Urine Olfactomedin-4 is Associated with Furosemide Responsiveness and Receipt of Kidney Replacement Therapy

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Introduction

Anticipating who will need kidney replacement therapy (KRT) is essential to facilitate early and appropriate KRT initiation.

A recent multinational retrospective cohort study showed later KRT initiation is associated with increased mortality and persistent kidney dysfunction.

Furosemide stress test (FST) response can predict KRT receipt, but providers may avoid giving diuretics to hemodynamically unstable patients.

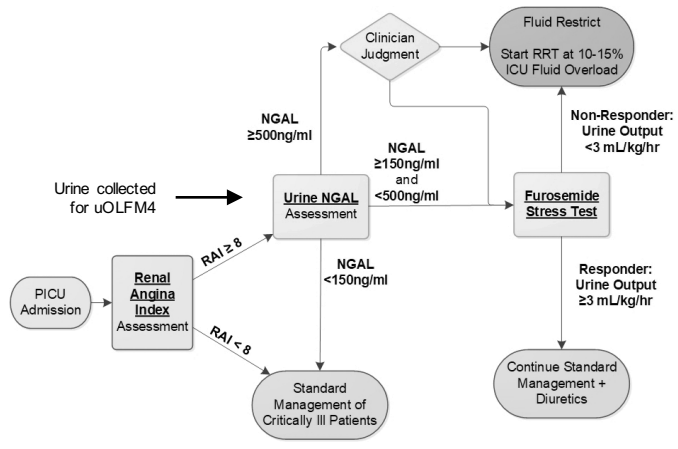
Furosemide acts in the Loop of Henle (LOH), so a LOH-specific acute kidney injury (AKI) biomarker may predict furosemide response without needing to wait for FST. Olfactomedin-4 (OLFM4) is a glycoprotein produced by injured LOH epithelial cells.

We hypothesize that urine OLFM4 (uOLFM4) collected within the first two days of admission may predict furosemide responsiveness and KRT receipt in patients at risk for severe AKI.

Methods

From May 2022 to November 2023, all patients in a single center pediatric intensive care unit (PICU) were screened with the renal angina index (RAI) within 24 hours of admission through TAKING FOCUS 2 (Trial in AKI using NGAL and Fluid Overload to Optimize CRRT Use).

RAI >8 (RAI+) identifies patients at risk of KDIGO Stage 2/3 AKI and triggers NGAL collection.



We collected urine from lab residuals or bladder catheter waste daily for up to 7 days. We primarily analyzed levels from the first two days of admission and samples two days before, one day before, and day of FST.

We measured uOLFM4 levels via enzyme-linked immunosorbent assay.

We staged AKI using KDIGO creatinine criteria.

To capture clinical FSTs, we measured response in any patient who received a furosemide dose > 0.75 mg/kg. Urine output > 3 mL/kg/hr within 4 hours was considered responsive.

We performed Mann-Whitney tests and one-way ANOVAs to compare groups. We used Youden's index to determine optimal cut offs for uOLFM4 to predict furosemide responsiveness and KRT receipt.

Optimal uOLFM4 to predict FST response 1 day after sampling and to predict KRT receipt

	Sensitivity	Specificity	Youden's Index
uOLFM4 level 603 mg/mL for FST	52%	78%	0.32
uOLFM4 level 603 mg/mL for KRT	54%	78%	0.3

Figure 1

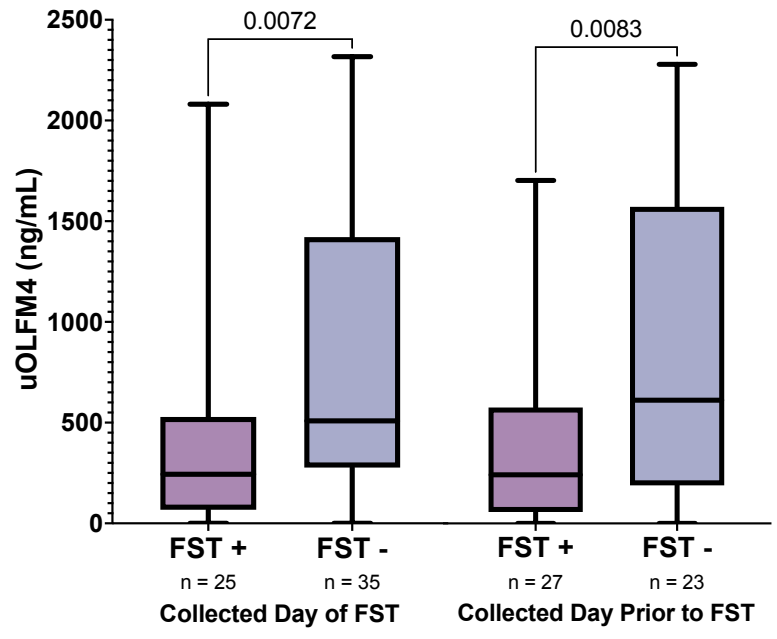
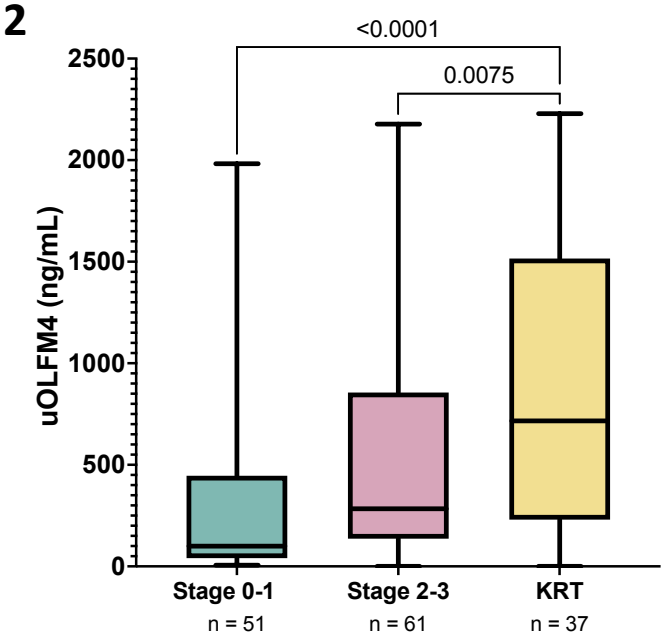


Figure 2



Results

127 RAI+ patients provided 294 samples. 54 samples were from day 0, 97 from day 1, 95 from day 2, 24 from day 3, and 24 from days 4-7.

52 patients underwent 147 FSTs; 33% of FSTs were performed in the first 2 days after admission (median 2; IQR 1-4).

29 patients received KRT; 76% started within the first 3 days (median 2; IQR 1-2).

uOLFM4 was increased in patients who failed FST on day of sampling ($p<0.01$, AUC 0.70, 95% CI 0.57, 0.84; Fig. 1) and 24h after sampling ($p<0.01$, AUC 0.72, 95% CI 0.57, 0.85: Fig. 1).

uOLFM4 collected in the first two days increased with AKI severity and KRT receipt ($p <0.01$; Fig. 2) and had fair predictive performance for KRT receipt (AUC 0.71; 95% CI 0.61 – 0.81).

Conclusions

uOLFM4 is increased in RAI+ patients who fail FST on day of sampling and one day after sampling with slightly lower p-value on day of FST. It increases incrementally in those with AKI and those who receive KRT.

As more data emerge supporting the benefits of earlier KRT initiation in certain patients, providers will need timely and efficient tools to predict who will receive KRT. We suggest uOLFM4 may provide an early assessment of ultimate diuretic responsiveness and could potentially be included as a biomarker in clinical decision algorithms.

Enrollment is ongoing at multiple centers to extend generalizability beyond our single center and to capture more FST with the goal of establishing which day of admission is most accurate to capture future FST response and receipt of KRT.

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