Cholemic nephrosis is a distinct form of renal dysfunction in patients with acute on chronic liver failure with a potential of reversibility

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INTRODUCTION

The diagnosis of cholemic nephrosis requires renal histology which cannot be performed in patients with ACLF.
Cholemic nephrosis (CN) is an underestimated cause of renal dysfunction in patients with acute-on-chronic liver failure (ACLF).

AIM

To study a panel of biomarkers, for identification and characterization of CN and its differentiation from Hepatorenal Syndrome (HRS) and acute tubular necrosis (ATN).
Pathogenic mechanism of cholemic nephrosis.
The role of therapeutic plasma-exchange in management.

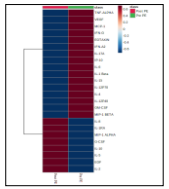
MATERIALS & METHODS

ACLF patients with volume non-responsive AKI; HRS (n=15), CN (n=15) and ATN (n=15) and no AKI (as controls) (n=15) were included.
A panel of 30 different cytokines in plasma and 17 biomarkers in urine multiplex Cytokine bead array. Immunohistochemistry (IHC) for markers of cytoprotection (sirtuin-1; SIRT-1) and ischemia (hypoxia-inducible factor-1; HIF-1) were performed in post-mortem kidney biopsies.
Linear discriminant analysis (LDA) approach was used to predict the spectrum based on the biomarkers.
Genes of mitochondrial biogenesis; peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC); cyclo-oxygenase-1 (COX-1); nuclear receptor factor (NRF); succinate dehydrogenase (SDH); transcription factor A, mitochondrial (TFAM). When we analyzed the expression of various genes related to mitochondrial biogenesis (PGC1, Cox 1, NRF, SDH, TFAM) in exfoliated urine epithelial cells.

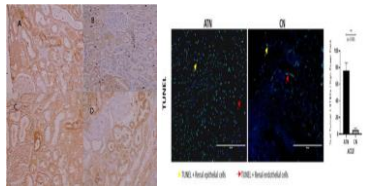
RESULTS

Baseline characteristics of study cohort

Variable	ATN (n= 15)	CN (n=15)	HRS (n= 15)	No AKI (n=15)	P Value
Age (yrs)	43.7 ± 9.3	50.1 ± 11.6	47.8 ± 11.8	40.1 ± 9.8	0.18
Gender, males (%)	93.3%	80.0%;	100%;	93.3%	
Alcohol; n (%)	10(66.6)	5(33.2)	8 (53.3)	12 (80%)	
MELD	37.7 ± 5.5	40.1 ± 3.9	39.7 ± 4.0	37.4 ± 6.2	0.35
SOFA	14.7 ± 3.3	11.6 ± 2.5	10.2 ± 3.6	9.0 ± 2.3	<0.001
AARC	11.3 ± 1.4	11.00 ± 1.1	10.2± 1.7	8 ± 1	<0.001
HR (beats/min)	93.7 ± 12.5	94.1 ± 13.2	92.1 ± 12.8	96.0 ± 17.6	0.81
RR (/min)	21.5± 4.6	19.9 ± 2.2	20.1± 1.67	21.1 ± 3.3	0.32
MAP (mm of Hg)	84.7 ± 11.0	81.9 ± 10.5	84.3 ± 11.1	84.1± 13.1	0.73
Hb (gm/dl)	9.00 ± 1.84	9.42 ± 1.57	9.06 ± 1.78	9.90 ± 1.99	0.356
TLC (x10^3 cumm)	18.9 ± 8.5	12.7 ± 7.1	12.9 ± 8.0	12.6 ± 7.6	0.07
Neutrophil to lymphocyte ratio	16.7 ± 20.4	9.9 ± 7.4	9.30 ± 5.7	8.9± 7.1	0.22
Platelet (~x10^9/L)	94.9 ± 70.1	116.3 ± 101.1	104.4 ±66.1	90.7 ± 52.9	0.75
INR	2.83 ± 0.77	2.47 ± 0.73	2.48 ± 0.82	2.60 ± 1.23	0.47
Bilirubin (mg/dl)	22.3 ± 9.5	27.1 ± 7.3	17.2 ± 8.3	15.9 ± 6.6	0.23
SGOT (IU/L)	129.3 ± 39.6	179.5± 212.6	201.9 ± 259.1	130.5 ± 110.2	0.38
SGPT (IU/L)	45.7 ± 29.6	90.9 ± 119.8	101.0± 144.2	63.1 ± 39.8	0.28
Arterial ammonia (ug/dl)	180.1 ± 61.2	188.4 ± 102.3	184.6 ± 96.1	194.1 ± 129.9	0.68
Procalcitonin (ng/ml)	2.13 ± 2.0	1.28 ± 0.9	1.51 ± 0.97	0.95 ± 0.70	0.20
Blood Urea (mg/dl)	113.7 ± 50.7	78.6 ± 40.9	95.60± 38.2	35.3 ± 1.2	0.08
Creatinine (mg/dl)	2.45 ± 1.39	2.03 ± 0.78	2.14 ± 0.92	0.70 ± 0.14	0.26
Sodium (meq/L)	131.8 ± 7.3	129.6 ± 9.0	127.8 ± 8.8	131.3 ± 7.5	0.66
Ptassium (meq/L)	4.22 ± 0.87	4.32 ± 0.66	4.56 ± 0.62	3.93 ± 0.53	0.85
Cloride (mmol/L)	101.6 ± 7.9	100.7 ± 8.9	100.1 ± 8.1	89.1 ± 30.9	0.86
Uric Acid (mg/dl)	6.0 ± 2.1	5.3 ± 2.2	6.4 ± 1.7	3.9± 1.7	0.62
Bicarbonate (mmol/L)	18.5 ± 2.7	18.3± 5.2	17.090 ± 4.9303	23.22 ± 4.01	0.35
Phosphate (mg/dl)	3.2 ± 1.3	2.9 ± 1.1	3.1 ± 1.3	2.7 ± 0.9	0.73
Ph	7.41 ± 0.07	7.45 ± 0.08	7.46 ± 0.08	7.48 ± 0.05	0.54
PaO2 (mmhg)	115.3 ± 36.2	103.1 ± 25.7	109.6 ± 28.8	97.8 ± 30.5	0.49
PaCO2 (mmhg)	33.2 ± 6.3	29.6± 6.0	27.3 ± 5.3	37.6 ± 11.2	0.03
Arterial lactate (mmol/L)	1.99 ± 1.43	1.72 ± 0.99	1.53 ± 0.69	1.43 ± 0.84	0.24

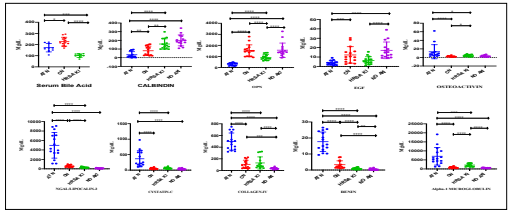


Heat map showing change in cytokines with plasma exchange in Cholemic nephrosis.

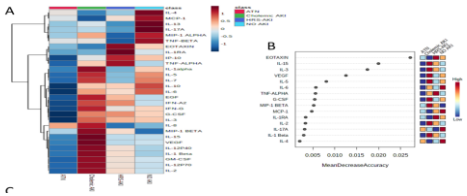


Renal histopathology and immunohistochemistry A: Higher staining of SIRT-1 in and lower staining of hypoxia-inducible factor-1(HIF-1) in cholemic nephrosis C. Lower intensity of SIRT-1 staining and a higher intensity staining of HIF-1 in ATN

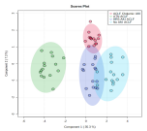
Urine cytokine profile

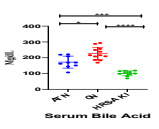


Dot plot representation of renal biomarkers in urine of ACLF patients. (a) Tubular injury markers such as **NGAL, Cystatin-C, Collagen-IV, Renin, Alpha-1 microglobulin** were significantly higher in ATN (acute tubular necrosis) as compared to other causes of AKI. However, Analysis of renal biomarkers in urine showed significant increase in repair markers (**Calbindin, OPN, EGF**) in CN (cholemic nephrosis) and HRS (hepatorenal syndrome) compared to ATN. Also, the quantified **serum bile acid** was high in CN as compared to ATN and HRS. And, (b) the inflammatory cytokines were significantly elevated in CN in comparison with other causes of AKI. Furthermore, (c) it showed changes in serum cytokines of ACLF patients with CN after plasma exchange.

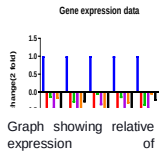


A. Heat map showing differential cytokines between ATN and CN AKI, HRS and no AKI **B. Mean Decrease accuracy plot** showing cytokines expression by random forest





Serum bile acids significantly higher in cholemic versus other AKI



Graph showing relative expression of mitochondrial biogenesis associated genes in ATN vs CN.

CONCLUSION

Cholemic nephrosis is a distinct form of renal dysfunction in patients with ACLF.
Systemic inflammation, toxicity of bile acids are key pathogenic mechanisms driving CN.
Activation of renal repair and lesser tubular injury is a hallmark of renal involvement in CN.
Renin and NGAL can accurately discriminate CN from ATN and HRS.
Plasma exchange should be explored as a therapeutic modality for CN. Management algorithms should be revised incorporating diagnosis and management of CN in patients with ACLF.
A cut-off (in mg/dl) renin >9.44 and NGAL >1131 classified ATN with 100% accuracy. Renin >1.34 mg/dl discriminated CN from HRS-AKI with 93% accuracy.

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DISCLOSURE

None

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