I am thankful and acknowledge the guidance and mentorship of Prof S.k.Sarin in all the work and his continuous support and encouragement. I also acknowledge the work of my co-investigators Dr Jaswinder Sindh Maras who performed the metabolomics and proteomics, Dr Anupam Kumar for analysing the cytokine data and experiments on mitochondrial bioenergentics and Dr Archana Rastogi for helping with the immunohistochemistry and biopsy data. I am also thankful to the junior research fellow Asini Kumar Hidam for executing and collecting the samples. I confirm myself as the principal investigator behind these useful scientific data and managing these very sick and challenging group of liver patients. Our results have, for the first time, demonstrated the following key findings in critically ill patients with cirrhosis admitted to the intensive care unit the following

I. We have discovered novel protein-based urinary biomarkers to stratify critically ill cirrhotic patients regarding the presence or absence of renal injury and the subsequent course.
II. We have discovered the biomarkers in the development of hepatorenal syndrome (HRS) and its differentiation from acute tubular necrosis (ATN) in the context of bacterial infections. The data could enable effective and appropriate management with vasoconstrictors for HRS and renal replacement therapy for ATN.
III. data demonstrate defective mitochondrial biogenesis and fatty acid oxidation defects in these patients.. Defects in endothelial function and dysfunctional renin-angiotensin-aldosterone system were the pathophysiological hallmark of AKI in cirrhotics. These findings were distinctly higher in patients with AKI progression compared to patients with regressive AKI.

We elegantly demonstrated a maladaptive repair process with histological specimens. Injury to the proximal tubules is a hallmark of inflammation-related AKI in the context of critically ill. The lack of neutrophil infiltration and predominance of monocyte-macrophage in the kidney biopsies suggests the pathogenic role of macrophages in renal fibrosis in the context of inflammation-related AKI in critically ill cirrhotics. This correlated with severity of endothelial dysfunction, defective mitochondrial dynamics and renal biomarkers. Future studies exploring the macrophage dynamics in chronic kidney disease (CKD) would be helpful in the development of targeted therapeutic strategies. We also propose studying the proximal tubules' molecular targeting for preventing fibrosis progression and CKD after AKI in CICs.

Strategies targeting systemic inflammation, sepsis, and endothelial dysfunction and ameliorating the impaired mitochondrial function could improve the outcomes of AKI in critically ill cirrhotics. Further, early risk stratification and appropriate therapeutic intervention with the help of protein biomarkers could improve outcomes of AKI in sick patients with cirrhosis admitted to the intensive care unit.

In patients with acute on chronic liver failure

I. Signature biomarker was developed to differentiate phenotype of volume non-responsive AKI in ACLF patients for identification of acute tubular necrosis and its differentiation from hepatorenal syndrome
II. For the first time, we developed a non-invasive biomarker signature comprising urine NGAL, renin and osteopontin to identify cholemic nephrosis. Cholemic nephrosis is an under-recognised cause of renal dysfunction in patients with acute on chronic liver failure (ACLF) and classically is a histological diagnosis and requires kidney biopsy
III. We demonstrate the pathophysiologic basis of cholemic nephrosis with key features being systemic inflammation, defects in bile acid homeostasis and failure of mitochondrial biogenesis. We substantiated the findings on histology and performed detailed immunohistochemistry substantiating these findings.

IV. We further demonstrated therapeutic plasma-exchange as an effective treatment modality for patients with ACLF and cholemic nephrosis which improves not only the kidneys but also have a survival benefit.

V. We further demonstrated ATN as the most severe form of AKI in patients with ACLF which is driven by increased hypoxia-induced ferroptosis and loss of renal repair due to failure of bio-energy metabolism. This finding may merit early initiation of renal replacement therapy particularly for this subset of patients and therapies ameliorating systemic inflammation and iron chelation needs to be explored.

VI. We identified protein biomarkers to differentiate HRS and ATN in ACLF patients which is being validated currently in another 200 patients.

I hope the Sun Pharma foundation would duly acknowledge our work and consider my application for the prestigious award.

Thanks and regards

Dr Rakhi Maiwall