Chronic liver diseases (CLDs) are characterised by leukocyte infiltration which drives chronic inflammation, fibrosis and cirrhosis. Hepatic sinusoidal endothelial cells (HSEC) play a critical role in liver homeostasis, regulating the immune microenvironment and maintaining tolerance. HSEC line the low shear environment of the hepatic sinusoids in which leukocyte recruitment occurs. They undergo substantial phenotypic changes during CLD, yet how this influences the immune microenvironment in liver disease remains poorly understood. Mannose receptor (MR) and plasmalemma vesicle-associated protein (PLVAP) are atypical adhesion molecules, expressed within specialised vascular beds, although their contribution to CLD remains unknown. We sought to characterise MR and PLVAP expression in normal and diseased human liver tissue and aimed to understand their regulation in primary human HSEC.

Immunohistochemistry studies demonstrated a distinct and mutually exclusive expression pattern, with homogenous MR expression throughout normal liver sinusoids, and PLVAP localisation to peri-venular sinusoids. In CLD, MR expression was lower, displaying disrupted homogeneity, whilst PLVAP was significantly upregulated, correlating spatially and quantitatively with collagen deposition and fibrosis independently of aetiology. Mutual exclusivity and endothelial identity of MR+ and PLVAP+ cells were confirmed by dual immunofluorescence. PLVAP co-localised with endothelial marker, CD31, whilst MR co-localised with sinusoidal marker L-SIGN (liver/lymph node-specific intercellular adhesion molecule-3 grabbing non-integrin). Primary HSEC were isolated from human liver tissue by immunomagnetic selection and MR/PLVAP expression was confirmed by immunofluorescence, allowing regulation studies to be conducted using these cells. Notably, whilst most HSEC were MR-positive, a subset of cells expressed PLVAP, recapitulating observations in situ within human liver. A high-content imaging assay was designed to investigate MR/PLVAP expression in response to various treatment conditions in a high-throughput manner. Contradictory to previous findings, MR levels did not fluctuate following pro-inflammatory stimulation (TNF-α, tumour necrosis factor-α; IL-1β, interleukin-1β; LPS, lipopolysaccharide), suggesting a distinct MR regulation mechanism within HSEC. Contrastingly, PLVAP expression increased following TNF-α and IL-1β treatment, and was significantly upregulated in the presence of VEGF (vascular endothelial growth factor), confirming previous reports.

In conclusion, these data define two sinusoidal endothelial cell subsets, characterised by reciprocal MR/PLVAP expression, which may have distinct roles in homeostasis and inflammation. Furthermore, MR and PLVAP are differentially regulated within HSEC in vitro, with PLVAP being increased by pro-inflammatory stimuli and growth factors, supporting its upregulation in CLD. Targeting HSEC, with the aim of reprogramming the balance between MR and PLVAP expression, may represent a novel therapeutic approach in CLD.
patients discussed at our weekly decompensated liver disease multidisciplinary (MDT).

Methods We prospectively collected data on admissions to the Hepatology ward between September 2019 and March 2020. Outcomes were defined by the key performance indicators from Improving Quality in Liver Services (IQILS) and the presence of the 5 evidence-based factors associated with poor prognosis. These include 1) Childs-Pugh C 2) more than 2 liver-related admissions in 6 months 3) current alcohol consumption 4) Unsuitable for transplant work up 5) WHO performance status 3–4. Those with over 2 factors have a poorer prognosis so this triggered discussions around ceiling of treatment and end of life care.

Results During this period, 55 individual patients were admitted to the hepatology ward with decompensated liver disease 44 (80%) had alcohol related liver disease (ArLD) and were referred to the alcohol liaison service.

Twenty-seven (49%) patients died within 6 months of admission, 14 (52%) were male, mean age 60 years and 20 (74%) had ArLD. Seventeen (63%) had ascites with a median MELD score of 21. The median number of days from admission to death was 35 (3–256).

Twenty-one (78%) of those who died had over 2 factors associated with poor prognosis compared with 12/28 (43%) who survived. Nineteen (70%) had Childs Pugh C cirrhosis, 15 (56%) with over 2 admissions within 6 months, 17 (63%) had current alcohol consumption, 26 (96%) were deemed unsuitable for a liver transplant and 13 (48%) had performance status 3 or 4.

Among the 27 patients who died, there were 38 (mean 1.4) readmissions before death. 10 paracentesis were performed in 4 patients in the Ambulatory Care Unit, 4 Palliative Care referrals were made and 5 died at home.

Conclusions This data confirms the utility of the prognostic tool in identifying patients at high risk of death. Utilisation of such prognostic models can change the focus of patient care particularly around ceilings of treatment, access to ambulatory facilities, decisions around end of life care and involvement of palliative care.