Austin Health

ANZICS/ACCCN INTENSIVE CARE ASM
FINDING THE FOREST THROUGH THE TREES

Conventional and novel biomarkers for the early prediction of AKI

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The challenges of AKI prediction

- A frequent **syndrome** associated with mortality and morbidity
- Defined by **functional** parameters (sCr and UO)
  - Altered once > 50% of nephrons are already lost function
- Early **detection** = 1st mandatory step in the study/development of **interventions**

AKI biomarkers

- Measure urinary **TIMP-2** and **IGFBP-7** (NephroCheck®)
  - Cell-cycle arrest biomarkers
  - Secreted by the proximal tubule
  - Excellent predictive performance in a broad range of ICU patients

Kashani *et al. Critical Care* 2013, **17**:R25
http://ccforum.com/content/17/1/R25

CRITICAL CARE

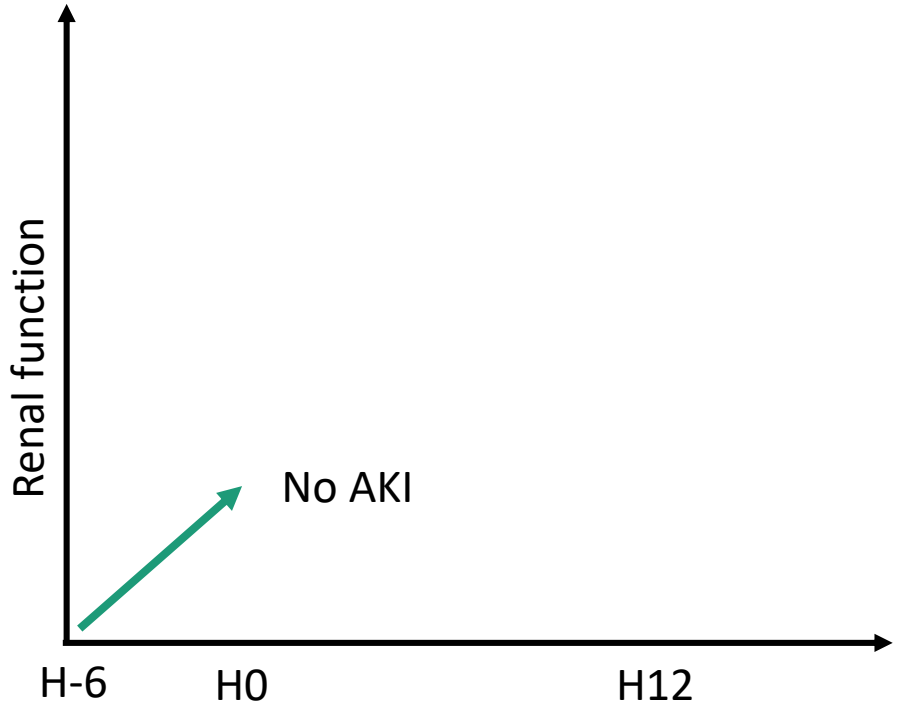
RESEARCH Open Access

Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury

N=744

AKI biomarkers

- Detect small changes in UO or sCr
  - UO is usually measured hourly
  - ABG point-of-care assays measure sCr



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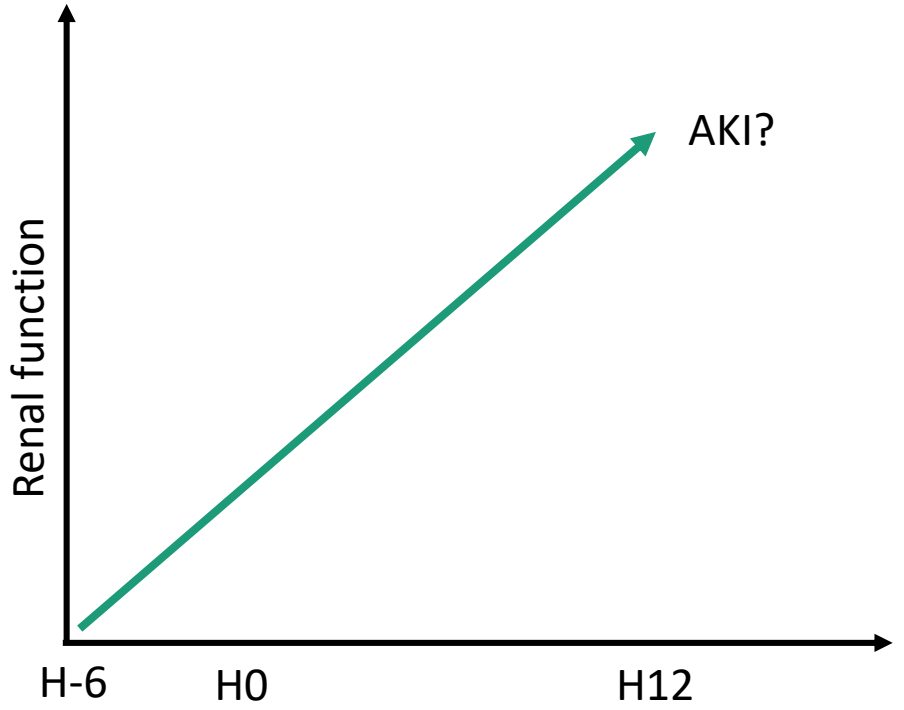


Objectives

To assess and compare the predictive performance of:

- Novel validated biomarkers of AKI: TIMP-2 and IGFBP-7
- Conventional biomarkers of AKI: urine output and serum creatinine, both assessed 6-hourly

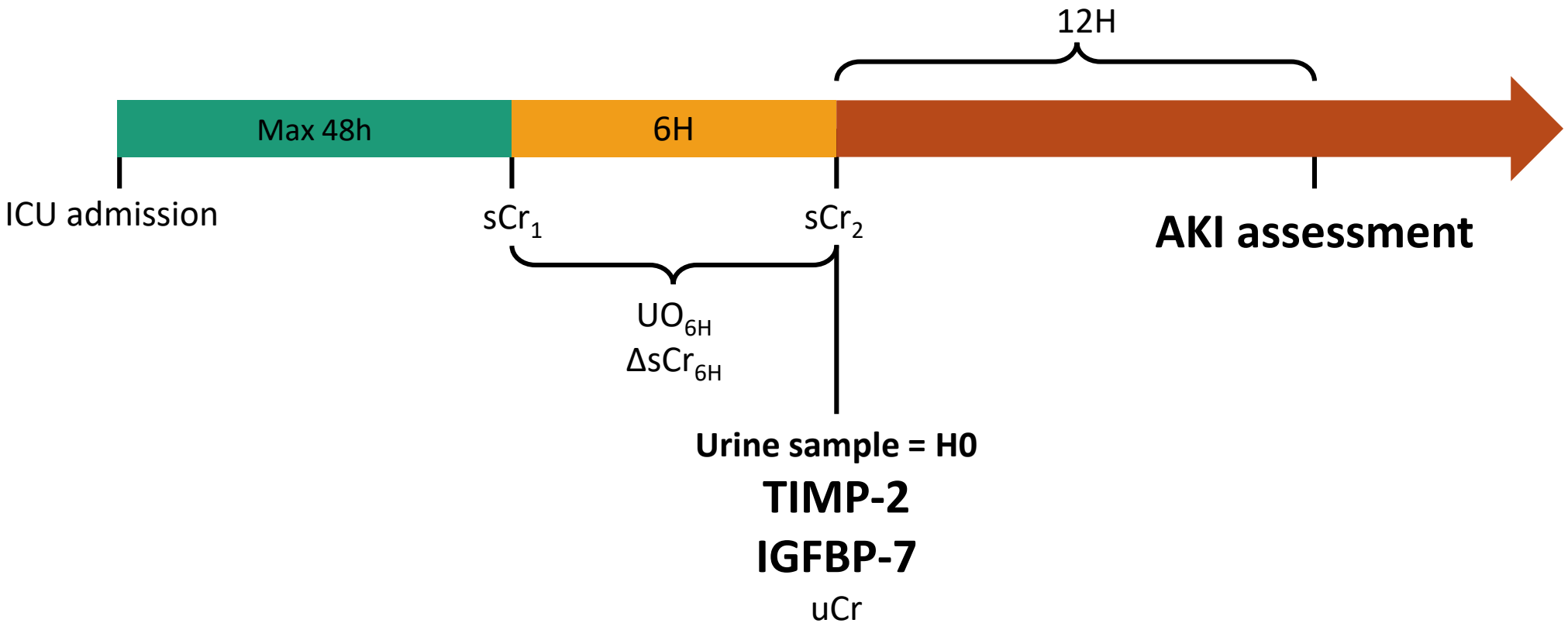
Methods

- Prospective, single centre study
- General tertiary ICU, Melbourne

- 2 cohorts of adult ICU patients
  - AKI high-risk cohort (increase in sCr > 1.4 µmol/L/h or UO < 0.5 mL/kg/h over 4 hours)
  - SAPPHIRE Study-like cohort (SOFA respiratory ≥ 2 or SOFA cardiovascular ≥ 1)

- Exclusion:
  - Known AKI stage 2 and 3

Methods (2)



- **Main endpoint**: AKI stage 2 or 3 (KDIGO) at H12 of urine collection

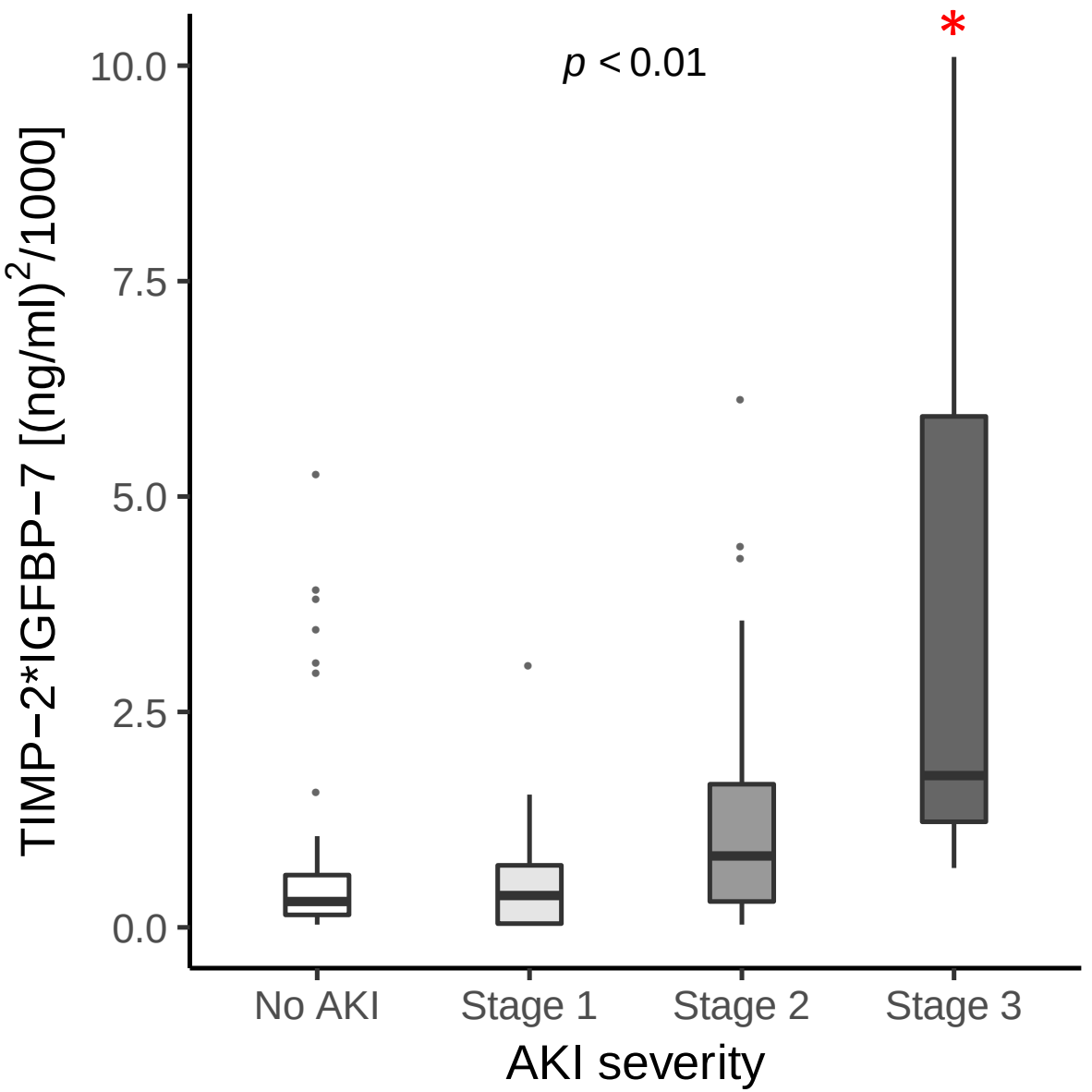
Results

	AKI – N = 64	AKI + N = 32
Demographics		
Age (years)	63 [50 to 74]	63.3 [54 to 73]
Gender (male)	30 (47%)	20 (62%)
Weight (kg)	79 [68 to 88]	87 [75 to 96]†
Main comorbidities		
Hypertension	28 (44%)	19 (59%)
Diabetes mellitus	10 (16%)	10 (31%)
Baseline creatinine (µmol/L)	69 [53 to 85]	84 [74 to 96]
Severity of disease		
Mechanical ventilation	44 (69%)	22 (69%)
Vasopressor requirement	41 (64%)	20 (62%)
Sepsis	24 (38%)	8 (25%)
Lactate (mmol/l)	2.6 [1.7 to 4.2]	2.6 [1.6 to 4.5]
Serum creatinine (µmol/L)	80 [67 to 113]	107 [80 to 154]†

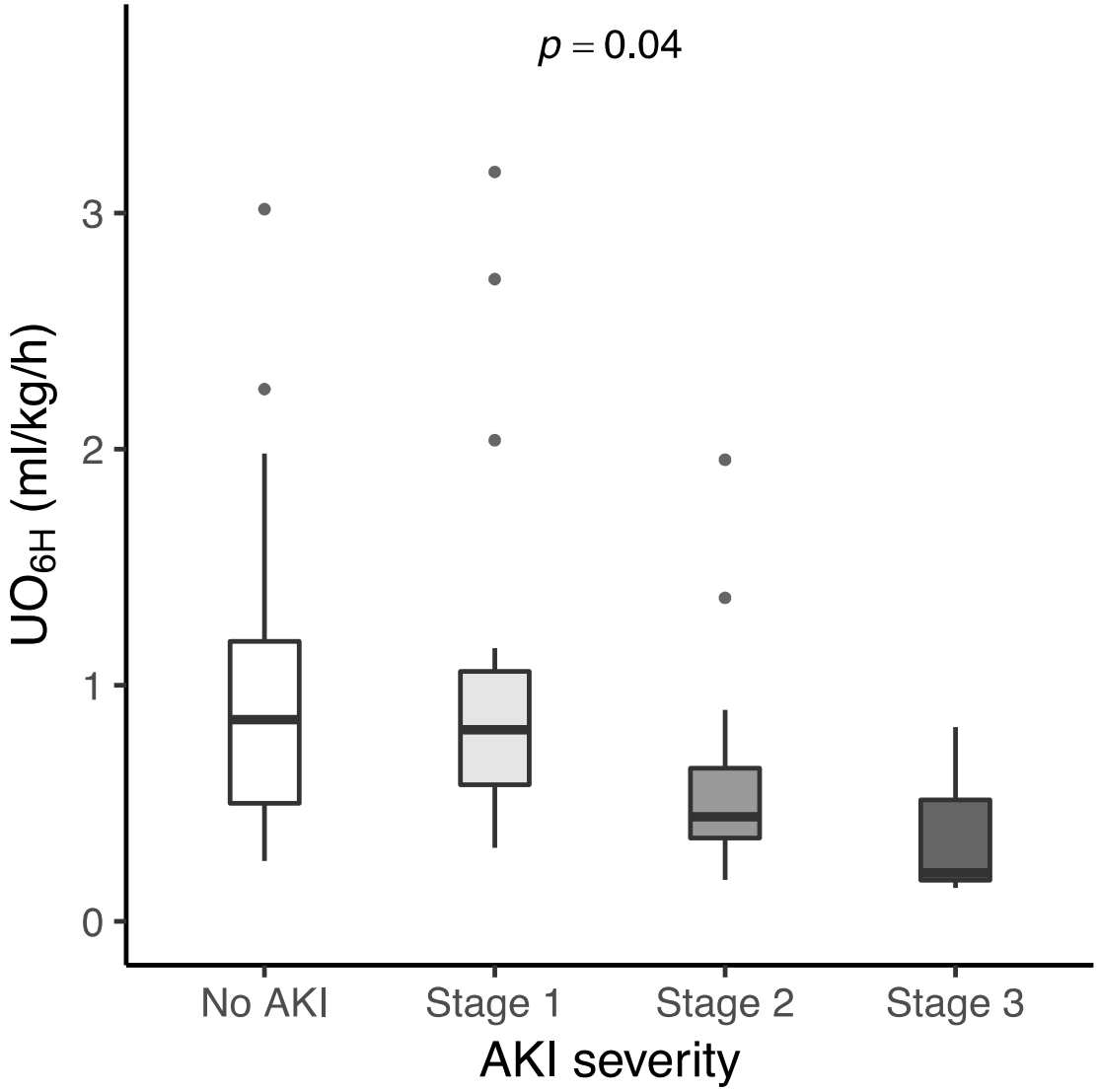
Results (2)

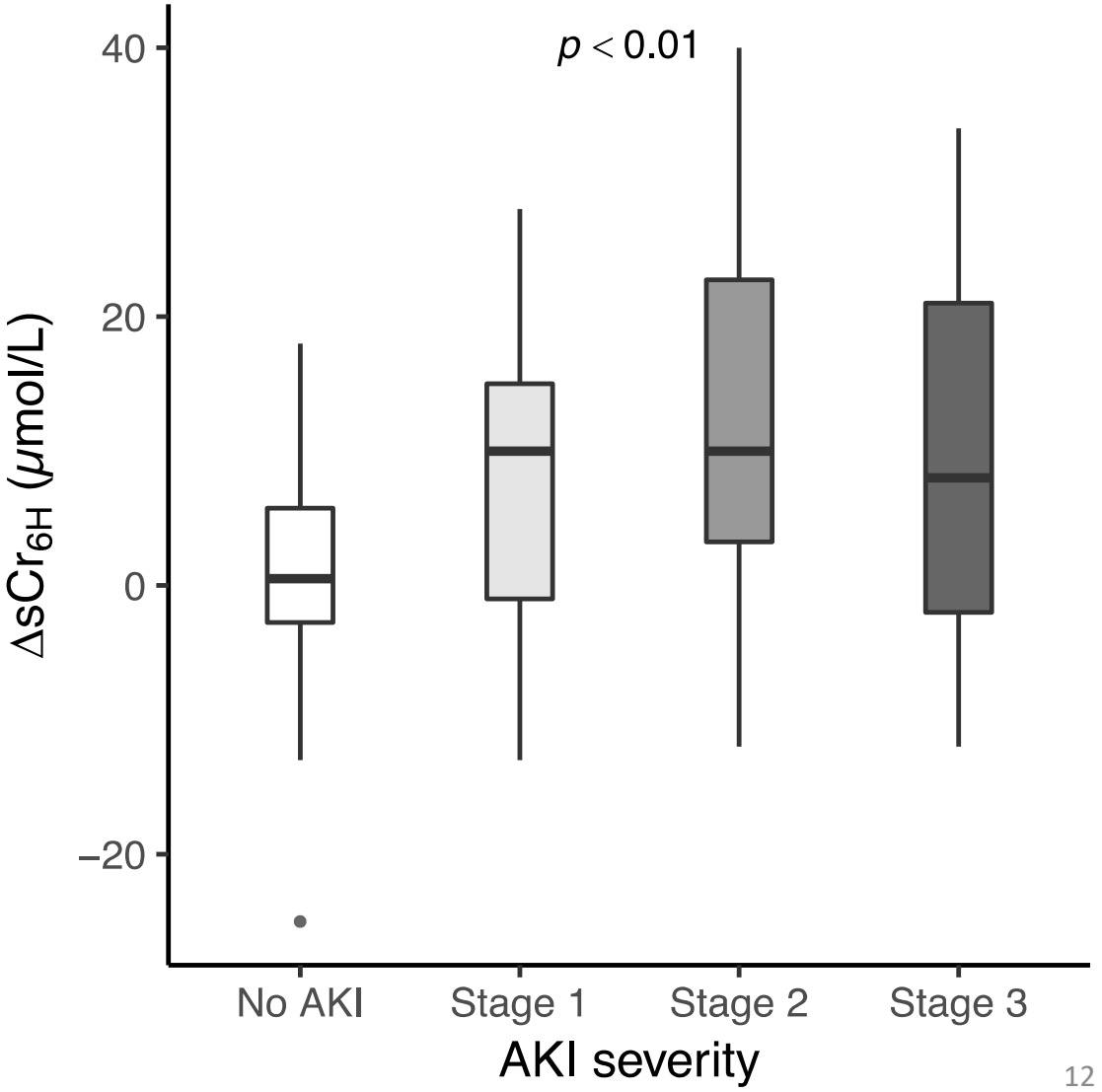
	AKI –	AKI +
TIMP-2•IGFBP-7 [(ng/ml)^2/1000]	0.3 [0.1 to 0.7]	0.9 [0.4 to 1.8]†
TIMP-2•IGFBP-7 normalized to uCr (µg/mmol)^2	5.6 [1.8 to 14.4]	4.9 [2.9 to 8.8]
UO_{6H} (mL/kg/h)	0.8 [0.5 to 1.1]	0.4 [0.3 to 0.7]†
ΔsCr_{6H} (µmol/L)	2 [-2.5 to 8]	10 [3 to 23]†
Renal score	2.1 [0.7 to 3.5]	4.2 [3.0 to 7.6]†

Results (3)


p < 0.01
*
10.0
7.5
5.0
2.5
0.0
TIMP−2*IGFBP−7 [(ng/ml)²/1000]
No AKI
Stage 1
Stage 2
Stage 3
AKI severity

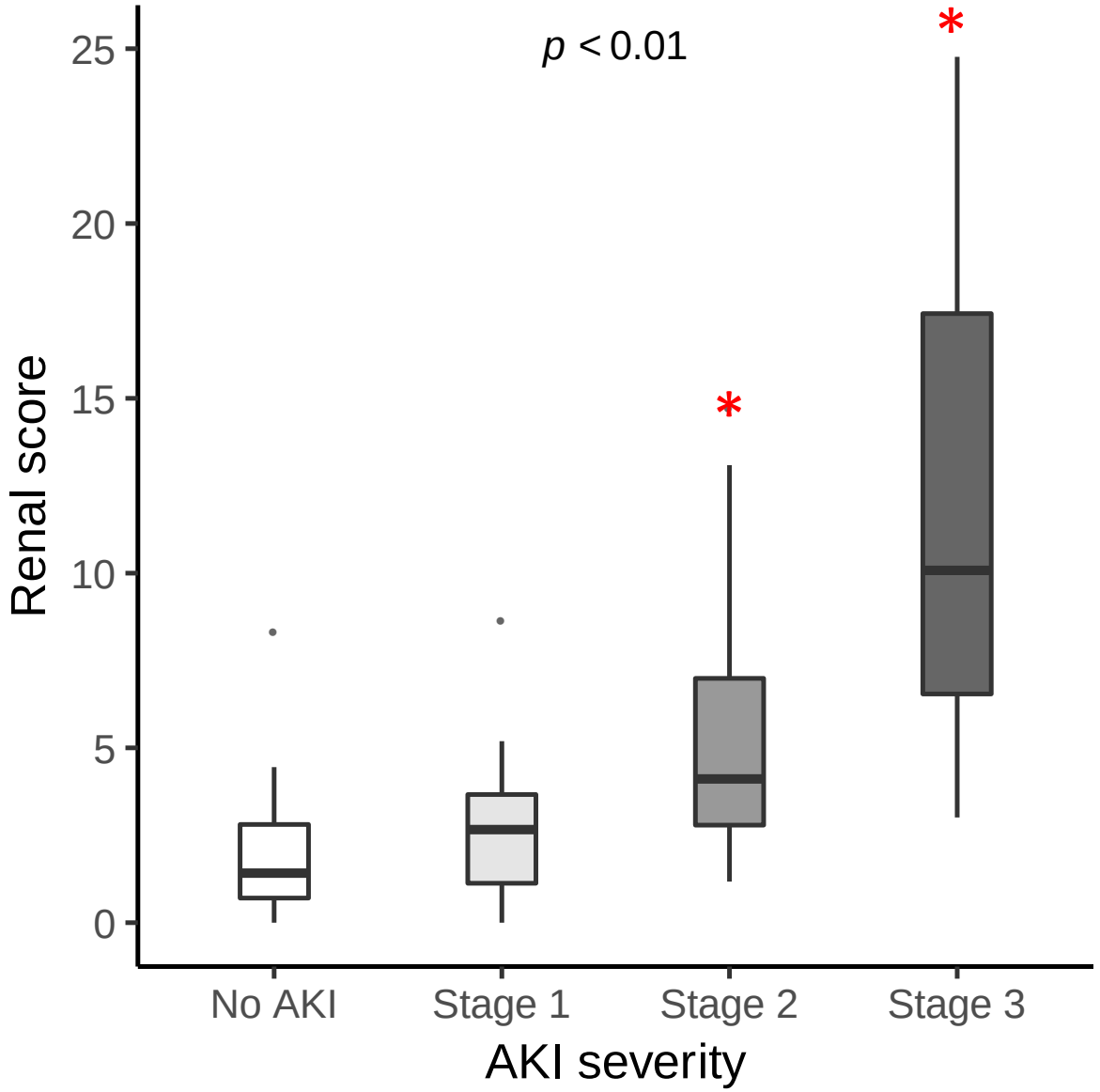
Results (4)


p = 0.04
UO6H (ml/kg/h)
3
2
1
0
No AKI
Stage 1
Stage 2
Stage 3
AKI severity

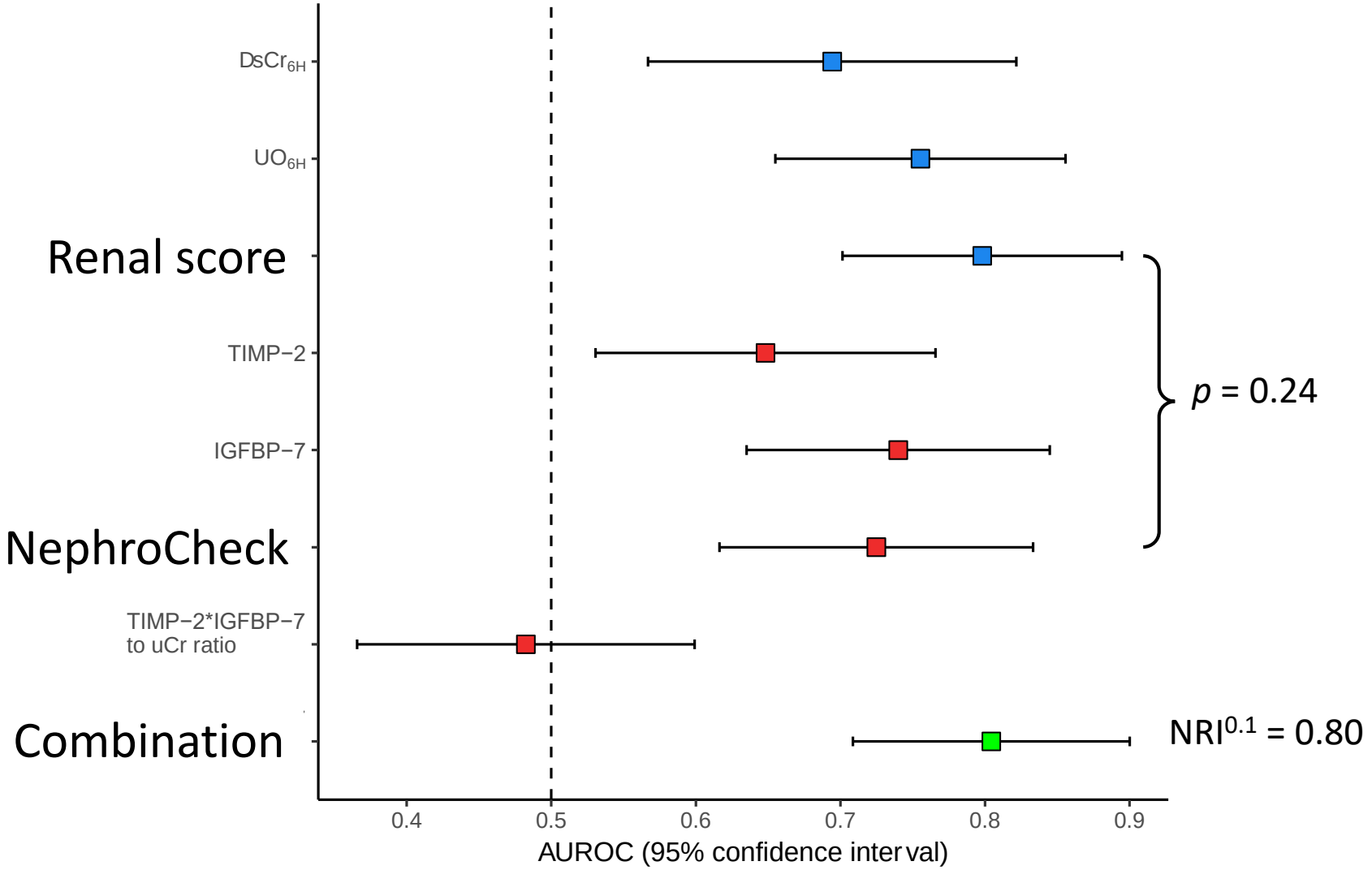

p < 0.01
ΔsCr6H (μmol/L)
40
20
0
−20
No AKI
Stage 1
Stage 2
Stage 3
AKI severity

Results (5)

$$Renal\ score = \frac{\log_e(|\Delta sCr_{6H}|)}{UO_{6H}}$$

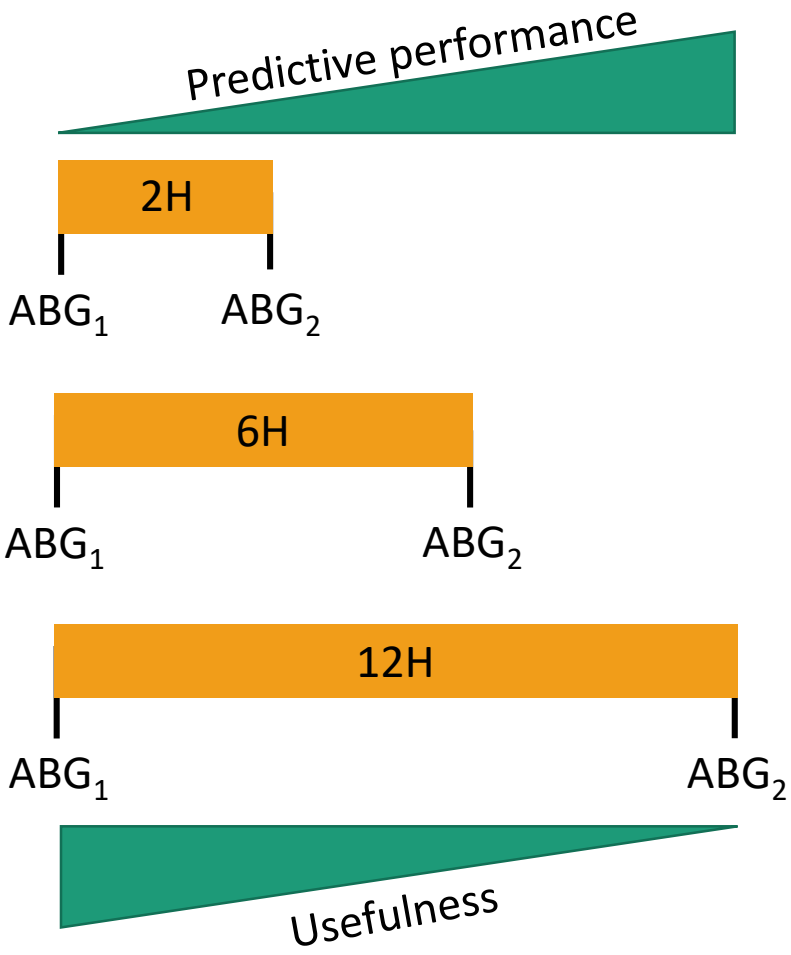


Results (6)


DsCr6H
UO6H
Renal score
TIMP−2
IGFBP−7
NephroCheck
TIMP−2*IGFBP−7
to uCr ratio
Combination
p = 0.24
NRI0.1 = 0.80
0.4
0.5
0.6
0.7
0.8
0.9
AUROC (95% confidence interval)

Discussion

- TIMP-2•IGFBP-7 performance
  - Different population?
  - TIMP-2•IGFBP-7 may be detecting another phenomenon (stress ≠ function ?)
  - Poor performance of normalized TIMP-2•IGFBP-7 (value dependent of function ?)
- Conventional biomarkers may be equivalent to novel biomarkers
  - Effect of timeframe duration
- Perspectives:
  - Explore effect of urine concentration of TIMP-2•IGFBP-7
  - Effect of tested population (pre-test probability)



Conclusions

- Conventional and novel AKI biomarkers showed equivalent performance in the prediction of AKI at H12

- Implementing them may help predict short-term AKI, and drive interventions modifying its course