The predictive ability of urinary biomarkers for progression of early stage 1/2 Acute Kidney Injury in critical illness.

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Background

- Acute Kidney Injury (AKI) is a common hospital complication associated with high morbidity, mortality and the risk of progression to CKD[1].
- Currently clinicians are unable to accurately predict which patients will progress to Stage 3 AKI.
- AKI progression biomarkers are needed to inform clinical management and the design of future clinical trials. NGAL and the Albumin to Creatinine ratio (ACR) have previously been reported to increase with AKI.
- NGAL has previously been identified as a promising candidate biomarker for the progression of mild-moderate AKI[2].
- The Dublin Acute Biomarker Group Evaluation (DAMAGE) Study is a prospective multi-center observational study with a heterogenous cohort of critically ill patients.
- We hypothesised that urinary NGAL and ACR would predict clinical progression from stage I/II to stage III or death.

Methods

- A subset of patients from the DAMAGE biorepository were included in the study.
- Those with KDIGO Stage I/II AKI within 48 hours of admission chosen.
- Urinary NGAL, Albumin and Creatinine from the day of diagnosis were measured on the Abbott Architect ci4100 platform. NGAL and Albumin were corrected for urinary Creatinine to account for dilutional effects.

Statistical Methods

In the univariate analysis, numerical variables were compared using the Student t-test or Mann Whitney U-Test, as appropriate. Categorical variables were compared using the Chi-Square test.

Biomarkers with right-skew were log-transformed and entered into a binary logistic regression model. ROC curves, sensitivity and specificity of tests were calculated. AUCs were compared using De Longe's method. SPSS Version 24 and R Vers 3.5 were used.

Results

- 87 patients with Stage 1/2 AKI were included in the study. 17 patients (19.5%) progressed to the primary endpoint of Stage III or death within 7 days.
- Baseline demographics were similar apart from a higher APACHE score in the progression group (Table 1).
- A univariate analysis of the Day of Diagnosis Biomarker is reported in Table 2. There was no statistically significant difference in the urine output or serum creatinine.

However, uAlbumin, ACR, uNGAL and uNGAL/uCreat were significanty higher in the progressor group.

- The combination of uNGAL/uCreat and ACR was strongly predictive for Stage III AKI/ Death with an AUC of 0.8.
- The AUC for the prediction of progression to Stage 3/ Death was 0.83 for the clinical model with the addition of the biomarkers and 0.66 for the clinical model alone (P-Value = 0.04).

Table 1. Baseline Demographics

Characteristic	Progressor, n (%) 17 (19.5%)	Non-Progressor, n (%) 70 (80.5%)	P-Value
Age (mean)	63.7	65.0	0.75[a]
Gender - Female	5 (29.4%)	25 (35.7%)	0.62[b]
APACHE II - median (Q1-3)	30 (23 - 36.5)	21 (14 - 25.25)	0.001[c]
Diabetes Mellitus	3 (17.6%)	12 (17.1%)	0.96[b]
Hypertension	7 (41.2%)	32 (45.7%)	0.74[b]
CKD (excl. ESKD)	1 (5.9%)	6 (8.6%)	0.72[b]
Serum Creatinine (µmmol/L) - median (Q1-3)	109 (99 - 143.5)	100.5 (80.75 - 120.25)	0.84[c]

a. Student's T-Test b. Chi-Square test c. Mann Whitney U-test

Table 2. Day of Diagnosis Biomarker Univariate Analysis

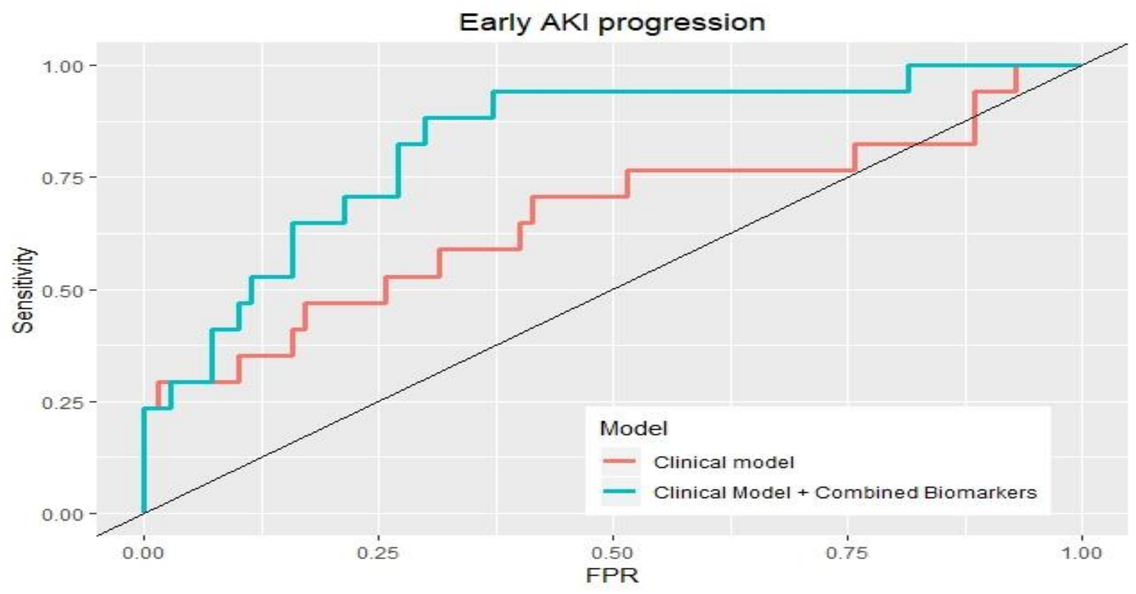
Urinary AKI Biomarkers	Progressor, n (%) 17 (19.5%)	Non-Progressor, n (%) 70 (80.5%)	P-Value[a]
Urine Output (ml/hr) median (Q1-3)	46.46 (18.35-65.42)	60.52 (35.66-96.67)	0.1
Serum Creatinine (µmmol/L) - median (Q1-3)	161 (140-200.5)	143 (121-172.75)	0.06
Urinary Creatinine (mg/dL) - median (Q1-3)	80.33 (39.48-121.6)	75.39 (37.94-131.22)	0.773
Albumin (mg/L) - median (Q1-3)	63 (33.5-253)	28 (10-42.5)	<0.001
NGAL (ng/mL) - median (Q1-3)	587.6 (175.1-1816.8)	107.45 (32.3-372.63)	0.001
ACR (mg/g) - median (Q1-3)	1279.36 (425.5 - 3291.4)	332.12 (197.28-652.85)	0.001
Corected NGAL - median (Q1-3)	9.3 (2.3-30.12)	1.32 (0.45-6.64)	0.002

a. Mann-Whitney U-test

Table 3. AUCs for Prediction of Progression to Stage 3/ Death

Clinical Variables	AUC (95% CI)	Sensitivity	Specificity	P-Value[a]
Serum Creatinine	0.65 (0.51-0.79)	0.59	0.67	0.06
Urine Output (ml/hr)	0.63 (0.47-0.79)	0.71	0.61	0.095
Combined Clinical Model	0.66 (0.49–0.82)	0.71	0.59	0.04
a. Null hypothesis: true area = 0.5				
Biomarker corrected for uCreatinine	**AUC (95% CI)**	**Sensitivity**	**Specificity**	**P-Value[a]**
NGAL	0.75 (0.63-0.87)	0.71	0.74	0.001
Albumin (ACR)	0.76 (0.62-0.89)	0.71	0.71	0.001
Combined	0.8 (0.68 – 0.93)	0.82	0.77	<0.001
Predictive Models	**AUC (95% CI)**	**Sensitivity**	**Specificity**	**P-Value[b]**
Clinical Model	0.66 (0.49-0.83)	0.71	0.59	NA
NGAL	0.76 (0.63-0.89)	0.65	0.81	0.09
ACR	0.81 (0.69-0.92)	0.76	0.79	0.05
Combined Biomarkers	0.83 (0.72-0.94)	0.88	0.7	0.04
b. Comparison with Clinical Model alone using De Longe's Method for comparing AUCs.				

Figure 1. ROC Curves for prediction of Stage III/ Death



Conclusion

In this study of AKI progression, the addition of NGAL and ACR improved the prediction of the primary endpoint, KDIGO Stage 3 or death, over a clinical model of the kidney function biomarkers that are currently used to define, stage and assess AKI.

References

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2. Koyner JL, Davison DL, Brasha-Mitchell E, Chalikonda DM, Arthur JM, Shaw AD, et al. Furosemide Stress Test and Biomarkers for the Prediction of AKI Severity. Journal of the American Society of Nephrology. 2015;26(8):2023-31.

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