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Urinary Clusterin and Monocyte Chemoattractant Protein-1 (MCP-1) Predict Long-term Major Adverse Kidney Events with Nephrotoxicity

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Introduction

- Reliable methods are needed to detect risk early and predict major adverse kidney events (MAKE) in drug induced kidney injury.
- Elevated urine biomarkers of kidney tubular injury could detect subclinical acute kidney injury (AKI) and predict long-term MAKE.

Methods

- Single centre prospective cohort study from February 2015 to February 2022 was conducted.
- Patients admitted to the general ward who were treated for at least 5 days with Aminoglycosides, Vancomycin, Amphotericin B, Polymyxins, Forscanet or Ganciclovir were recruited. Their clinical progress was followed up for 1 year.
- MAKE was defined as death, initiation of renal replacement therapy or doubling of serum creatinine.
- Urinary Clusterin and MCP-1 was measured using ELISA within three days of patients developing AKI (or final day of nephrotoxic exposure).

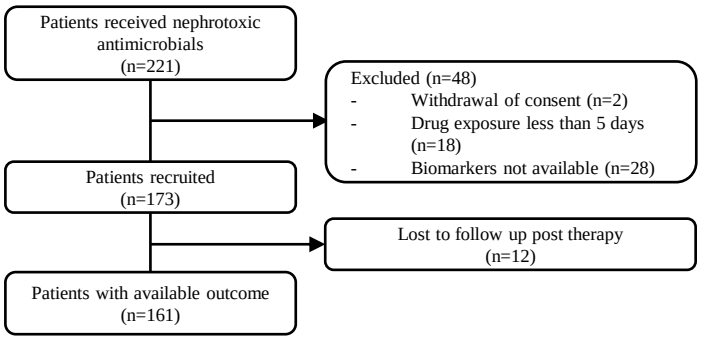

Figure 1. Flow chart of the study cohort.

Results

- In this cohort of 161 patients with baseline median estimated glomerular filtration rate (eGFR) was 102 ml/min/1.73m², 26% of patients had AKI whilst 43% experienced MAKE.

Table 1. Baseline cohort characteristics.

Patient Profile	Entire Cohort (n = 161)
Age, mean (±SD), years	56 (±16)
Male gender, No. (%)	110 (68)
Comorbidities, No. (%)	
Diabetes mellitus	58 (36)
Hypertension	77 (48)
IHD	31 (19)
Malignancy	62 (39)
Baseline kidney function	
eGFR, mean (±SD), mL/min/1.73m2	101 (±27)
eGFR < 90 mL/min/1.73m², No. (%)	47 (29)
eGFR < 60 mL/min/1.73m², No. (%)	11 (7)
Nephrotoxic drug exposure	
Aminoglycosides, No. (%)	35 (22)
Vancomycin, No. (%)	101 (63)
Others	25 (16)
Duration of exposure, days, median (IQR)	14 (9)
Initial outcome	
AKI, No. (%)	42 (26)
Peak AKI stage 1, No. (% of AKI)	20 (48)
Peak AKI stage 2/3, No. (% of AKI)	22 (48)
KRT, No. (%)	2 (1)
Hospital mortality, No (%)	9 (6)

SD, standard deviation; IHD, ischemic heart disease; eGFR, estimated glomerular filtration rate; IQR, interquartile range; AKI, acute kidney injury; KRT, kidney replacement therapy.

- Biomarker levels were significantly higher (<0.001) in MAKE cases versus none. Median Clusterin and MCP-1 was 239ng/mL and 0.63ng/mL respectively in patients who developed MAKE, versus 64ng/mL and 0.19ng/mL in patients who did not.

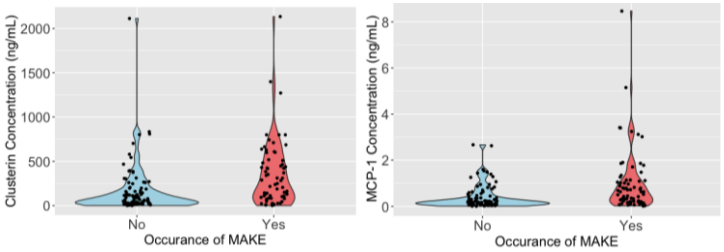

Figure 2. Distribution of Clusterin and MCP-1 concentration and relationship with MAKE (MCP-1, Monocyte chemoattractant protein-1; MAKE, Major adverse kidney event)

- The area under the receiver operating characteristic curve (AUROC) for predicting MAKE for Clusterin, MCP-1, and combined were 0.68, 0.69 and 0.71, respectively. When combining both biomarkers and initial AKI, AUROC was 0.76.
- Increased accuracy in stepwise fashion in MAKE prediction was observed when development of index AKI was combined with biomarkers

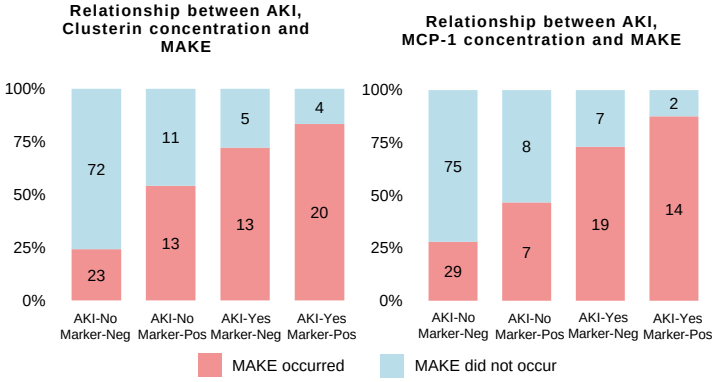

Figure 3. Stepwise increase in the accuracy of MAKE prediction is observed when AKI status is combined with biomarker positivity (with Clusterin set at 250ng/mL and MCP-1 set at 1ng/mL). (MAKE, major adverse kidney events; AKI, acute kidney injury; Neg, negative; Pos, positive)

- An ideal urine biomarker concentration, derived using the Youden index from 50 randomly selected patients in this cohort, was tested on the 111 remaining patients and an independent cohort of 28 patients who received platinum-based chemotherapy.

Table 2. Performance Metrics of Urinary Biomarkers for MAKE Prediction in the Validation Cohort (n=111) and Independent Cohort (n=28)

	Precision	Sensitivity	Specificity	Accuracy
Internal Validation Cohort (n=111)				
Clusterin >280ng/mL and MCP-1 >0.4ng/mL	0.65	0.32	0.88	0.64
Clusterin >280ng/mL or AKI	0.70	0.68	0.78	0.74
MCP-1 >0.4ng/mL or AKI	0.67	0.77	0.72	0.74
Independent Cohort (n=28)				
Clusterin >280ng/mL and MCP-1 >0.4ng/mL	0.64	0.70	0.76	0.74
Clusterin >280ng/mL or AKI	0.47	0.70	0.53	0.59
MCP-1 >0.4ng/mL or AKI	0.57	0.80	0.65	0.70

MCP-1, monocyte chemoattractant protein-1; AKI, acute kidney injury.

Conclusion

- Our study demonstrates that urinary Clusterin and MCP-1 predict MAKE in patients following nephrotoxicity with enhanced accuracy beyond the presence of initial AKI.

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