Biomarkers of kidney stress during early in critical illness identify patients with impaired kidney function at ICU discharge when assessed using Cystatin-c but not Creatinine.

Aroon Bhardwaj Shah[1], Anna Gillespie[1], Ryan W Haines[1], John R Prowle[1]

Critical Care and Perioperative Medicine Research Group, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London UK

Abstract

- We examined the ability of the Nephrocheck™ (TIMP-2.IGFBP-7) assay at to predict adverse kidney outcomes close to ICU Discharge
- Peak Nephrocheck values within the first week were compared against ICU discharge eGFRs using both Creatinine and Cyastatin C
- 91% of patients displayed elevated Nephrocheck but only 40% conventional AKI criteria
- A correlation was found between peak Nephrocheck™ values and discharge Cystatin C eGFR but not with Creatinine-based eGFR
- Biomarkers may play an important role in identification of risk for persistent kidney damage however this may not be evident if serum creatinine is used as a gold standard of kidney function

Introduction

During critical illness kidney injury may be sub-clinical but still lead to adverse kidney outcomes. The Nephrocheck™ assay is a combination two urinary biomarkers (TIMP-2.IGFBP-7) which identifies renal tubular stress and predicts risk of Acute Kidney Injury (AKI). We hypothesised that early renal stress might also be associated with impaired renal function at ICU discharge independent of overt AKI. We further hypothesised that this effect might only be evident if Cystatin-c was used to assess kidney function due to the confounding effect of muscle wasting on serum creatinine.

Methods

Participants were all inpatients at a tertiary critical care unit London, UK, half were major trauma admissions. TIMP-2.IGFBP-7 was measured on days 1,3,5, and 7. Patients who died in ICU were excluded. For each patient peak TIMP-2.IGFBP-7 within first 7 days of ICU admission was categorised as: Low risk (<0.3), Low-Medium Risk (0.3-0.99), High-Medium Risk (1-2) or High Risk (2+). Estimated Glomerular filtration rate (eGFR) at ICU discharge was assessed using Creatinine and Cystatin C. Differences in eGFR between groups based on kidney stress were assessed using the Jonckheere-Terpstra test.

Table

	All	NephC <0.3	NephC 0.3-1	Neph C 1-1.99	NephC >/=2
Total N	35	3 (9%)	11 (31%)	11 (31%)	10 (29%)
Female N(%)	12 (34%)	0 (0%)	4 (36%)	4 (36%)	4 (40%)
Age	51 (21-76)	43 (21-54)	45 (23-68)	58 (35-73)	51 (25-76)
BL Creat	98 (54-338)	76 (64-98)	84 (54-129)	78 (57-105)	141 (59-338)
BL eGFR	85 (16-121)	104 (97-109)	94 (56-121)	88 (50-117)	64 (16-110)
AKI	14 (40%)	0 (0%)	2 (18%)	4 (36%)	8 (80%)
RRT N(%)	7 (20%)	0 (0%)	1 (9%)	1 (9%)	5 (50%)
Peak NC in first 7 days	4 (0.17-42.67)	0.22 (0.17-0.25)	0.8 (0.33-0.98)	1.36 (1.01-1.88)	11.8 (2.08-42.67)
Discharge eGFR (Creat)	105 (12-146)	115 (105-135)	116 (98-133)	103 (70-127)	94 (12-146)
Discharge eGFR (Cys)	70 (8-140)	104 (92-113)	80 (30-123)	70 (8-140)	57 (8-140)
Discharge eGFR (Cys-Creat)	86 (9-144)	112 (101-119)	96 (52-130)	81 (49-121)	72 (9-144)

NephC categories are based on the peak Nephrocheck recorded during the first 7 days of ICU admission

Results

35 (12 Female) patients were included. Median age was 54 years (range 21-76). Median ICU stay was 16 days (range 5-54). Median baseline eGFR-Cr was 96 ml/min/1.73 m^2 (range 16-121). 14 (40%) of patients developed creatinine defined AKI in the first 10 days with 7 receiving kidney replacement therapy (KRT). Conversely 32 (91%) of patients had a peak Nephrocheck >0.3 within the first 7 days. Distribution of peak TIMP-2.IGFBP-7 within the first 7 days was: Low risk (N 3), Low-Medium Risk (N 11), High-Medium Risk (N 11), High Risk (N 10). Cystatin C eGFR (Median 70ml/min/1.73m^2) at discharge was significantly lower than Creatinine eGFR (Median 108) at ICU discharge (P<0.001). No patient remained on KRT at ICU discharge. While peak TIMP-2.IGFBP-7category did not correlate with discharge Creatinine eGFR (P=0.166) it did significantly correlate with discharge Cystatin C eGFR (P=0.0128) (Figure 1).

Creatinine Vs Cystatin C

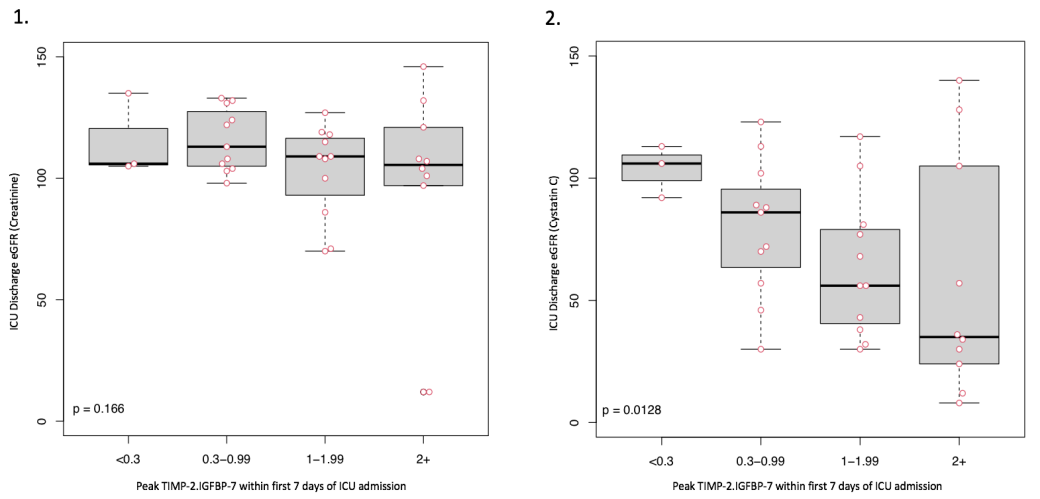

Figure 1: Whisker and Boxplot charts of findings. Charts show peak TIMP-2.IGFBP-7 (Nephrocheck) within first 7 days against ICU discharge eGFR (Creatinine – Chart 1) (Cystatin C – Chart 2). P values shown are based on Jonckheere-Terpstra test for trend.

Discussion

In critical illness assessment of kidney function using creatinine may be impeded by falls in creatinine generation. Here kidney stress was detected in 86% of cases whereas creatinine defined AKI was only observed in 40%. When kidney function was assessed using a measure less-confounded by muscle mass change (Cystatin-c) severity of early kidney stress identified worse kidney function at ICU discharge. This was not observed using Creatinine. TIMP-2.IGFBP-7 may help risk-stratify long term renal function following critical illness. Future evaluation of kidney biomarker tests in critical illness should consider using Cystatin C rather than Creatinine to assess kidney outcomes.

Funding

NEPHROCHECK Test System and Astute140® Meter kindly supplied by bioMérieux SA