Urinary Angiopoietin-2 Levels are Associated with Risk of Adverse Kidney Outcomes in the Intensive Care Unit

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Introduction

- Acute kidney injury (AKI) is a heterogeneous syndrome associated with increased mortality, and hospital stay, affecting 30-60% of critically ill patients
- Limitations to serum creatinine (SCr) and urine output as a kidney function indicator
- Treatment is mainly supportive and not targeted to treat AKI
- Angiopoietin-2 (Ang-2) promotes endothelial dysfunction by increasing vascular permeability and destabilization
  - Elevated plasma Ang-2 are associated with adverse kidney outcomes
- **Here we sought to understand the association between urinary Ang-2 (uAng-2) and kidney outcomes**

Methods and Materials

Clinical Cohort
We analyzed 192 COIVD-19 ICU participants. AKI was defined as an increase in SCr during hospitalization ≥ 0.3 mg/dl or 50% from the SCr on study enrollment, consistent with KDIGO guidelines.

Immunoassay measurement
Urinary and plasma samples were collected to measure Ang-2 by immunoassay using the MesoScale Discovery platform.

Statistical Analysis
Participants were stratified into tertiles (n=64) based on uAng-2 concentrations normalized to urine creatinine. Participants with uAng-2 concentrations below the lower limit of detection (LLOD) of the assay were imputed using (0.5)*LLOD. Then a log-linear regression was used to determine the risk of AKI, mortality and renal replacement therapy (RRT).

Table 1: Patient Characteristics	N=64	N=64	N=64
	Tertile 1	Tertile 2	Tertile 3
Age, years, mean (SD)	55±18	56±15	55±15
Sex, male (%)	41 (64)	44 (68)	40 (62)
BMI kg/m2, mean (SD)	30±8	33±12	30±8
Serum Creatinine (mg/dL)	1.19	1.07	1.87
SOFA Score, mean (SD)	6.7±4.2	6.0±4.3	7.9±5.1
uAng-2 Range (pg/mg)	1 - 16	16 - 123	130 – 189,129
Diabetes mellitus, n (%)	14 (21)	18 (28)	27 (42)
Hypertension, n (%)	34 (53)	37 (57)	31 (48)
Invasive Mechanical Ventilation, n(%)	41 (64)	38 (59)	51 (79)

Table 2: Outcomes	N=64	N=64	N=64
	Tertile 1	Tertile 2	Tertile 3
Hospital Mortality, n (%)	17 (26)	20 (31)	30 (46)
Hospital RRT, n (%)	6 (9)	3 (5)	14 (22)
Acute Kidney Injury, n (%)	22 (34)	21 (32)	42 (65)
Stage 1	10	10	12
Stage 2	2	6	6
Stage 3	10	5	24

Results

Demographics (65% men, 55 years old)
- 44% developed AKI during hospitalization
- 35% in-hospital mortality
- 12% received renal replacement therapy

Tertile 2
- No significant difference from tertile 1 in risk AKI, death or RRT

Tertile 3
- Participants had an increased risk of AKI development or mortality during hospitalization compared to tertile 1
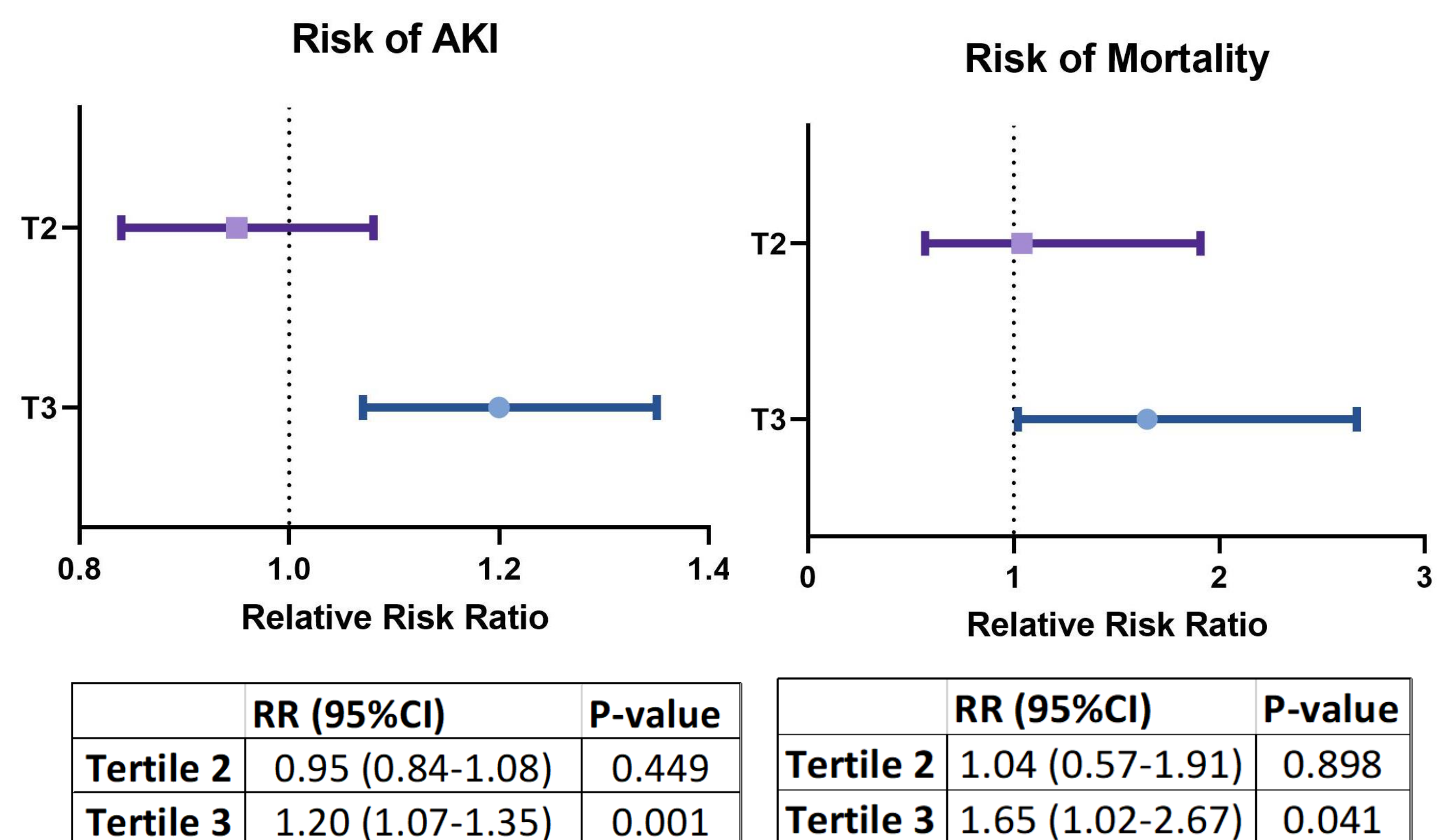- Higher rate of RRT, although not statistically significant

	RR (95%CI)	P-value
Tertile 2	0.95 (0.84-1.08)	0.449
Tertile 3	1.20 (1.07-1.35)	0.001

	RR (95%CI)	P-value
Tertile 2	1.04 (0.57-1.91)	0.898
Tertile 3	1.65 (1.02-2.67)	0.041

Figure 1: Risk exposure for hospital AKI and mortality in creatinine-normalized urine Ang-2

Discussion

- **Individuals with an increase in Ang-2 exhibit a higher risk of AKI and mortality compared to those with a low Ang-2 concentration**.

- Despite the non-significance in RRT, more than half of participants (61%) who underwent RRT had an elevated Ang-2 concentration.

- Interestingly, plasma and urinary Ang-2 were minimally correlated (Pearson's correlation r=0.28) suggesting possible local peritubular capillary leak.

Conclusions

Here we examined the association between Ang-2, an endothelial dysfunction biomarker, and kidney outcomes. **Elevated uAng-2 are associated with the development of AKI and mortality in the ICU.** Although the source of Ang-2 in the urine is not well understood, our findings suggest that urinary Ang-2 is a novel biomarker of kidney outcomes and may provide insight of kidney function.

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