Increased plasma Leukotriene B4 in decompensated cirrhosis associates with disease progression and leads to increased skin window neutrophil infiltration

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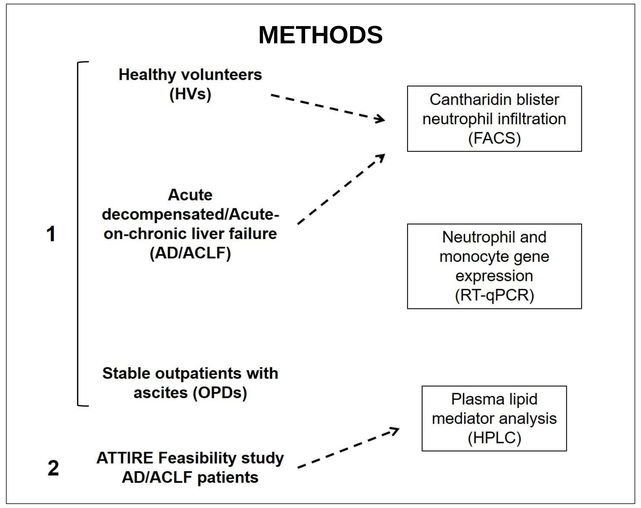
INTRODUCTION

- **Infection is the most common cause of death** in advanced cirrhosis patients with liver failure, known as acute decompensation (AD) or Acute-on-Chronic-Liver Failure (ACLF), **secondary to immune dysfunction**[1].
- Human and animal models to date have shown **decreased or no change in neutrophil trafficking** in cirrhosis patients[2].
- However, other studies have shown several circulatory **chemokines involved in leukocyte migration and chemotaxis to be increased** in decompensated cirrhotic patients, which correlated with survival[3].
- **Leukotriene B4 (LTB_4)** is a pro-inflammatory lipid mediator that displays strong chemoattractant properties, and its role in decompensated cirrhosis hasn't been studied in-depth.

METHODS



References

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AIM

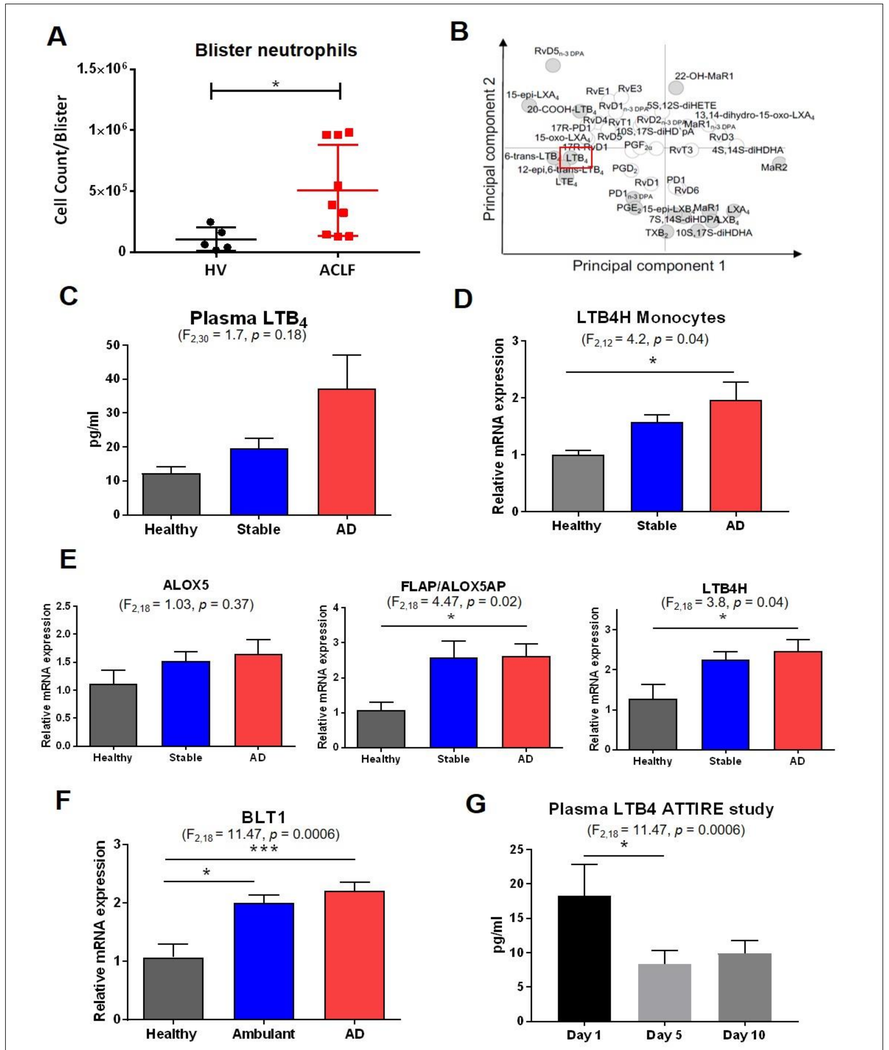
Investigate **neutrophil infiltration in ACLF** patients within 3 days of hospital admission using our cantharidin skin blister model of sterile inflammation and **study the role of lipid mediators**

	HV (n = 5)	OPD (n = 11)	ACLF (n = 10)
Age (Mean ± SD)	31 ± 11	60 ± 10	62 ± 14
Gender (M/F)	4/1	8/3	8/2
Child Pugh Score (A/B/C)	n/a	0/9/2	0/6/4
MELD Score (Mean ± SD)	n/a	13 ± 3	14 ± 7
Aetiology (EtOH/HepC/Other)	n/a	7/1/2	7/0/4
Albumin (g/L) (Mean ± SD)	47.8 ± 3.6	33 ± 2.1	30.3 ± 5.3
Bilirubin (mmol/L) (Mean ± SD)	10.6 ± 4	26 ± 7	36.2 ± 25
Creatinine (µmol/L) (Mean ± SD)	84.6 ± 14.6	107.5 ± 40	89.7 ± 25.3
CRP (mg/L) (Mean ± SD)	0.76 ± 0.7	8 ± 5.8	24.2 ± 4

Table 1. Healthy volunteers and patients characteristics

DISCUSSION

- ACLF patients display **significantly higher neutrophil recruitment** to a site of inflammation than healthy volunteers.
- Plasma levels of the chemotactic **LTB_4 increased according to cirrhosis disease severity**.
- Increased expression of **several members of the LTB_4 synthetic machinery is found in cirrhosis patients**' peripheral blood neutrophils and monocytes.



A) Total neutrophils as measured by flow cytometry in cantharidin skin blisters in HVs (n = 5) and ACLF (n = 10). Mean ± SD shown. Two-tailed unpaired Mann-Whitney test performed. B) 2-dimentional loading plot of human plasma from HV (n=6), stable liver outpatients (n=9) and AD/ACLF (n=18). C) Leukotriene B_4 levels in human plasma from HV (n=6), stable liver outpatients (n=10) and AD/ACLF (n=19). Results are expressed as mean ± SEM. D) mRNA levels in primary human monocytes isolated from HV (n=4), stable liver outpatients (n=5) and AD/ACLF (n=6). Results are normalised to expression of reference gene SNRPD3, and shown as mean ± SEM, relative to healthy levels. E,F) mRNA levels in primary human neutrophils isolated from HV (n=5), stable liver outpatients (n=5) and AD/ACLF (n=11). Results are normalised to the average expression of reference genes Cyclophylin and SNRPD3, and shown as mean ± SEM, relative to healthy levels. G) Leukotriene B4 levels in human plasma from acutely decompensated cirrhotic liver recruited in the ATTIRE Feasibility study at study timepoints day 1 (n=9), day 5 (n=15) and day 10 (n=13). Results are expressed as mean ± SEM. For multiple comparisons, significance was determined using single variance ANOVA followed by Bonferroni's test. * $p < 0.05$, ** $p < 0.005$, *** $p < 0.0005$.

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