Potential mechanisms underlying the protective effect of long-term albumin infusion in cirrhosis

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BACKGROUND

Chronic albumin administration has shown some signal of improved survival and reduced symptom burden in liver decompensation, although the mechanism of this remains unknown. The aim of this study is to investigate whether the administration of albumin has an impact in cirrhosis and acute-on-chronic liver failure (ACLF) models clinically, and its impact on TLR4 pathways and the gut microbiome.

METHODS

10 treatment groups of 5 NAR (analbuminaemic rats) and 5 Sprague Dawley (SD) rats were studied. Naïve, cirrhosis (4-w after bile duct ligation (BDL)) and ACLF models (induced by lipopolysaccharide (LPS) 0.025 mg/kg i.p. to BDL) ±albumin infusion (1.5 g/kg i.p. for 2 weeks) were modelled in each animal type. Plasma biochemistry and TUNEL staining of liver were used to investigate liver injury, plasma D-lactate assay for gut permeability, and liver toll-like receptor 4 (TLR4) expression through PCR and RT2 PCR profiler.

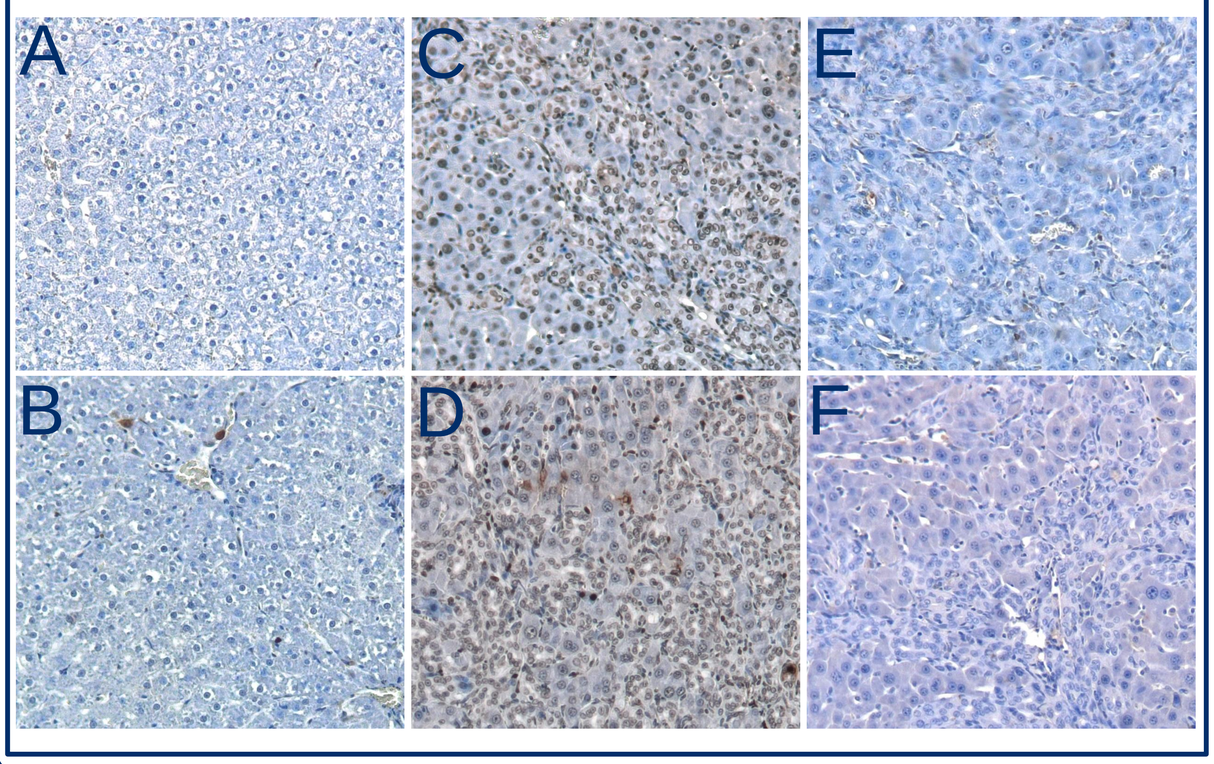
RESULTS

Liver injury:

ALT levels showed significant improvement after albumin administration in SD BDL LPS group (p=0.011), and non-significant improvement in SD BDL LPS and NAR BDL LPS (figure 2).

TUNEL positive areas were significantly higher in BDL animals for both SD and NAR groups, with a non-significant reduction with albumin administration (figure 1). The effect of LPS administration: coma-free survival was higher in SD rats than NAR rats (80% vs 63.6%), with 100% survival in NAR rats exposed to LPS after albumin infusion.

Figure 1: TUNEL staining of liver tissue: (A) SD sham (B) NAR sham (C) SD BDL (D) NAR BDL (E) SD BDL +albumin (F) NAR BDL +albumin



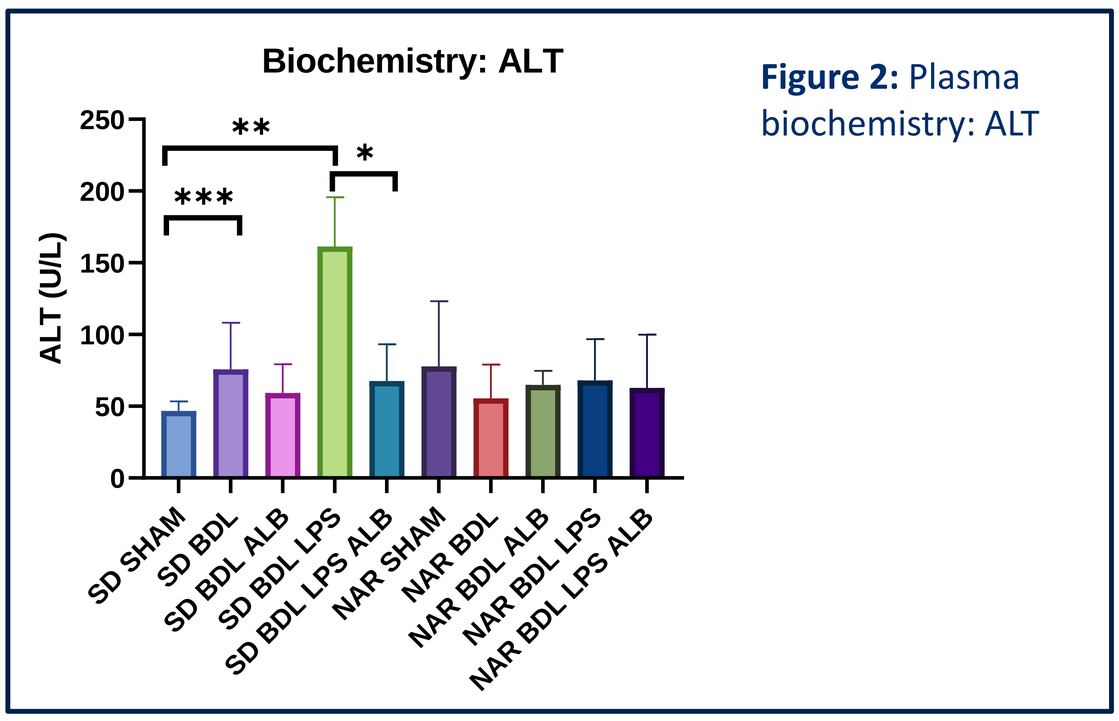


Figure 2: Plasma biochemistry: ALT

Markers of gut permeability:

D-lactate was quantified in plasma, showing albumin administration reduced plasma concentrations in BDL and LPS models, with NAR animals having higher levels than their respective SD animal models (figure 3).

Hepatic expression of TLR4 and associated pathways:

Cirrhotic NAR animals had greater hepatic TLR4 expression, compared to SD, with both showing a reduction by albumin administration. TLR4 expression was reduced after albumin administration in LPS animals.

Hepatic TLR4 gene array confirmed the activation of TLR4 dependent pathways in the cirrhotic NAR animals, which was abrogated by albumin infusion.

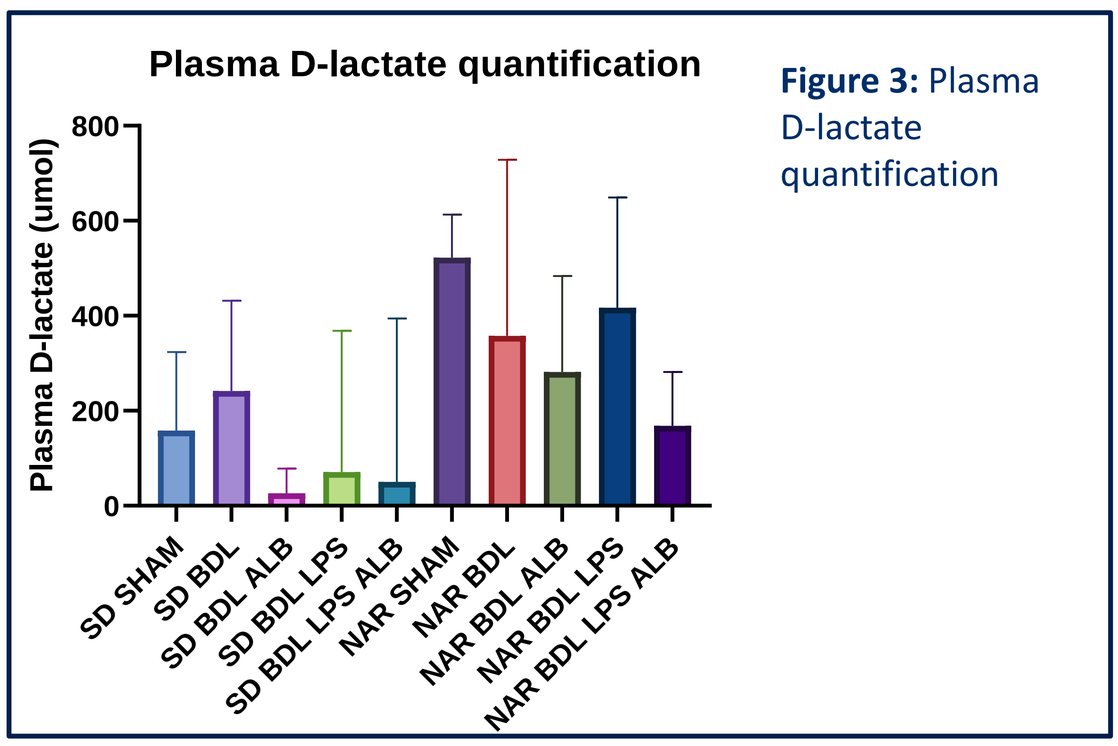


Figure 3: Plasma D-lactate quantification

CONCLUSIONS

We have shown analbuminaemic animals have increased mortality, significantly increased liver injury and increased sensitivity to LPS compared to those producing native albumin. Chronic administration of albumin showed partial reversal of these effects. Administration of albumin reduced plasma D-lactate in all disease models, indicating its beneficial effect on gut integrity and reduction in gut translocation, in addition to its decrease in TLR4 pathway activation. This gives us a greater understanding of the mechanism of action of albumin in cirrhosis and ACLF patients.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 825694. This reflects only the authors' view and the European Commission is not responsible for any use that may be made of the information it contains.

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