

Metabolic, biochemical and histological effects of semaglutide in a CDAA-HFD-induced non-obese and biopsy-confirmed rat model of NASH with progressive fibrosis and tumor development

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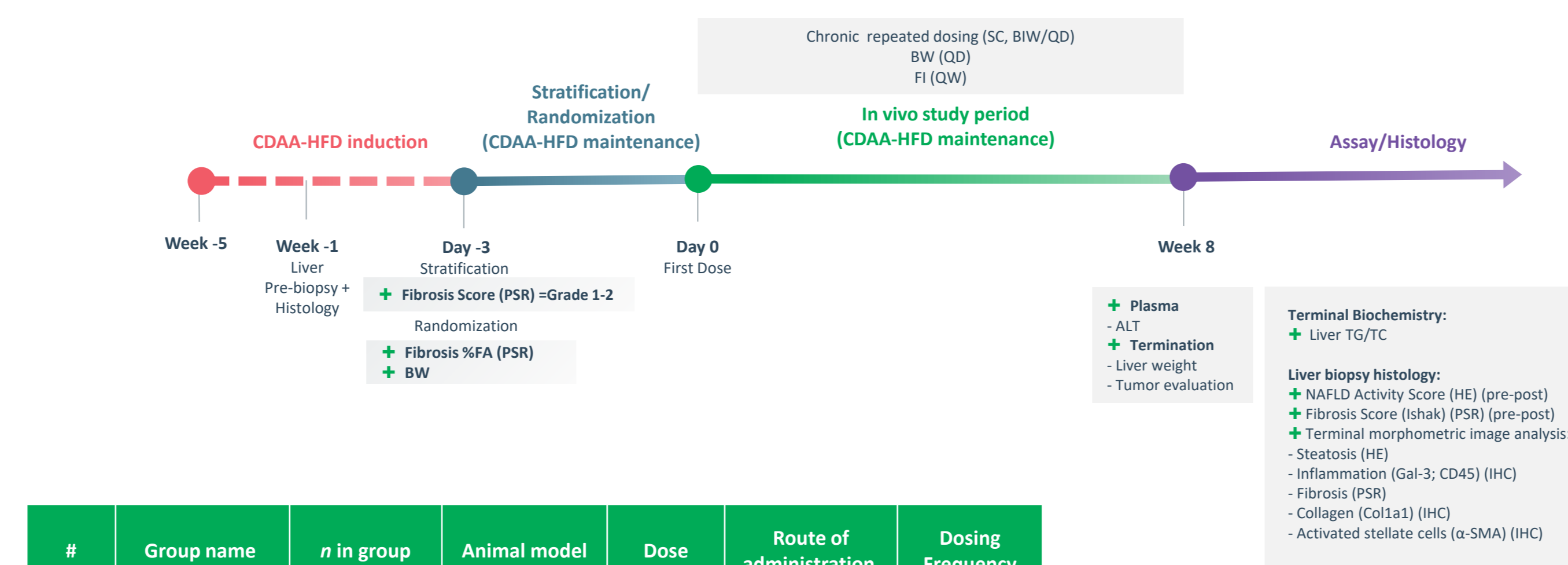
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Background & Aim

The glucagon-like-peptide (GLP)-1 analogue semaglutide, currently approved for the treatment of type 2 diabetes and obesity, is in late-stage clinical development for non-alcoholic steatohepatitis (NASH). The present study evaluated the therapeutic effects of semaglutide in a Choline-Deficient L-Amino-Acid-defined High-Fat Diet-induced (CDAA-HFD) non-obese rat model of NASH with progressive fibrosis and tumor development.

Study outline



| # | Group name | n in group | Animal model | Dose | Route of administration | Dosing Frequency |
|---|-------------------------|------------|--------------|------------|-------------------------|------------------|
| 1 | Chow | 8 | LEAN-CHOW | NA | SC | BIW |
| 2 | Vehicle | 15 | CDAA-HFD | NA | SC | BIW |
| 3 | Semaglutide | 15 | CDAA-HFD | 30 nmol/kg | SC | QD |
| 4 | Chow reversal (Vehicle) | 15 | CDAA-HFD | NA | SC | BIW |

Metabolic and biochemical parameters

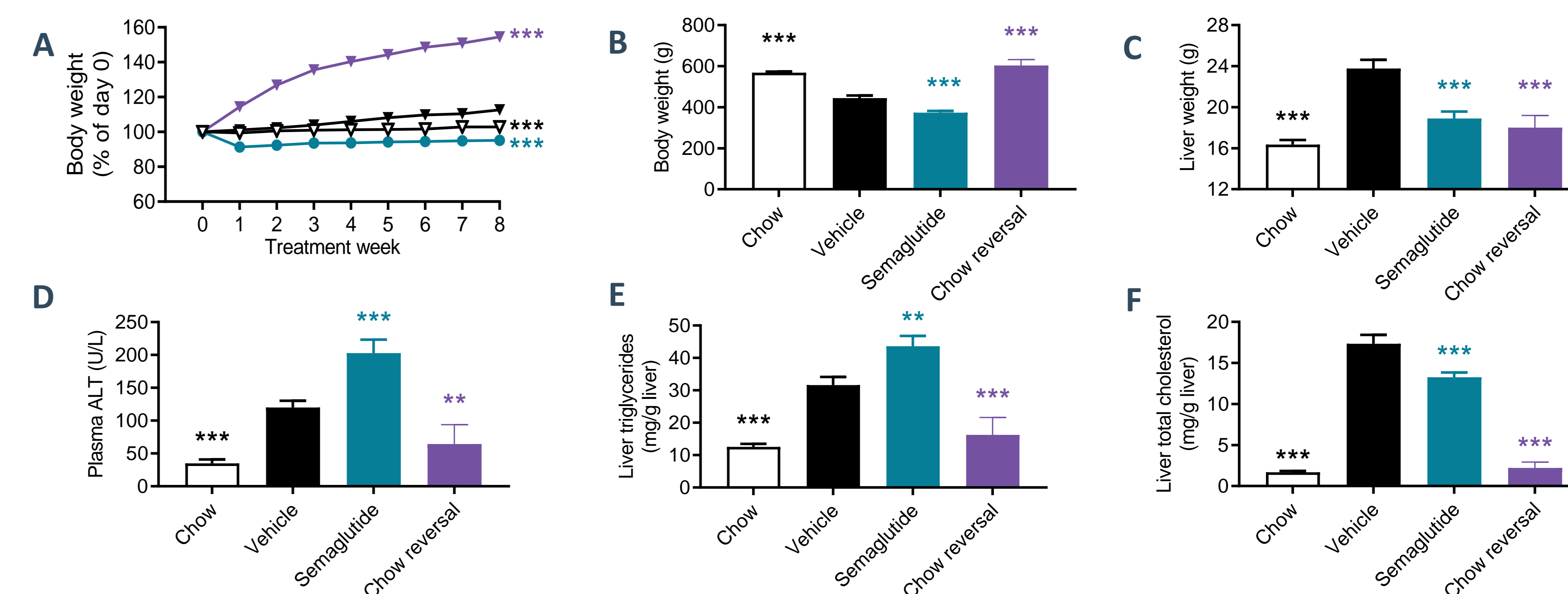


Figure 1. Semaglutide reduces body weight, liver weight and biochemical parameters in CDAA-HFD non-obese rat model of NASH. (A) Body weight change relative to baseline (day 0). (B) Terminal body weight (g). (C) Terminal liver weight. (D) Terminal plasma alanine aminotransferase (ALT). (E) Terminal liver triglycerides. (F) Terminal liver total cholesterol. *p<0.05, **p<0.01, ***p<0.001 compared to corresponding Vehicle control (Dunnett's test one-factor linear model).

Histopathological NAFLD Activity Score and Fibrosis Score

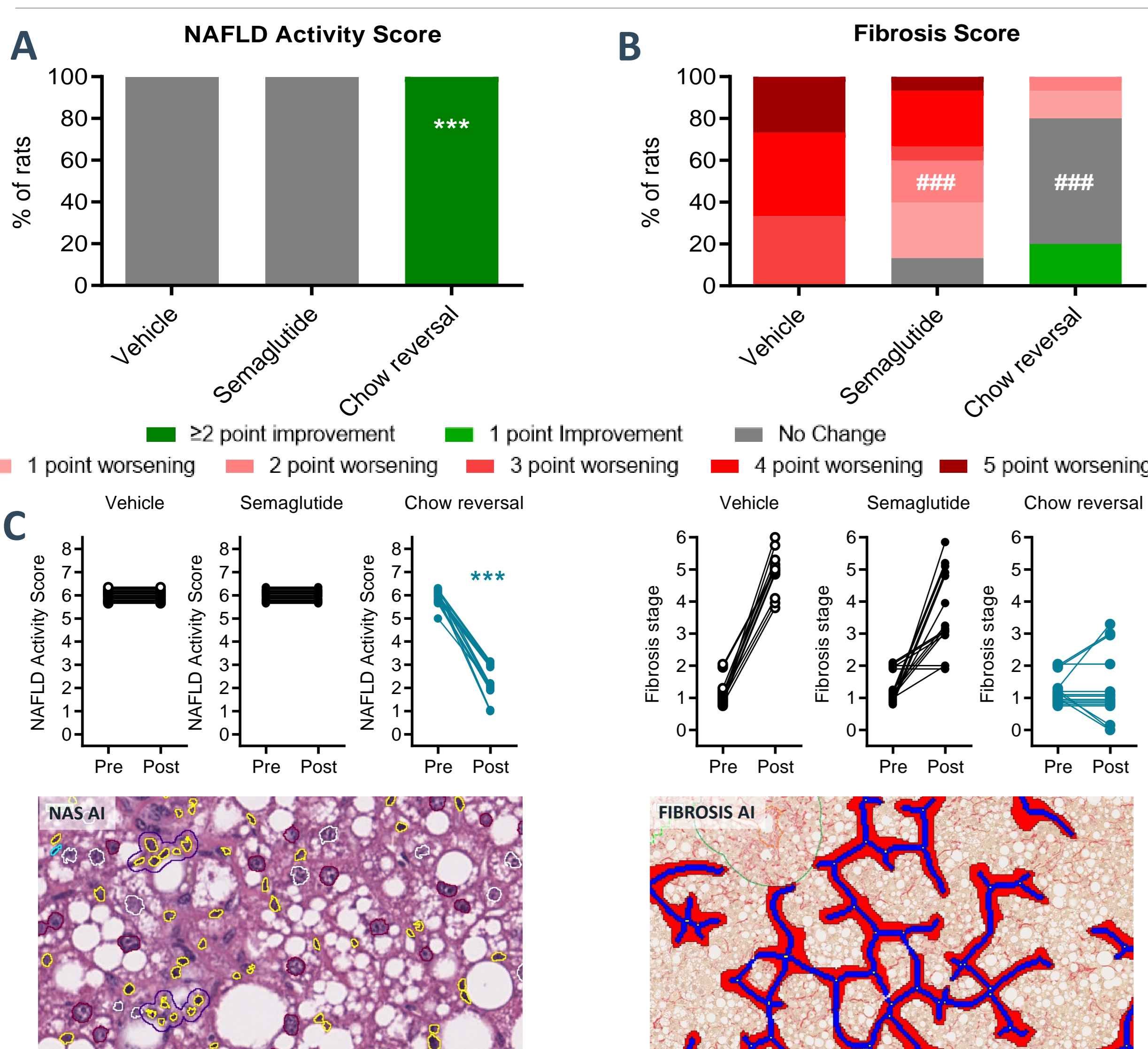


Figure 2. Semaglutide improves liver histopathological fibrosis score in CDAA-HFD non-obese rat model of NASH. (A) NAFLD Activity Score (NAS) determined by Gubra Histopathological Objective Scoring Technique (GHOST) deep learning-based image analysis. (B) Fibrosis Score (Ishak), manually scored. (C) Comparison of individual pre-post NAS and individual pre-post Fibrosis stage. ***p<0.001 compared to vehicle group (One-sided Fisher's exact test with Bonferroni correction). ###p<0.001 for ≥3 point worsening compared to vehicle group (One-sided Fisher's exact test). Bottom panels: Representative HE and PSR photomicrographs used for GHOST evaluation.

Histological quantitative markers of steatosis, inflammation and fibrosis

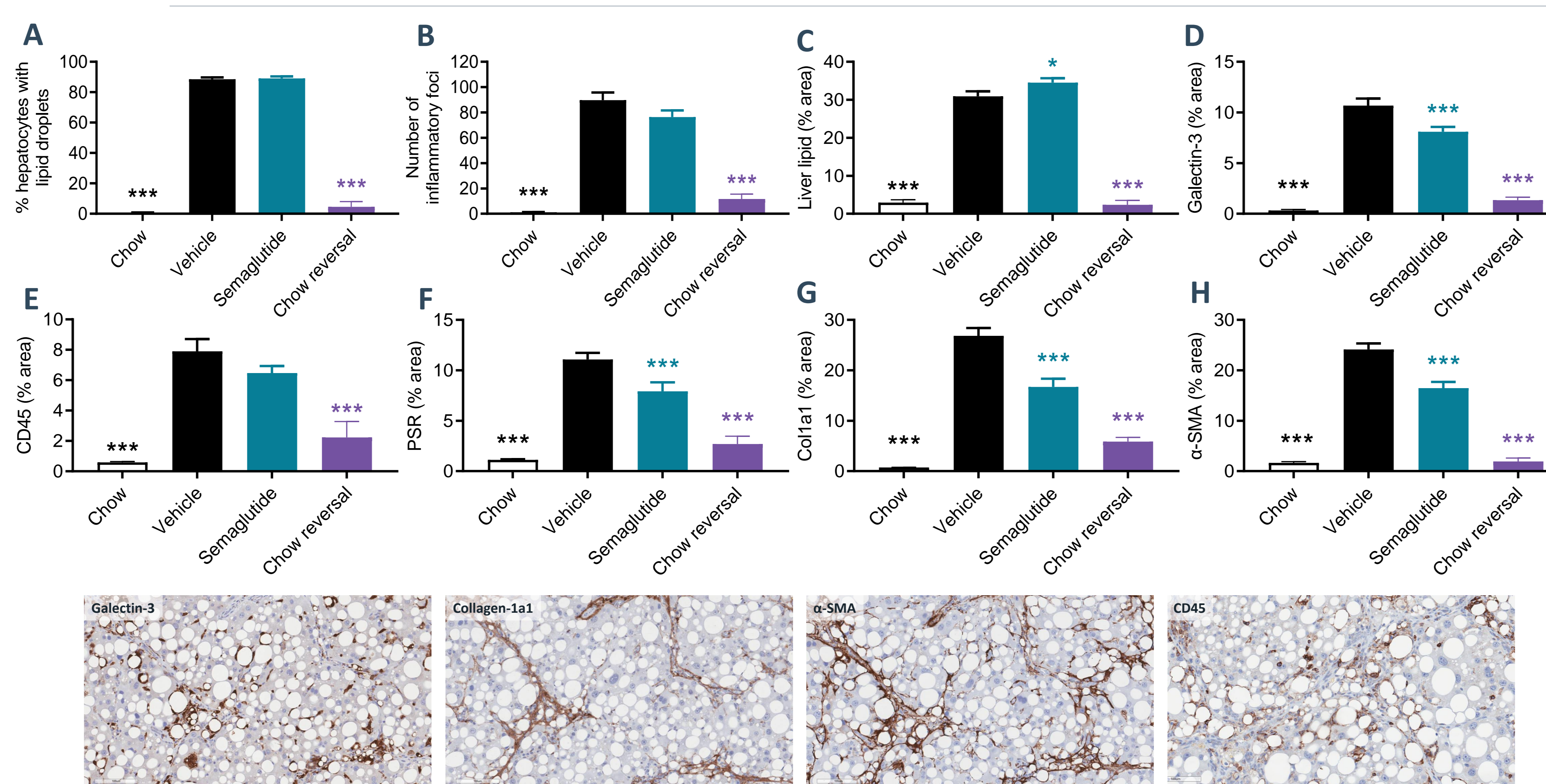


Figure 3. Semaglutide improves quantitative liver histological markers for fibrosis in CDAA-HFD non-obese rat model of NASH. Histomorphometric assessments were performed by GHOST deep learning-based image analysis on scoring-associated variables (panels A-B) and conventional IHC image analysis (panels C-H). (A) % hepatocytes with lipid droplets. (B) Number of inflammatory foci. (C) % area with liver lipids. (D) % area of galectin-3. (E) % area of CD45 (F) % area of PSR. (G) % area of collagen-1a1. (H) % area of alpha-smooth muscle actin (α-SMA) as marker for stellate cell activation. Mean ± SEM. *p<0.05, ***p<0.001 compared to vehicle group (Dunnett's test one-factor linear model). Bottom panels: Representative galectin-3, collagen 1a1, α-SMA and CD45 photomicrographs for semaglutide treatment group (scale bar, 100 μm).

Surface tumor evaluation

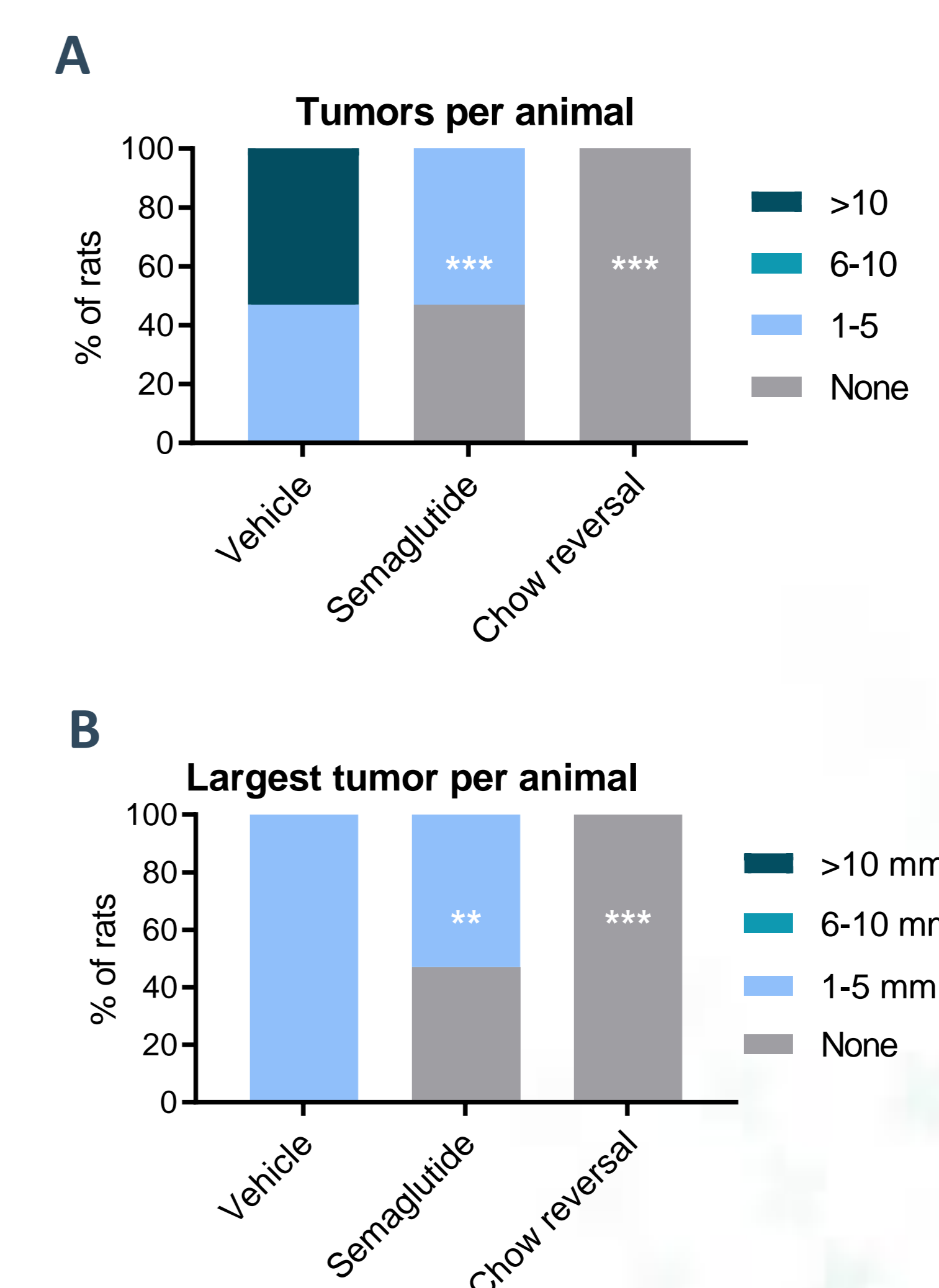


Figure 4. Semaglutide improves tumor burden in CDAA-HFD non-obese rat model of NASH. Macroscopic tumor assessment for (A) Number of tumors per animal, and (B) Largest tumor per animal (diameter, mm). **p<0.01, ***p<0.001 compared to vehicle group (Dunnett's test one-factor linear model).

CONCLUSION

- + Semaglutide reduces body weight, hepatomegaly and liver total cholesterol and preserve levels of plasma ALT and liver triglycerides.
- + Semaglutide do not improve NAFLD Activity Score, albeit significantly prevents ≥3-point worsening in fibrosis score.
- + Semaglutide reduces quantitative histological markers of fibrosis and stellate cell activation.
- + Semaglutide improves surface evaluated tumor burden.
- + Pre-biopsy confirmed CDAA-HFD non-obese rat model of NASH allows exploration of drug efficacy for progressive fibrosis and tumor development.