A Novel Murine Model of Metabolic Dysfunction-Associated Alcoholic Liver Disease (MetALD) for Therapeutic Drug Evaluation

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WuXi AppTec

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INTRODUCTION

Metabolic dysfunction-associated alcoholic liver disease (MetALD) has recently been recognized as a distinct category within metabolic dysfunction-associated steatohepatitis (MASH), representing a significant subset of these patients. MASH is a progressive liver disorder characterized by fat accumulation, chronic inflammation, and fibrosis. The redefinition of "NASH" to "MASH" has reversed the exclusion of alcohol consumption, bringing greater clinical attention to MetALD, which involves both metabolic dysfunction and significant alcohol intake.

While the high-fat diet (HFD) and Gubra-Amylin NASH (GAN) diet-induced MASH models are widely adopted for simulating liver pathology and metabolic dysfunction, they exclude alcohol consumption, thus failing to fully replicate the conditions seen in MetALD patients. The absence of effective animal models for MetALD has significantly restricted relevant drug development. Therefore, the development of an authoritative MetALD animal model is imperative.

AIM

This study aims to develop a MetALD model for preclinical drug evaluation that combines the HFD and GAN diet with alcohol consumption. Mechanistically, this model can accurately simulate the pathogenesis of MetALD. Pathologically, it effectively mimics liver pathology, metabolic features, and alcohol use characteristics of MetALD patients.

METHODS

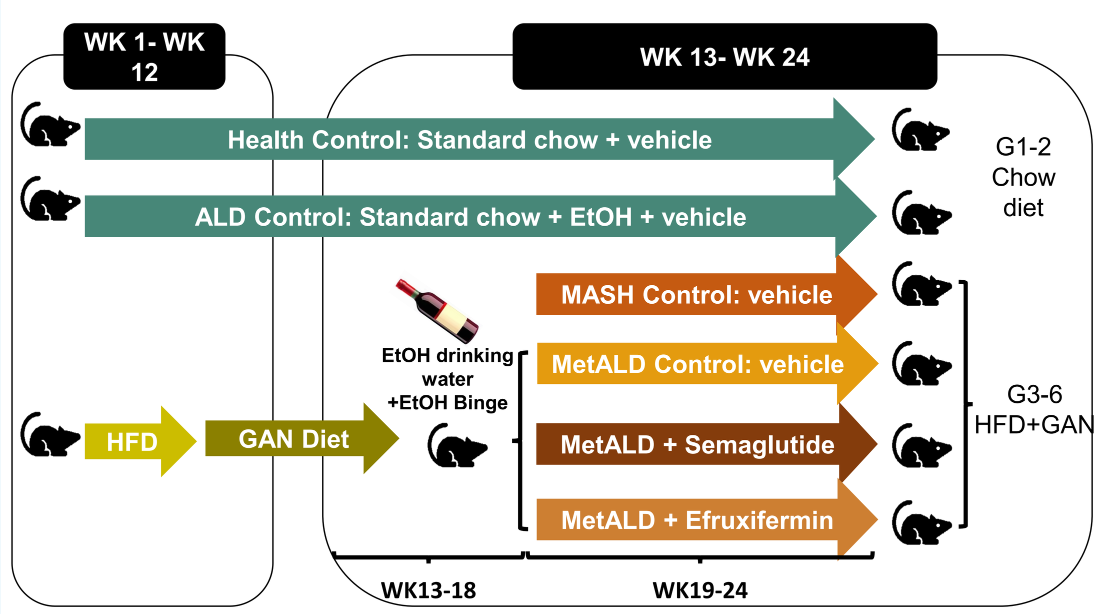

Figure 1. Generation of a novel MetALD Mouse Model and Treatments C57BL/6J mice were fed HFD followed by GAN diet for 24 weeks, with alcohol drinking water and alcohol binge started from week 13 to week 24. Vehicle, semaglutide and efruxifermin were administered for 6 weeks.

RESULTS

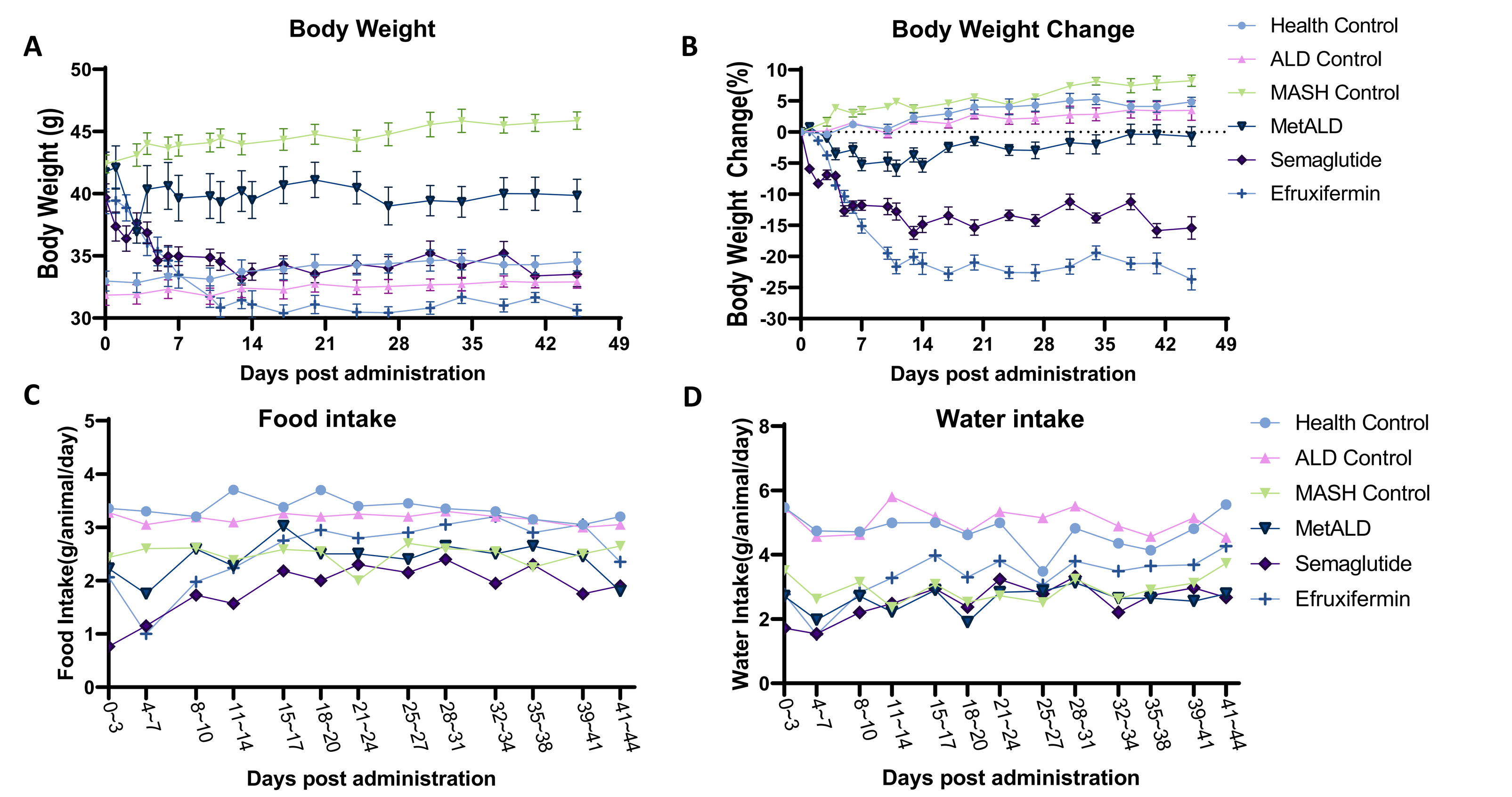

Figure 2. MetALD Mice Show Increased Body Weight Trend with Reduced Food/Water Intake. (A) Body weight record. (B) Trend of body weight change. (C) Food intake. (D) Water intake.

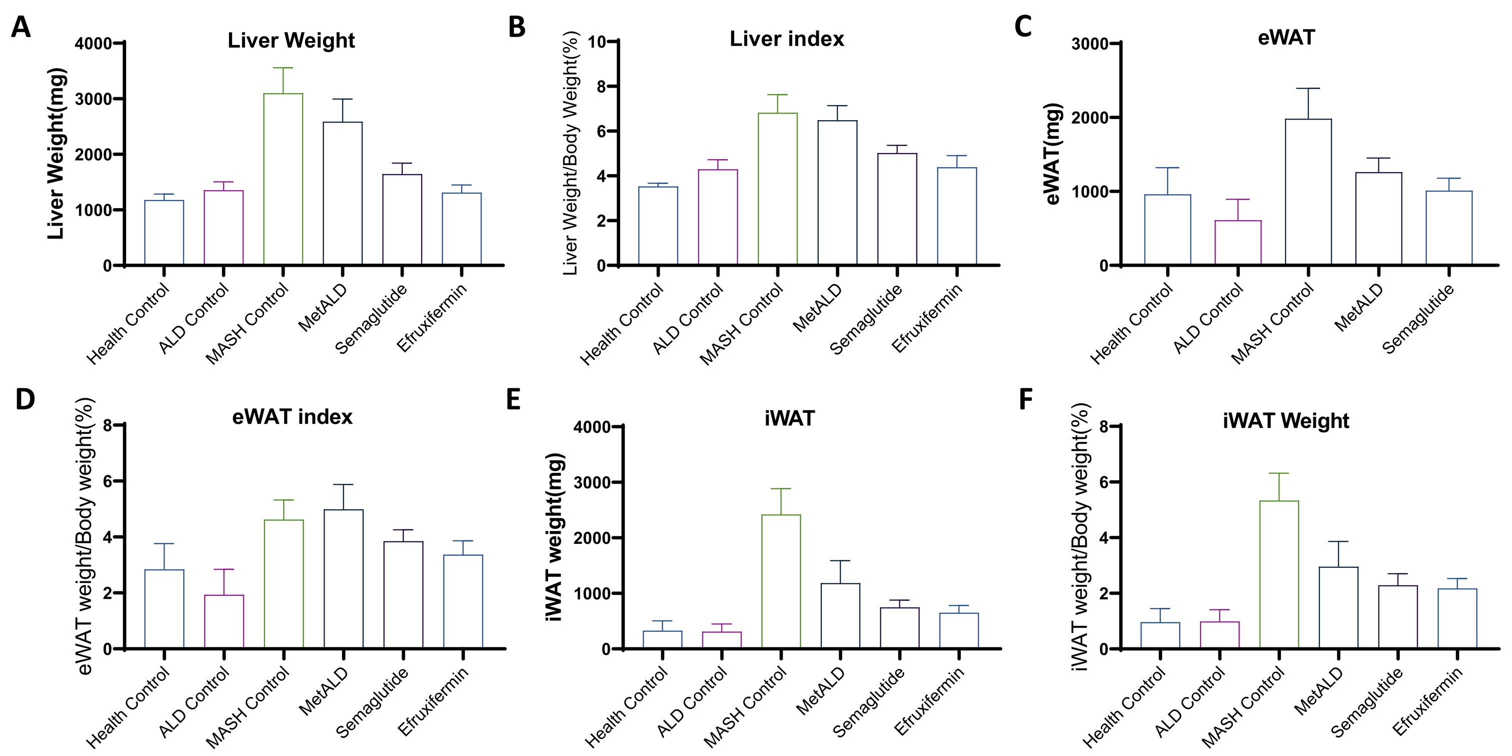

Figure 3. MetALD Mice Show Increased Liver Index and eWAT/iWAT Index. (A) Liver weight. (B) Liver index. (C, D) Epididymal white adipose tissue (eWAT) and eWAT index. (E, F) Inguinal white adipose tissue (iWAT) and iWAT index.

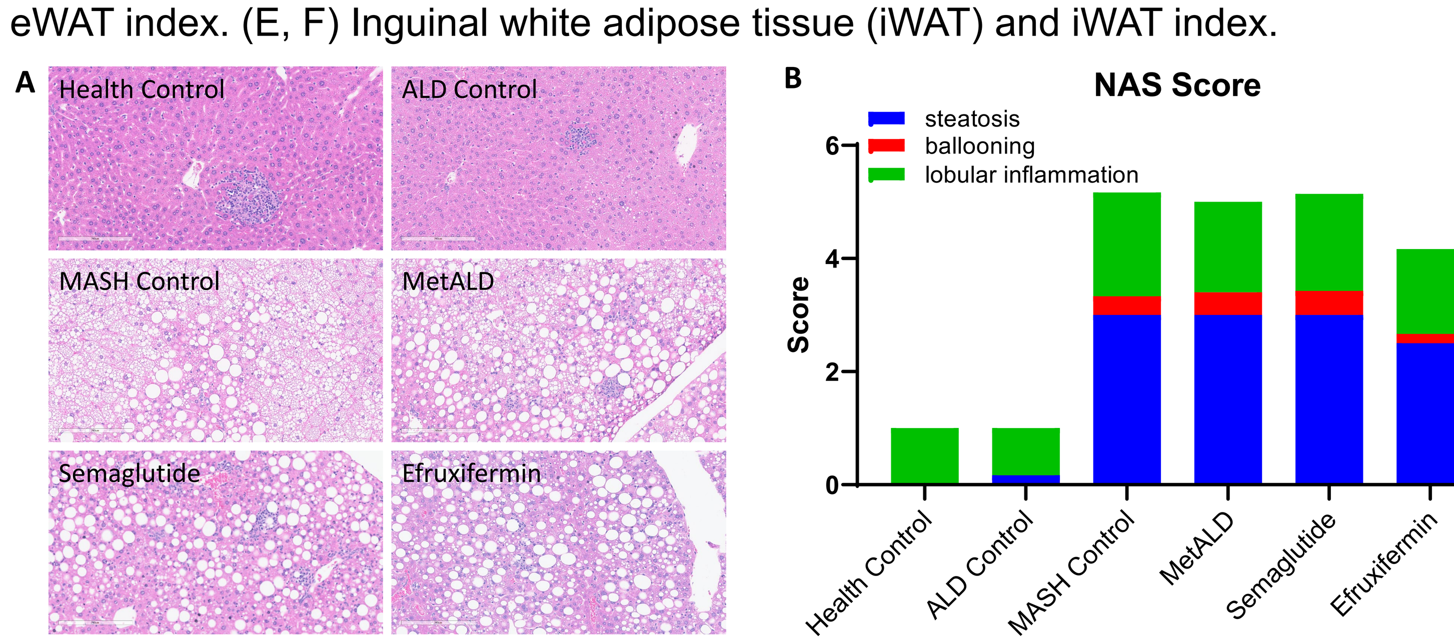

Figure 4. Liver Steatosis and Inflammation Appears in MetALD Mice and Alleviated by Efruxifermin Treatment. (A) Representative H&E staining results. (B) NAS Score.

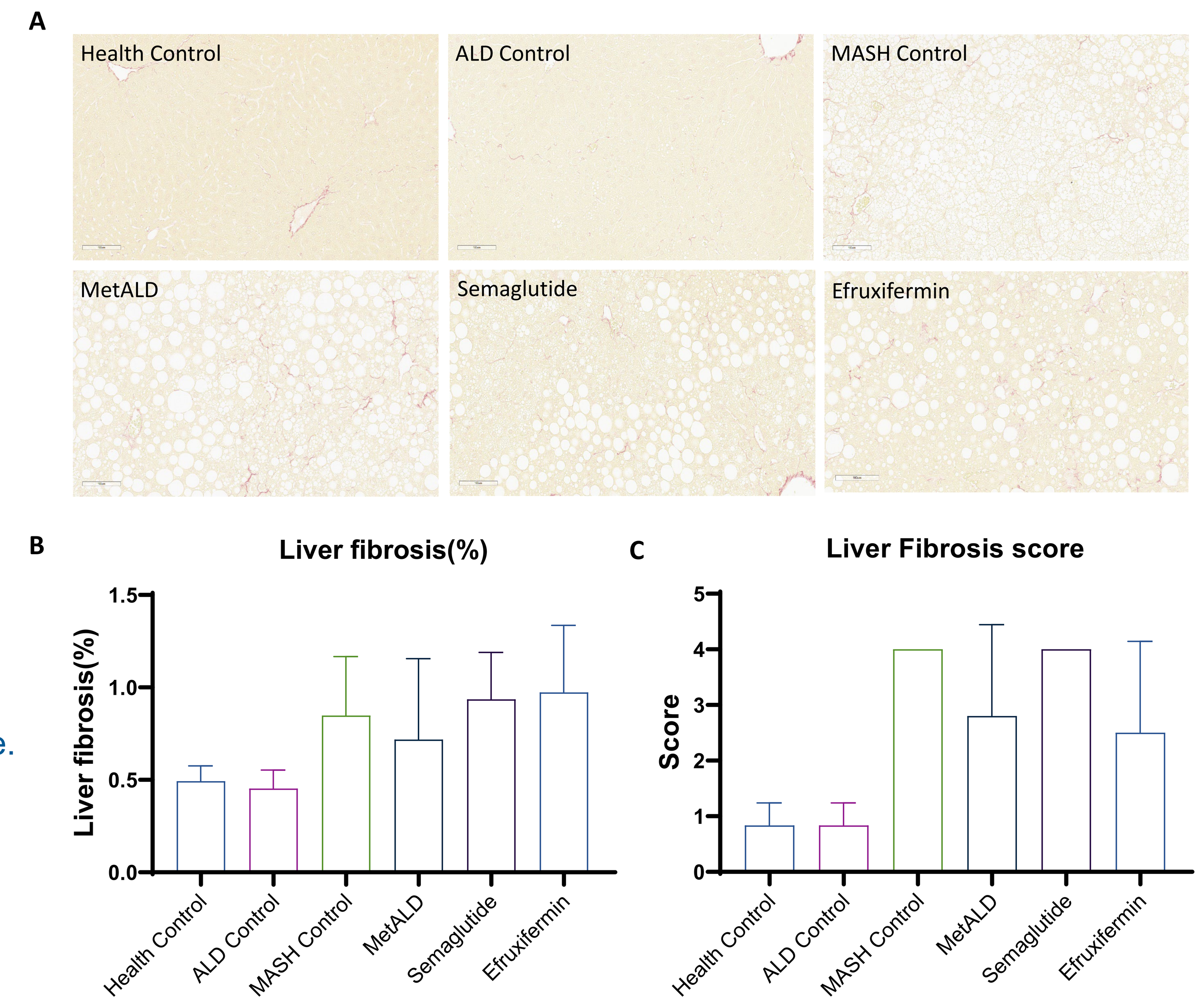

Figure 5. Mild Liver Fibrosis Appears in MetALD Mice.

(A) Representative Sirius Red staining results. (B) Liver fibrosis percentage. (C) Liver fibrosis score.

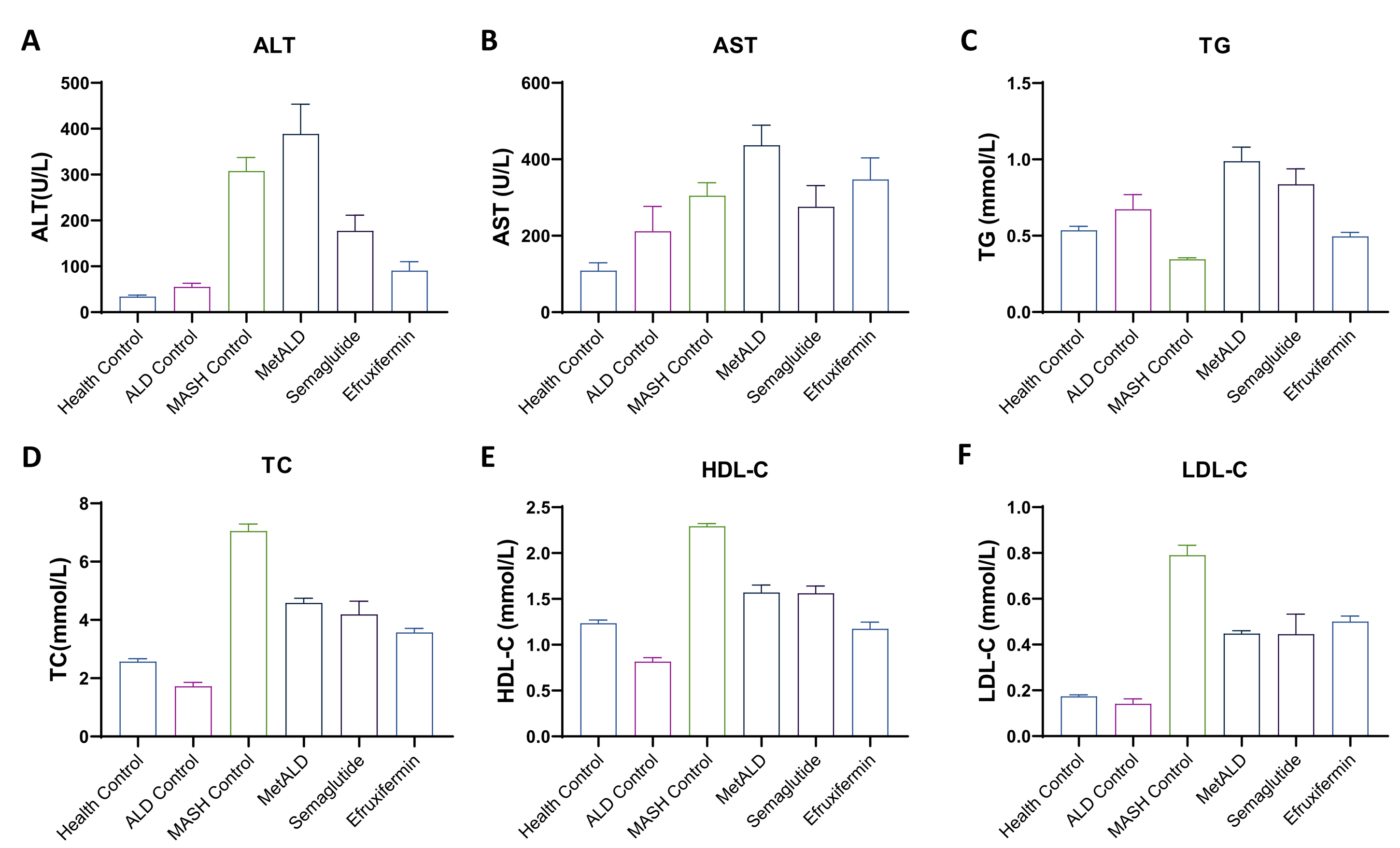

Figure 6. Effects of Combination Therapies on Serum Markers in MASH.

Serum profiles showing (A) alanine aminotransferase (ALT), (B) aspartate aminotransferase (AST), (C) triglycerides (TG), and (D) total cholesterol (TC) levels following treatment.

CONCLUSIONS

1. This novel murine model closely reproduces the key pathological features of human MetALD in the context of obesity and alcohol consumption, including marked liver steatosis, inflammation, and fibrosis.
2. Efruxifermin treatment markedly improved liver histology, lowering NAS. Hematology results revealed increased liver enzyme and lipid levels in MetALD model and reduced levels upon both treatments, indicating that the model not only mimics histological changes but also improved liver enzymes and lipid metabolism.
3. The results demonstrates that the model is responsive to pharmacologic interventions and suitable for preclinical efficacy testing of MetALD-targeted therapies.
4. By integrating metabolic dysfunction, alcohol exposure, and clinically relevant liver pathology, this MetALD model provides a powerful platform for dissecting disease mechanisms, identifying biomarkers, and systematically evaluating current and emerging therapeutic strategies.

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