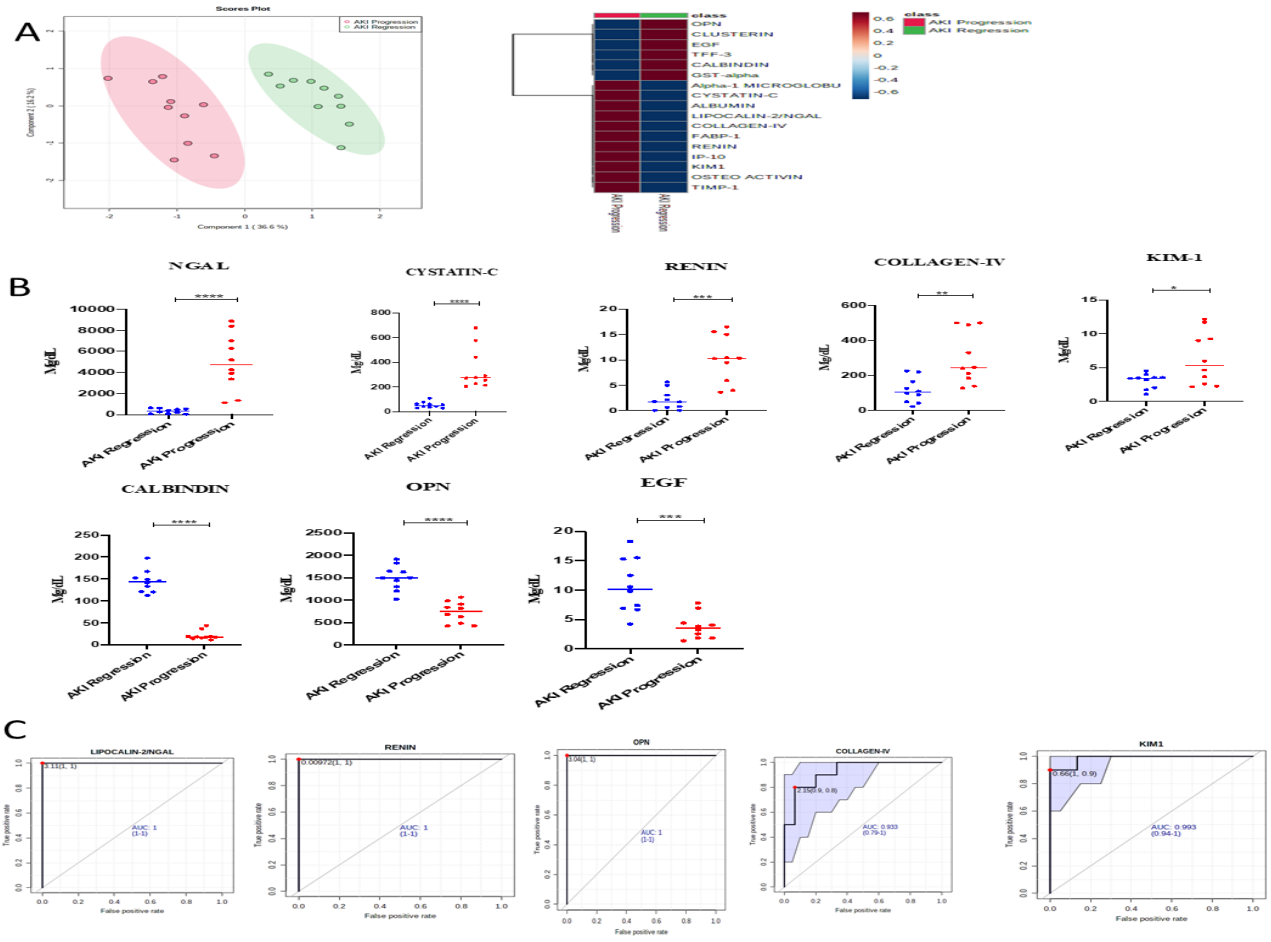
Our results have, for the first time, demonstrated the following key findings:

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.

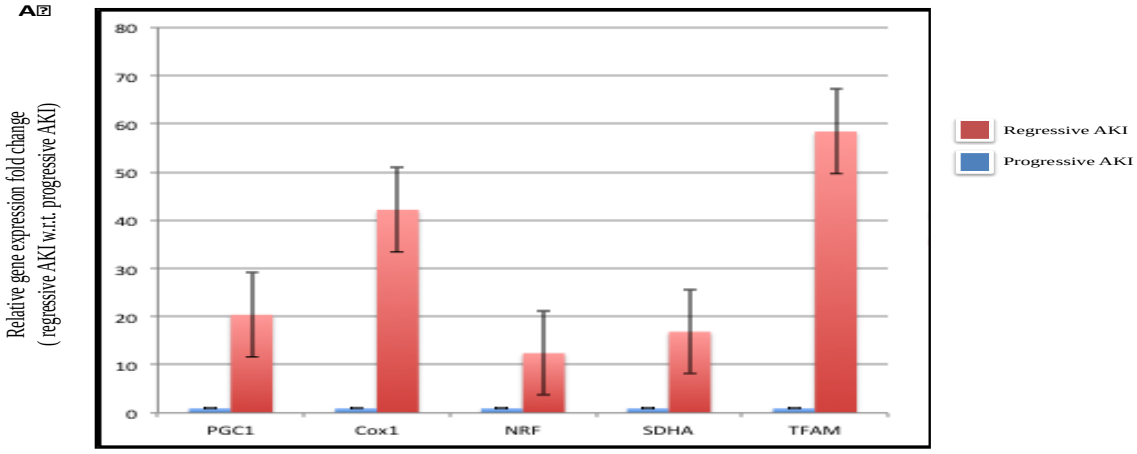
II. We have discovered the biomarkers in the development of hepatorenal syndrome (HRS) and its differentiation from acute tubular necrosis (ATN) in the context of bacterial infections. The data could enable effective and appropriate management with vasoconstrictors for HRS and renal replacement therapy for ATN.



A) Statistical representation showing PLS score 2D plot and Heatmap showing the components between regressive and progressive AKI in cirrhotics. (B) Dot plot showing injury markers

(NGAL, Cystatin-C, Renin, Collagen-IV and KIM-1) were significantly elevated in progressive AKI as compared to regressive AKI. However, repair markers (Calbindin, OPN and EGF) were significantly increased in regressive AKI with respect to progressive AKI. (C) Graphs showing AUROC levels of significant markers in cirrhotics with AKI.

III. Our 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.



Graph showing relative expression of mitochondrial biogenesis associated genes in regressive AKI with respect to progressive AKI in cirrhotics

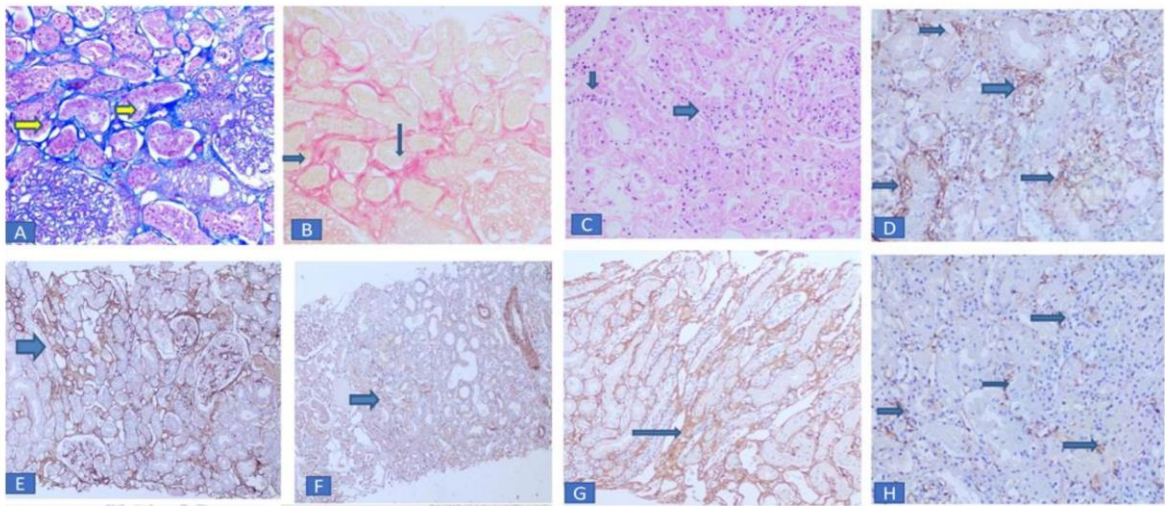


Figure.Representative images of postmortem kidney biopsies.
*(**A**) grade 2 interstitial fibrosis on metallothinein stain **(B)** interstitial fibrosis on picrosirius stain **(C)** IHC demonstrating mild inflammatory infiltrates mainly macrophages (HE, 200x) magnification **(D)** IHC for alpha smooth muscle actin (α-SMA) by labelled streptavidin biotin method (LSAB method) displays myofibroblasts **(E) and (F)** IHC showing collagen (col) 1 and collagen 3 by LSAB method displaying collagen 1 >collagen 3 (100x) magnification **(g)** Another case with col1 (C) equal to col 3 H (100x) magnification. **(h)** IHC for CD31 highlights several vessels and capillaries. (200x magnification)*

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..