IL-17A as a Biomarker in Critical Illness

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Disclosures

- Consulting for Vantive and CovarsaDx

Outline

- Role of IL-17A as a biomarker in Critical Care Nephrology
- IL-17A levels in simulated KOURAGE trial participants

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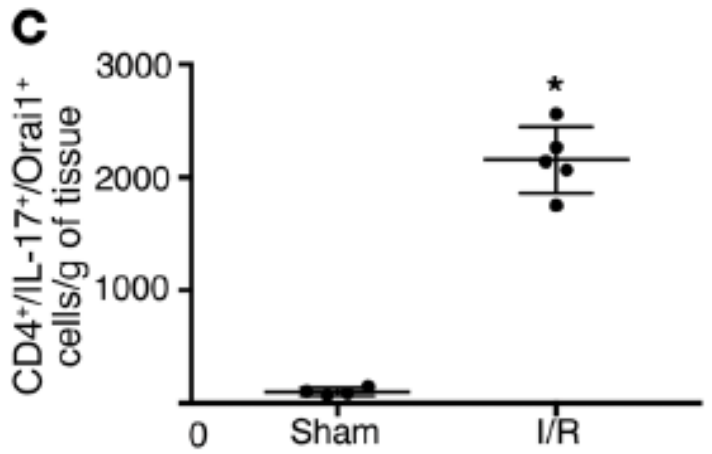
The Journal of Clinical Investigation RESEARCH ARTICLE

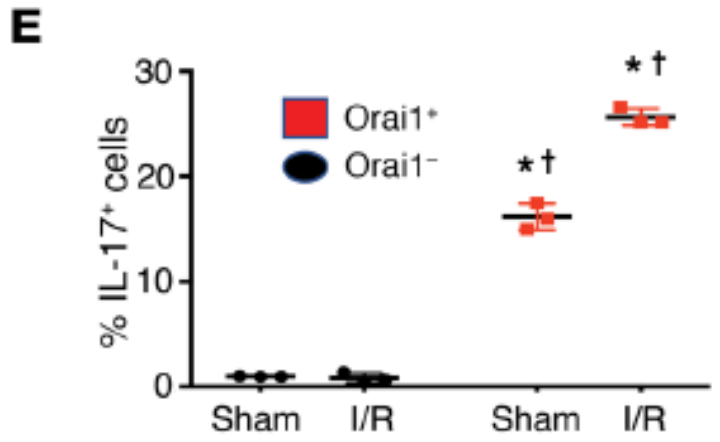
Calcium channel Orai1 promotes lymphocyte IL-17 expression and progressive kidney injury

Purvi Mehrotra,[1] Michael Sturek,[1] Javier A. Neyra,[2] and David P. Basile[1,3]

[1]Department of Anatomy, Cell Biology & Physiology, Indiana University, Indianapolis, Indiana, USA. [2]Department of Medicine, Division of Nephrology, Bor Lexington, Kentucky, USA. [3]Department of Medicine Division of Nephrology, Indiana University, Indianapolis, Indiana, USA.

- In rats, following renal ischemia/reperfusion (I/R), there was a rapid and sustained influx of Orai1+ CD4 T cells and IL-17 expression was restricted to Orai1+ cells





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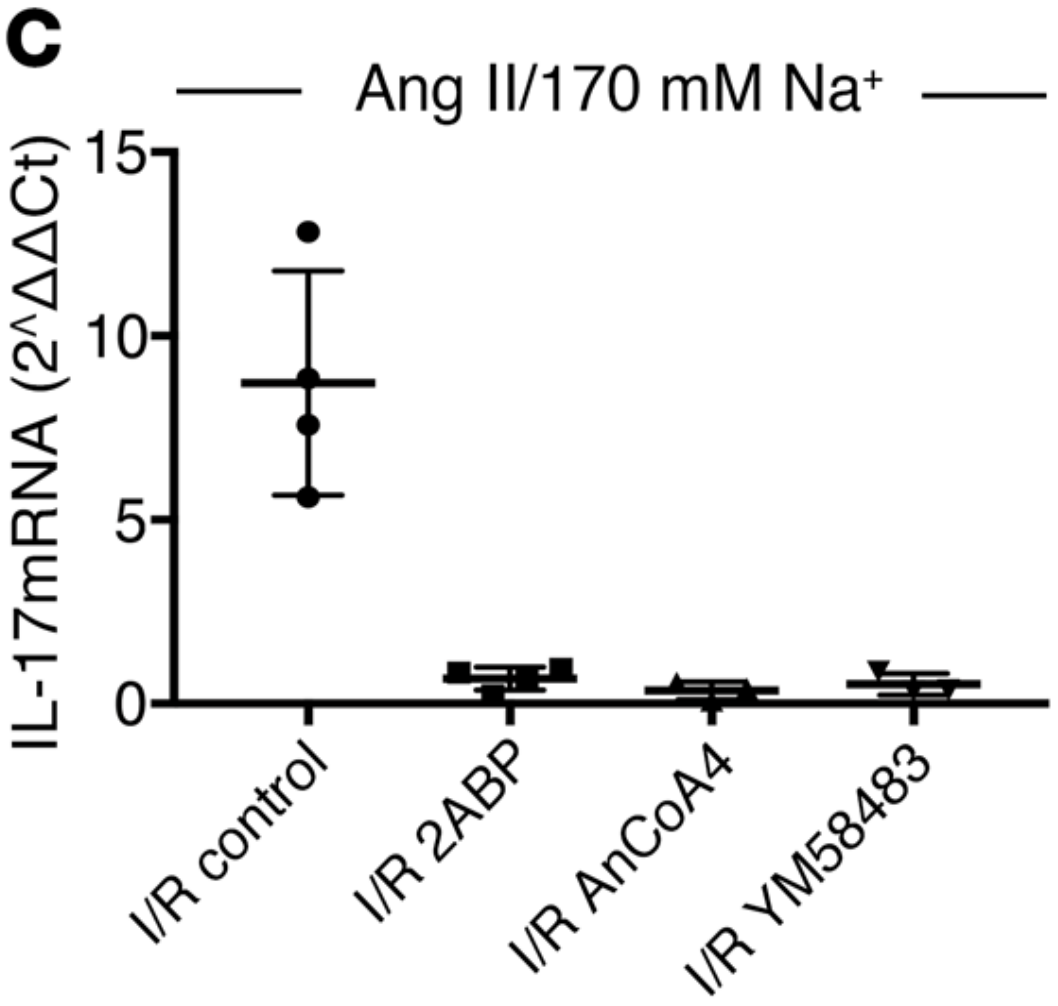
- When kidney CD4+ cells of post-AKI rats were stimulated with angiotensin II and elevated Na+ (10–7 M/170 mM) *in vitro*, there was an enhanced response in intracellular Ca2+ and IL-17 expression, which was blocked by store-operated calcium entry (SOCE) inhibitors



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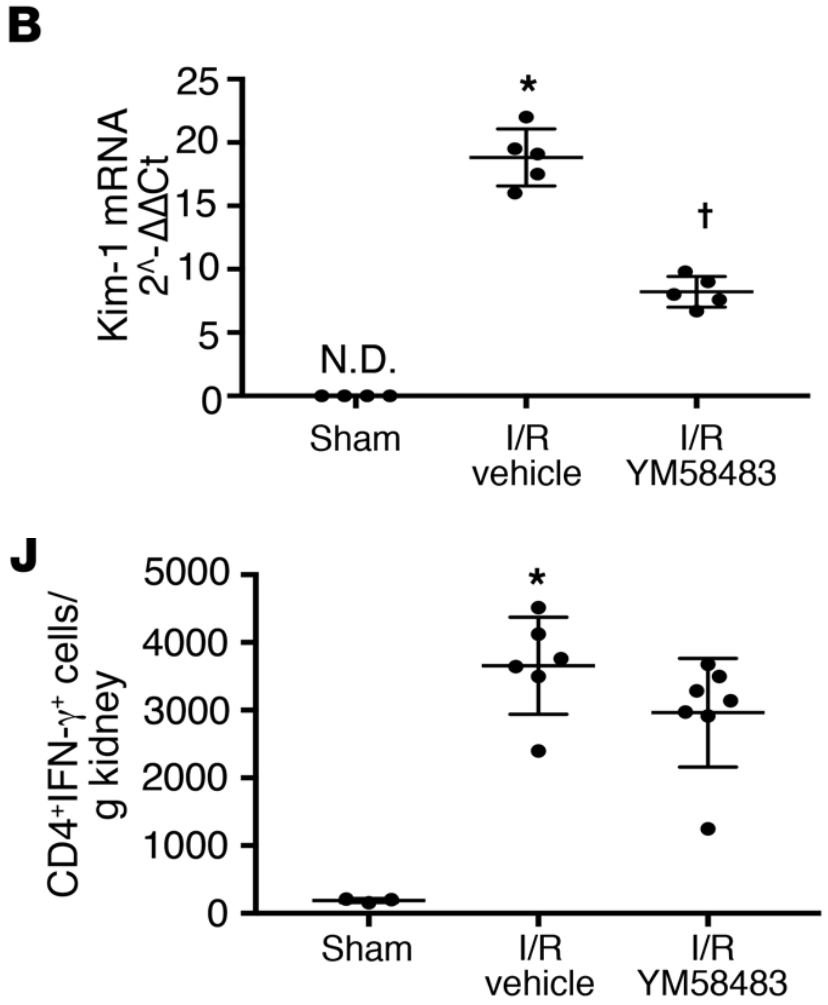
- *In vivo*, YM58483/BTP2 (1 mg/kg) attenuated IL-17+ cell activation, inflammation, and severity of AKI following either I/R or intramuscular glycerol injection
- Rats treated with high-salt diet (5–9 weeks after I/R) manifested progressive disease indicated by enhanced inflammation, fibrosis, and impaired renal function; attenuated by YM58483/BTP2



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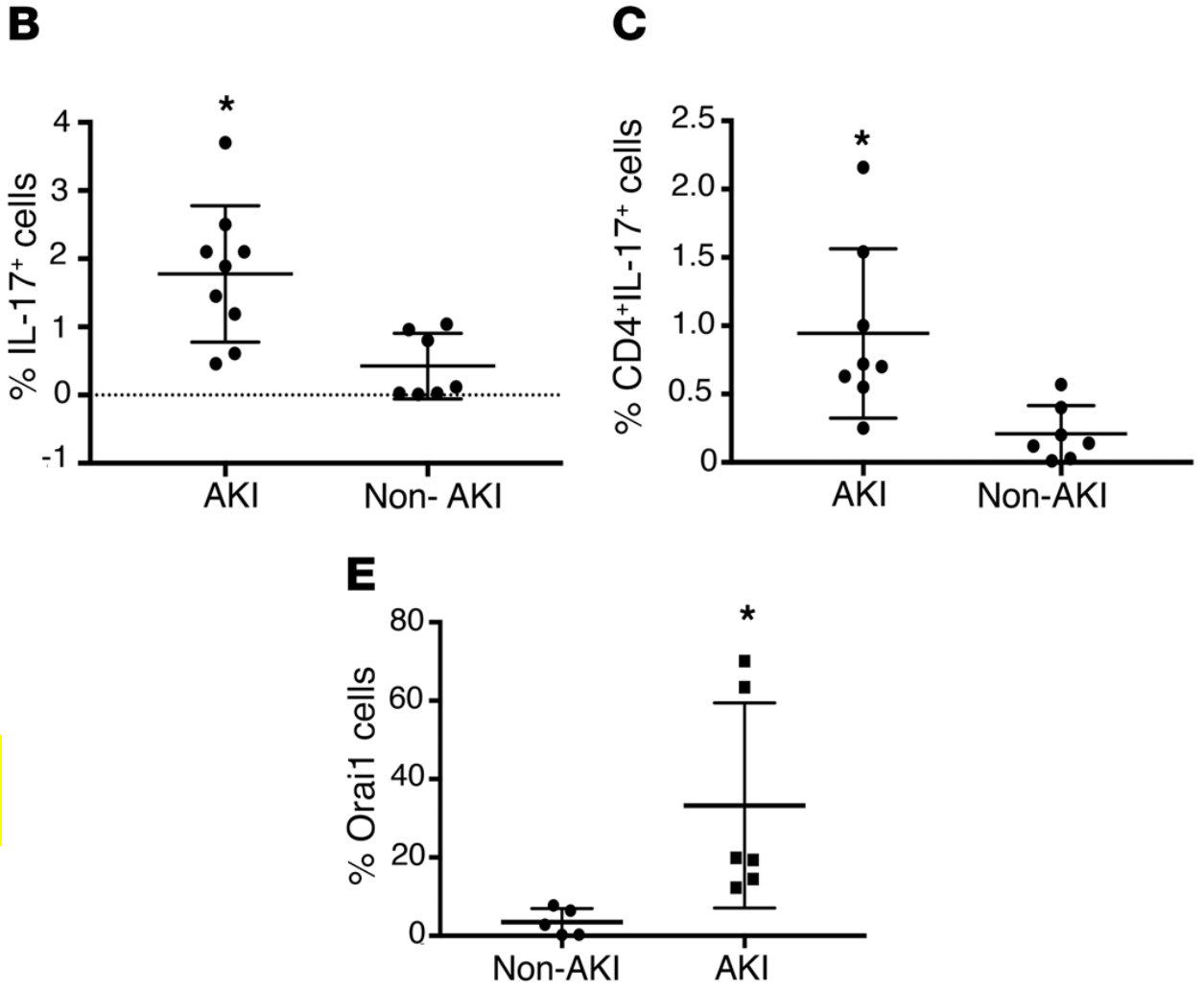
- In peripheral blood of critically ill patients, Orai1+ cells were significantly elevated by approximately 10-fold and Th17 cells were elevated by approximately 4-fold in AKI vs. non-AKI patients
- *In vitro* stimulation of CD4+ cells from AKI patients increased IL-17, which was blocked by SOCE inhibitors
- These data suggest that Orai1 SOCE is a potential therapeutic target in AKI and CKD progression



Collett *et al. Critical Care* (2022) 26:107
https://doi.org/10.1186/s13054-022-03976-4

Critical Care

RESEARCH Open Access

Serum IL-17 levels are higher in critically ill patients with AKI and associated with worse outcomes

Jason A. Collett[1], Victor Ortiz-Soriano[2], Xilong Li[3], Alexander H. Flannery[4], Robert D. Toto[3,5], Orson W. Moe[3,5], David P. Basile[1] and Javier A. Neyra[2,3*]

- Multicenter, prospective study of ICU patients with AKI stage 2 or 3 and without AKI
- Samples were collected at 24-48 h after AKI diagnosis or ICU admission (in those without AKI) [T1] and 5–7 days later [T2]
- MAKE was defined as the composite of death, dependence on kidney replacement therapy or a reduction in eGFR of ≥ 30% from baseline up to 90 days following hospital discharge

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RESEARCH

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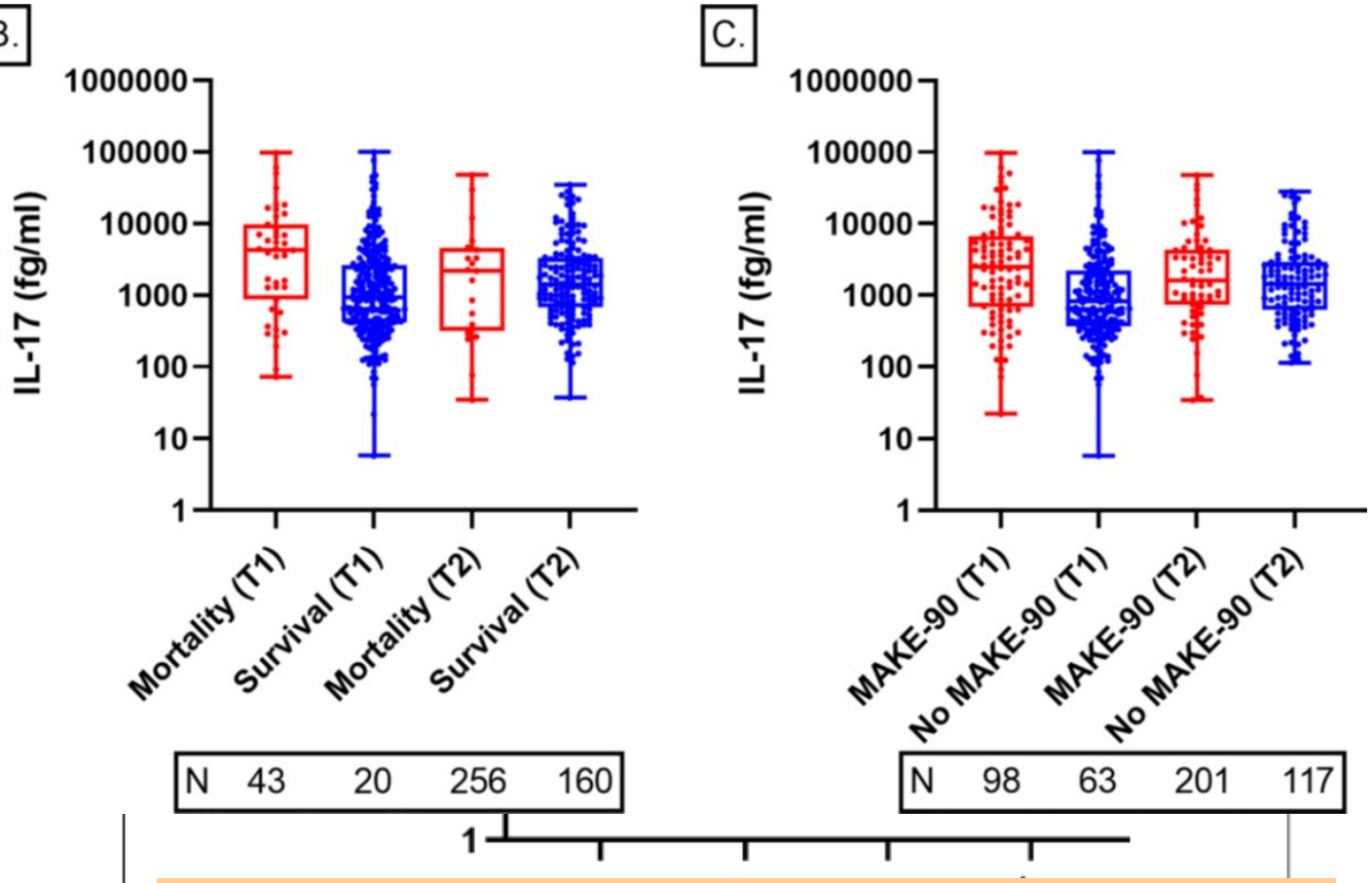
- N=299. Patients with AKI (vs. no AKI) had higher levels of IL-17A
- Every onefold higher serum IL-17A at T1 was independently associated with increased risk of hospital mortality (aOR 1.35, 95% CI: 1.06-1.73) and MAKE (aOR 1.26, 95% CI: 1.02–1.55)
- The highest tertile of IL-17A (vs. the lowest tertile) was also independently associated with higher risk of MAKE (aOR 3.03, 95% CI: 1.34–6.87)
- IL-17A levels remained significantly elevated at T2 in patients that died or developed MAKE



Serum IL-17A levels measured by the time of AKI diagnosis or ICU admission were differentially elevated in critically ill patients with AKI when compared to those without AKI and were independently associated with hospital mortality and MAKE

IL-17A Levels and Progression of Kidney Disease Following Hospitalization with and without Acute Kidney Injury

Jason A. Collett [1], Alexander H. Flannery [2], Lucas J. Liu [3], Tomonori Takeuchi [4], David P. Basile [1], and Javier A. Neyra [4]

Kidney360 Vol 5 November, 2024

- We hypothesize that IL-17A levels are elevated in hospitalized patients with AKI at diagnosis, and sustained elevation after discharge is associated with CKD
- This was an observational convenience sampling study of hospital survivors of stage 2 or 3 AKI and controls without AKI from ASSESS-AKI
- Patients were classified as progression or nonprogression on the basis of a composite of CKD incidence, progression, or ESKD
- IL-17A levels were evaluated with S-Plex assay (Meso Scale Discovery) at 0 (during hospitalization), 3 and 12 months post-discharge and analyzed along with clinical and biomarker data up to 84 months after discharge

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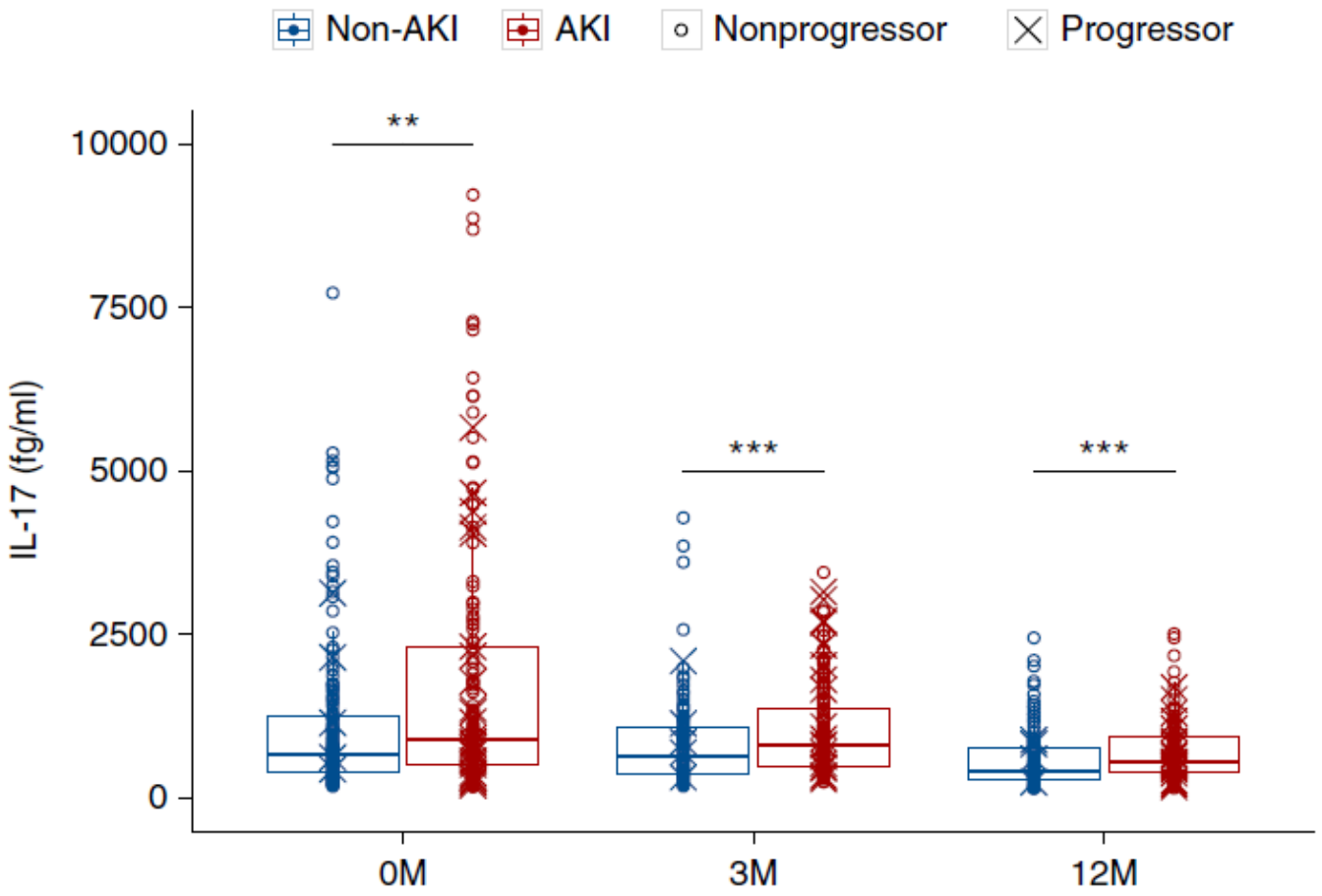
- Among 171 AKI and 175 non-AKI participants, IL-17A levels were elevated in AKI vs. non-AKI patients at 0-, 3-, and 12-month time points ($p < 0.05$ for all comparisons)
- IL-17A levels were elevated in the progression vs. nonprogression group at the 3- and 12-month time points for outcomes occurring at 3–6 and12–84 months, respectively ($p<0.05$ for both)
- In adjusted multivariable models, IL-17A levels were not independently associated with progression of kidney disease
- IL-17A levels were positively correlated with kidney disease and immune activation biomarkers at all time points ($p<0.001$)



IL-17A Levels and Progression of Kidney Disease Following Hospitalization with and without Acute Kidney Injury

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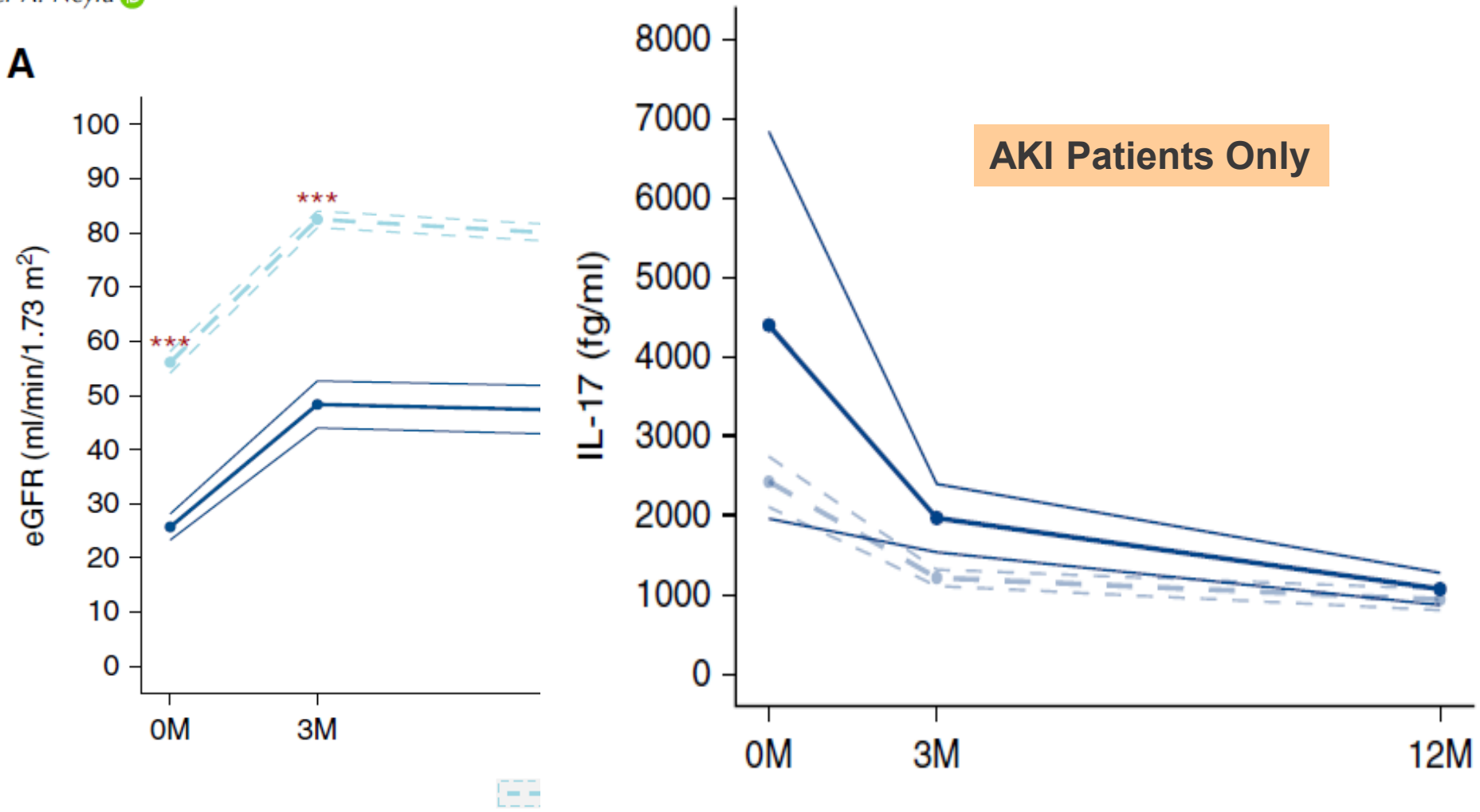
Javier A. Neyra[4]



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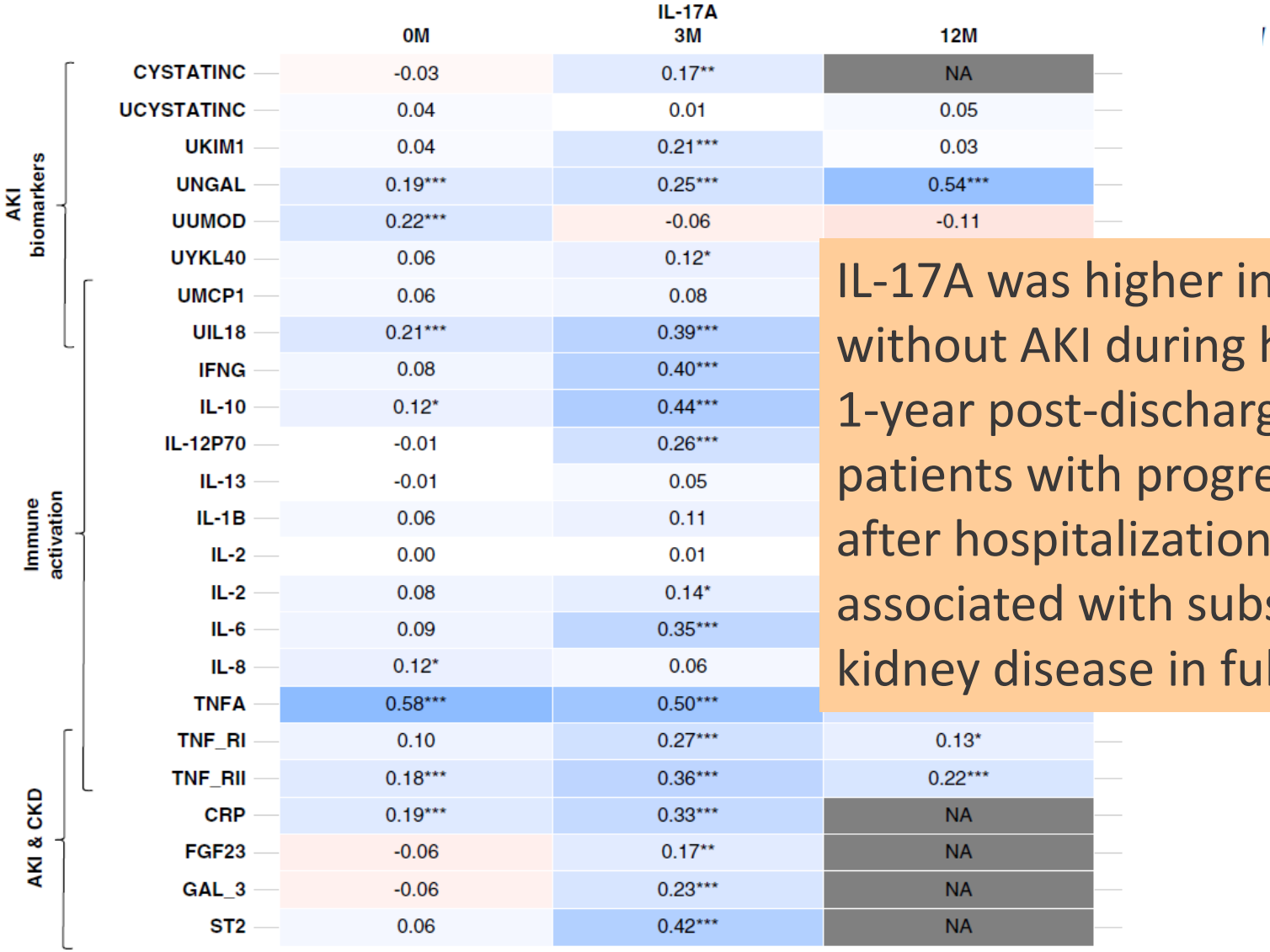


IL-17A was higher in patients with AKI vs. without AKI during hospitalization and up to 1-year post-discharge. IL-17A was higher in patients with progression of kidney disease after hospitalization but not independently associated with subsequent progression of kidney disease in fully adjusted models.

Outline

- Role of IL-17A as a biomarker in Critical Care Nephrology
- IL-17A levels in simulated KOURAGE trial participants

KOURAGE Inverse Simulation

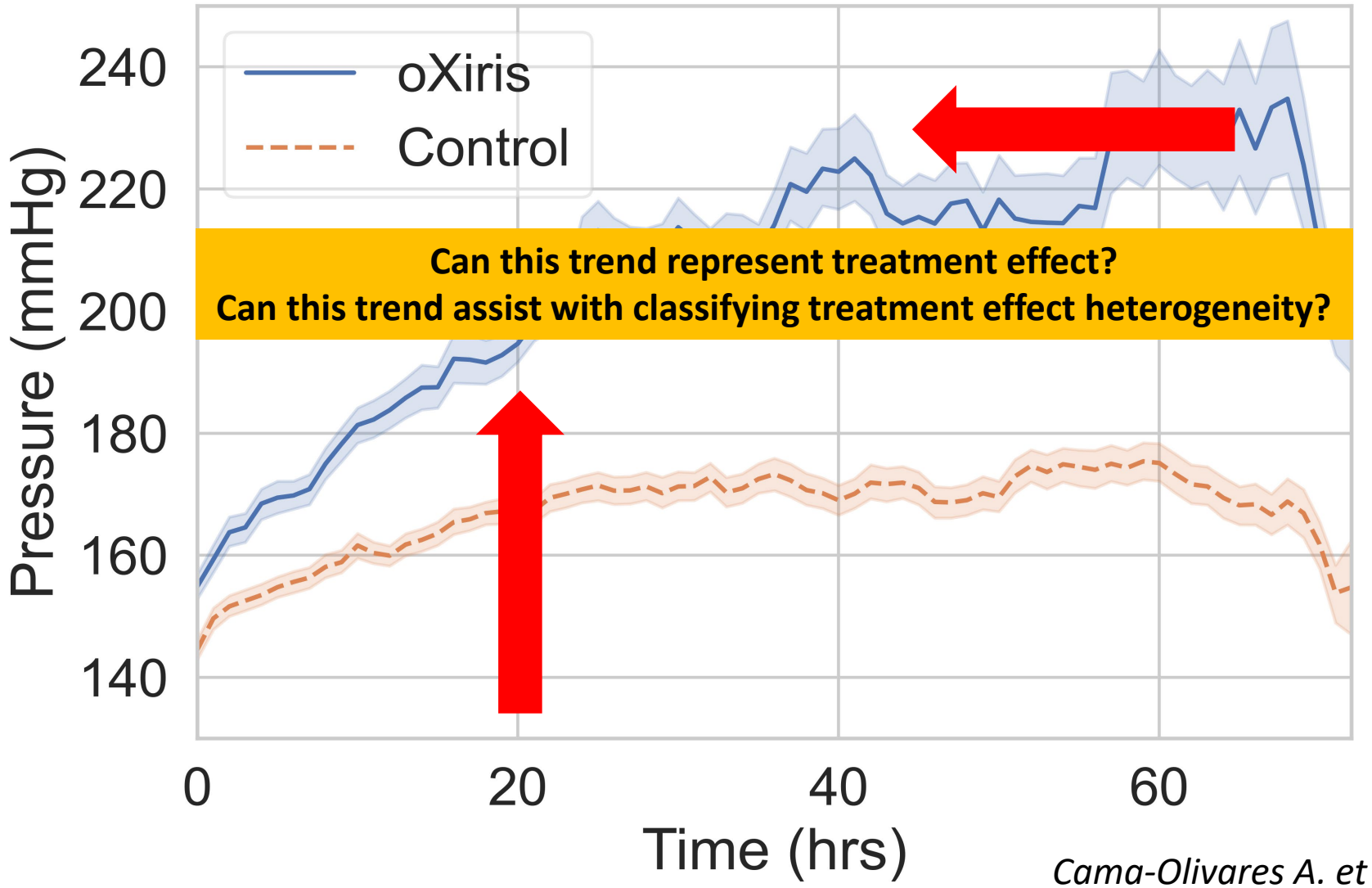
Inclusion criteria	Exclusion criteria
1. **The patient is ≥ 18 years of age.** 2. **The patient has developed Stage 2 or Stage 3 AKI.** 3. The patient has a documented PaO2/FiO2 (P/F) ≤ 300 in the prior 24 hours of informed consent, either imputed from SpO2 or obtained from an arterial blood gas that is not explained by cardiogenic pulmonary edema or volume overload. 4. **The patient is being treated with** either high flow nasal cannula with minimum flow rate ≥ 30 liters/min, or non-invasive mechanical ventilation, or **invasive mechanical ventilation at time of randomization.** 5. **A female patient of childbearing potential who is sexually active with a male partner is willing to practice acceptable methods of birth control for 30 days after the last dose of study drug.** 6. **A male patient who is sexually active with a female partner of childbearing potential is willing to practice acceptable methods of birth control for 30 days after the last dose of study drug. A male patient must not donate sperm for 30 days after the last dose of study drug.** 7. **The patient is willing and able to, or has a legally authorized representative (LAR) who is willing and able to provide informed consent to participate and to cooperate with all aspects of the protocol.**	1. The patient has a do not intubate directive. 2. The patient has chronic lung disease that requires supplemental non-invasive oxygen as an outpatient or home mechanical ventilation. 3. **The patient has been hospitalized for more than 10 days.** 4. **The patient has been receiving invasive mechanical ventilation for > 120 hours.** 5. The patient is receiving extracorporeal membrane oxygenation (ECMO). 6. **The patient has started or is planned to start kidney replacement therapy (KRT) before randomization.** 7. The patient has a serum triglyceride level of ≥ 500 mg/dL. 8. The patient has a direct bilirubin level > 3.0 mg/dL or both a direct bilirubin level ≥ 2.0 mg/dL and an INR ≥ 1.7. 9. **AKI is suspected to be secondary to: a) renal artery or renal vein thrombosis; b) hepato-renal syndrome; c) cholesterol emboli syndrome; d) acute glomerulonephritis; e) vasculitis; f) acute allergic interstitial nephritis; g) intrarenal or extra renal urinary tract obstruction; h) use of immune checkpoint inhibitor.** 10. **The patient has a known history of an organ transplant.** 11. **The patient has a known history of HIV infection.** 12. **The patient has known history of hepatitis B infection.** 13. **The patient is currently receiving chemotherapy.*** 14. The patient is currently receiving immunosuppressive medications (Section 5.2). 15. **The patient is known to be pregnant or is currently nursing.** 16. The patient is allergic to eggs. 17. **The patient is currently participating in another study of an investigational drug.**

Zegocractin is a calcium release-activated calcium (CRAC) channel inhibitor with potent anti-inflammatory and pulmonary endothelial protective properties. Preclinical and early phase clinical studies suggest that zegocractin may be an effective agent for the treatment of AKI

~60% of inclusion and exclusion criteria

Machine data evaluating oXiris vs. HF1400

18,875 hours of CRRT (n=85 critically ill patients with COVID)



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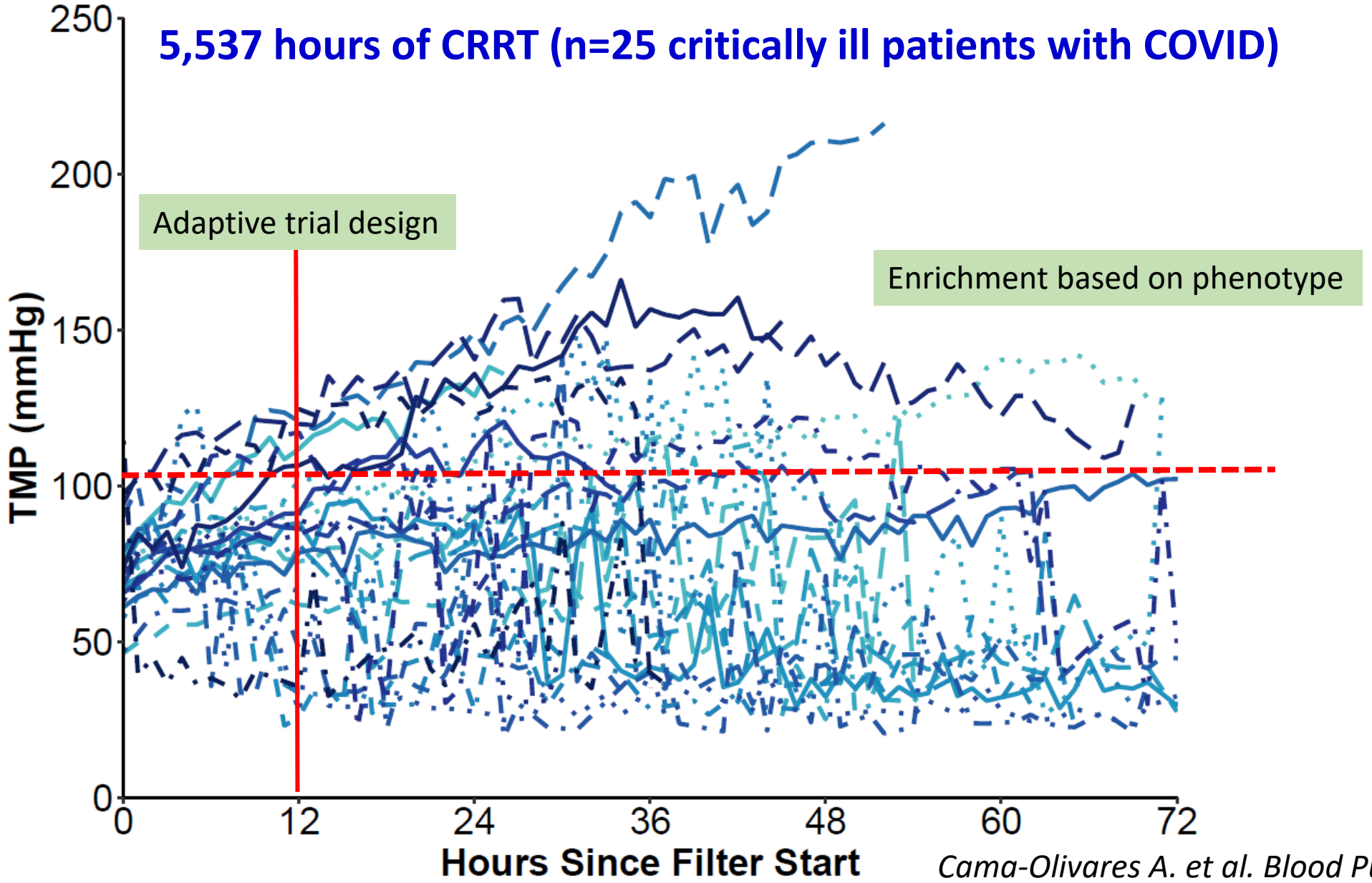
Machine data evaluating oXiris treatments



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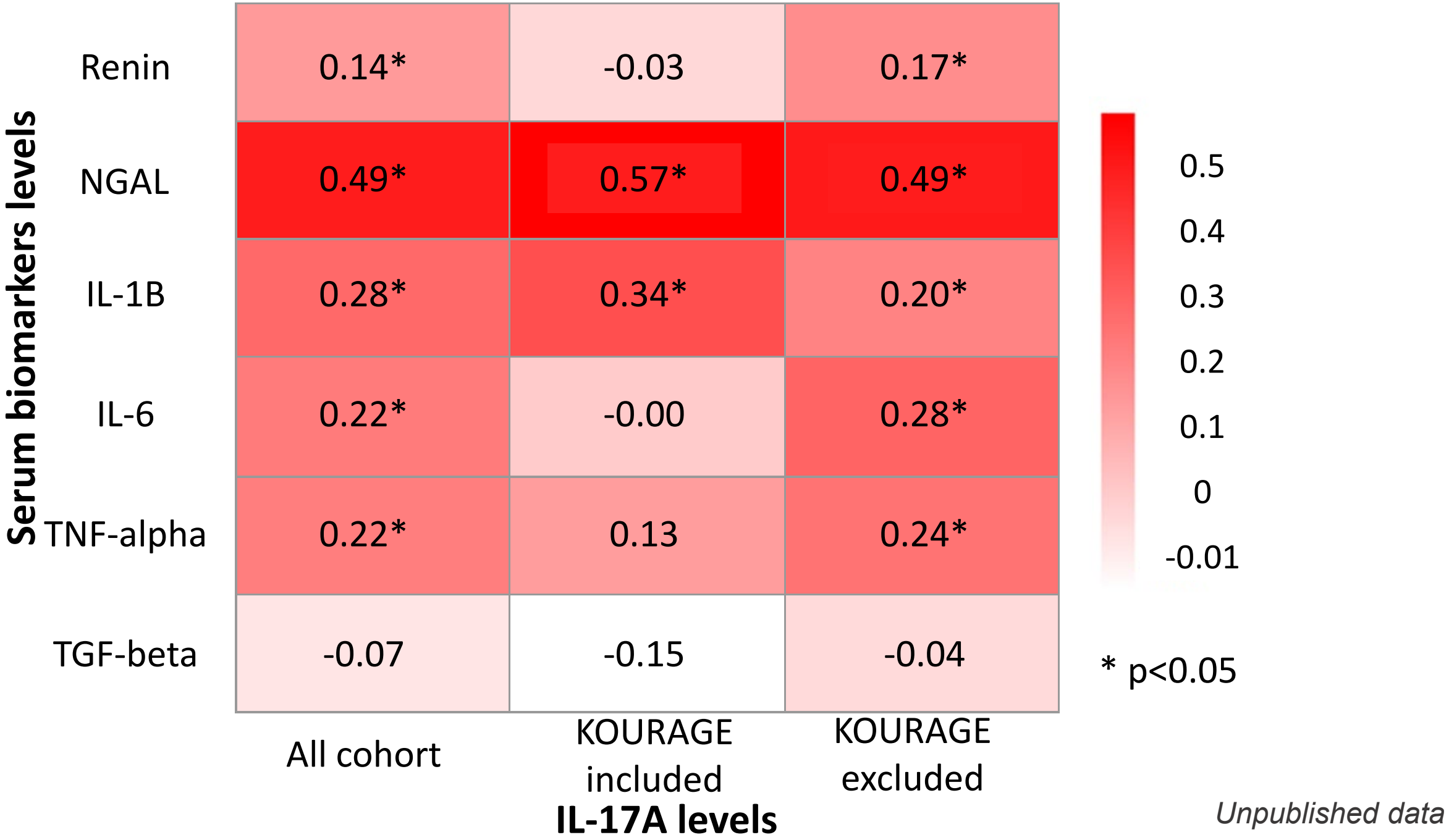

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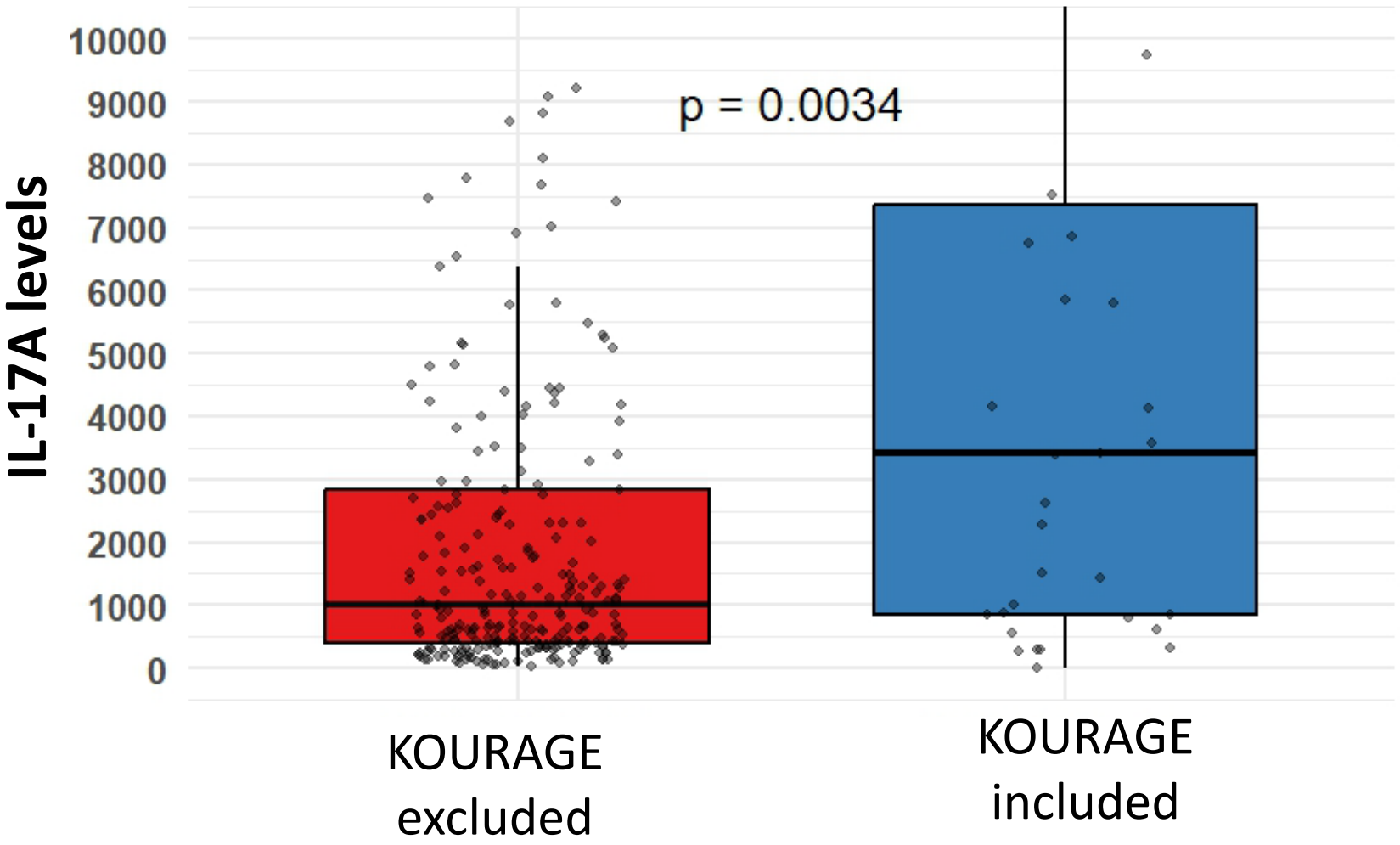

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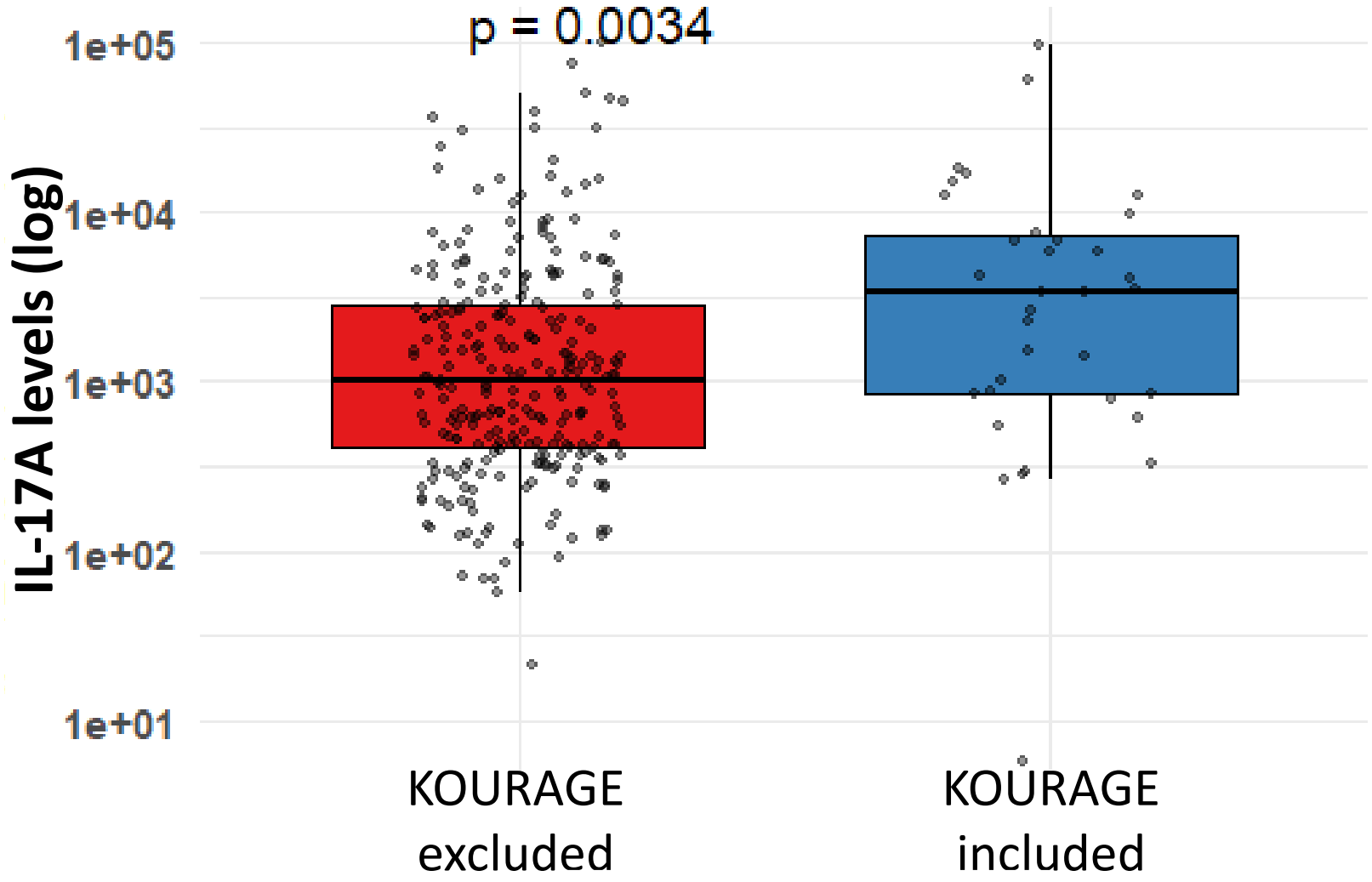

Unpublished data

Take-home Points

- IL-17A-associated endophenotypes provide an opportunity for immune-targeted risk-stratification and enrichment for AKI trials
- Calcium release-activated calcium (CRAC) channel inhibitors are a potential therapeutic target in AKI and AKI-to-CKD progression

Thanks!

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