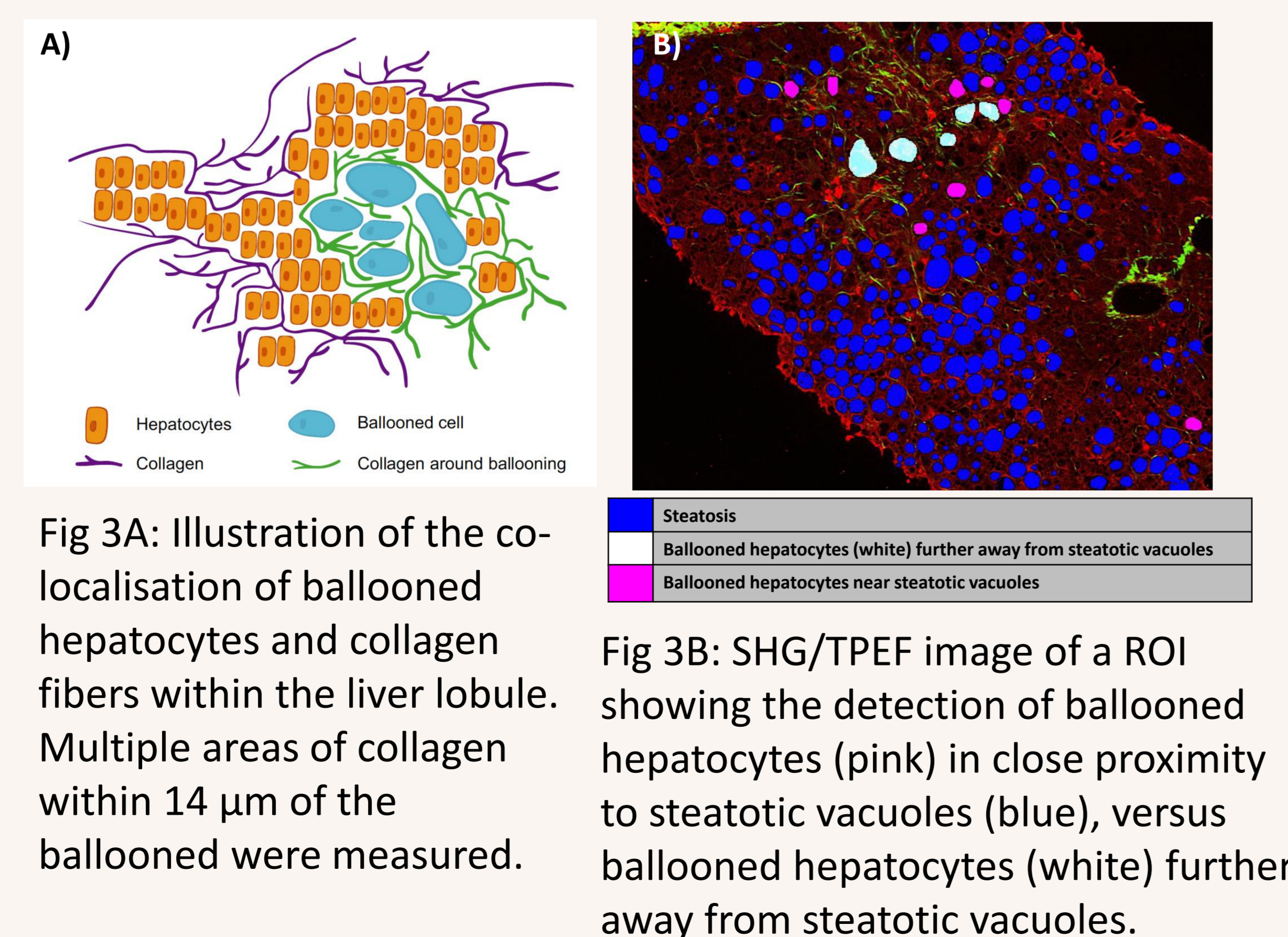
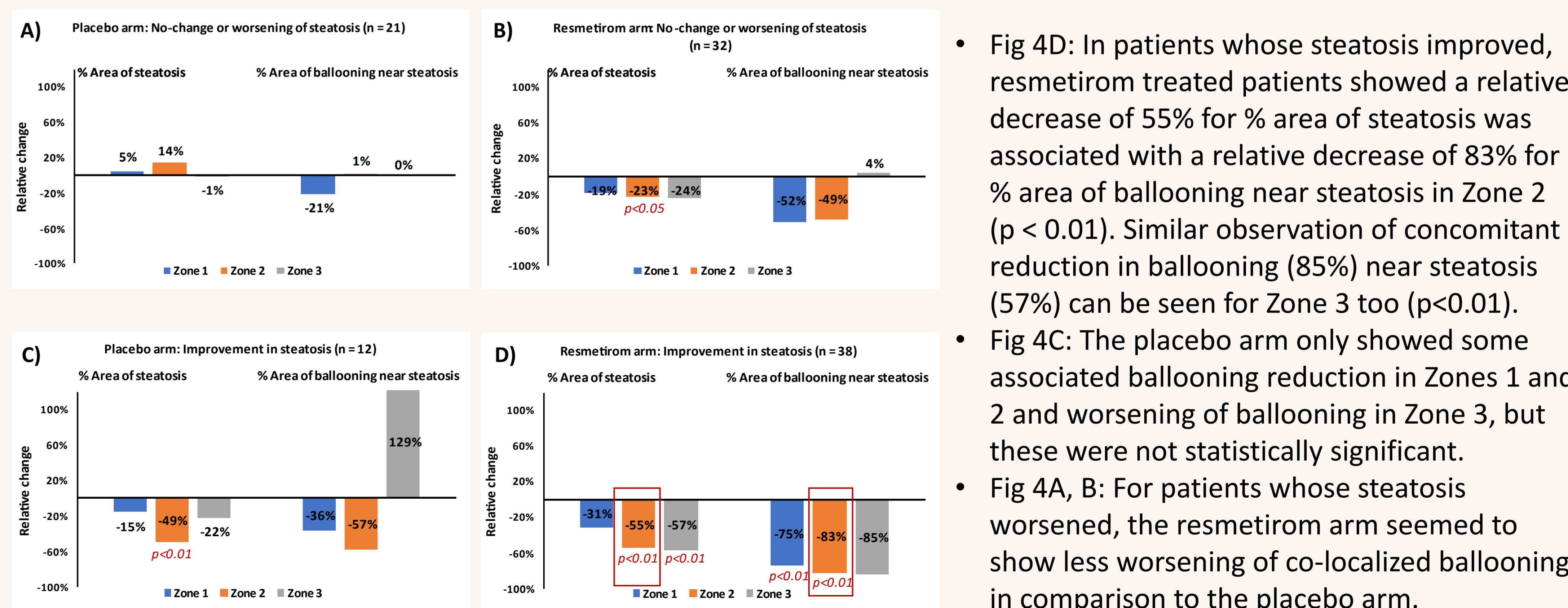


Figure 4. Co-localisation analysis of qBallooning and steatotic changes based on pathologist's reads.



CONCLUSION

- SHG/TPEF microscopy with AI provides greater granularity in assessing the dynamics between histological components associated with NASH.
- Qualitatively, a clear difference can be seen in the pattern of co-localization analysis of steatosis and ballooning in resmetirom-treated patients versus placebo-treated patients.
- The use of a continuous variable (qBallooning, qSteatosis) provides quantitation of zonal changes in ballooning and steatosis in serial liver biopsy studies which cannot be captured using the NASH CRN system.
- The clinical relevance of AI digital measurements of the NASH features will have to be established in future liver-related clinical outcomes study.

ACKNOWLEDGEMENTS

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REFERENCE

1) Liu F, et al. Hepatology 2020; 71: 1953–1966

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