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KIM-1 to Urinary Creatinine Ratio for Early Detection of AKI in Patients Undergoing Cardiopulmonary Bypass

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Abstract: ***Acute kidney injury (AKI) is a common serious complication among patients undergoing on-pimp cardiac surgery. Currently its diagnosis is based on the accumulation of nitrogen metabolism end products such as sCreat (serum creatinine) which is known to be late and unreliable marker for AKI for its levels are affected by different extrarenal variables. In recent years, several urinary markers of tubular damage have been proposed as more accurate alternatives to serum creatinine for the early detection of AKI in patients undergoing CPB (cardiopulmonary bypass). The objective of our study was to assess the performance characteristics of urinary KIM-1 measured 2-6 hours post surgery among adults undergoing CPB and to compare the predictive value of urinary KIM-1 with urinary KIM-1 to urinary creatinine ratio. ROC(receiver operator characteristics)-analysis revealed 2-6 hours post-CPB urinary KIM-1 AUC (area under the curve) of 0.84 (p<0.001). For calculated urinary KIM-1 to urinary creatinine ratio the ROC analysis revealed an enhanced performance with AUC 0.85 (p<0.001) giving ΔAUC of 0.01. Using normalized values demonstrated a higher predictive value for urinary KIM-1 to urinary creatinine ratio for early detection of AKI compensating some of the shortcomings of absolute values determination related with effective extrarenal modifiers of the results.***

Keywords: Acute kidney injury, early diagnosis, cardiopulmonary bypass, kidney injury molecule-1

1. Introduction

Acute kidney injury (AKI) is a common serious condition affecting a heterogeneous patients population. Currently its diagnosis is based on the accumulation of nitrogen metabolism end products such as sCreat (serum creatinine). Unfortunately, sCreat is a late and unreliable marker for AKI diagnosis for its levels are affected by a variety of extrarenal effective modifiers (Moran et al., 1985, Bonventre JV et at., 2003) and significant increase of its concentration lags 1-3 days after the initial injury. If detected early in the disease process, novel AKI treatment strategies may be effective (Liangos et al., 2009).

In recent years, several urinary markers of tubular damage have been proposed as more accurate alternatives to serum creatinine for the early detection of AKI in patients undergoing CPB (cardiopulmonary bypass).KIM-1 is a transmembrane tubule protein which structure suggests adhesive functions (Bailly et al., 2002). It has been identified as a phosphatidylserine receptor that transforms epithelial cells into phagocytes by recognizing cell surface-specific epitopes expressed by apoptotic tubular epithelia (Bonventre et al., 2009). Its expression in regenerating kidney is probably an active process allowing the dedifferentiated regeneratory cells to attach to exposed areas of the basement membrane, thus rebuilding a continuous epithelium (Baillyet al., 2002). Normally KIM-1 is not expressed in a healthy kidney but is markedly upregulated in experimental AKI settings (Van Timmerenet al., 2007). Its presence in urine is highly specific for kidney injury because no other organ shows such expression which can influence the kidney excretion. KIM-1 is included in FDA's list of kidney injury markers which need to be taken into consideration in the assessment of kidney affection during drugs development (FDA News,2008). In patients undergoing major cardiac surgery including CPB and developed AKI 1-3 days post surgery, urinary KIM-1 concentrations were significantly increased within 12 hours (Han et al., 2009, Krawczeskiet al., 2011).

The objective of this study was to assess the performance characteristics of urinary KIM-1 measured 2-6 hours post surgery among adults undergoing CPB and to compare the predictive value of urinary KIM-1 with urinary KIM-1 to urinary creatinine ratio.

2. Subjects and Methods

An ancillary prospective study was conducted between December 2014 and July 2015 at two university hospitals located in Sofia, Bulgaria, and is part of a scientific research evaluating early urinary markers for AKI following CPB. All consecutive subjects were scheduled to undergo major cardiac surgery including CPB. Exclusion criteria were age under 18 years, pregnancy, other major surgery 30 days prior CPB, CKD. All participants signed informed consent. The study protocol was approved by Medical University-Sofia research Ethics Commission and the study was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki of 1975, as revised in 1983.

3. Data and Sample Collection

Medical records were reviewed prospectively to retrieve hospitalization data. Urine samples for measurement of urinary KIM-1 and urinary creatinine were collected 2-6 hours after CPB, centrifuged 20 min at 1000g and the supernatant stored in aliquots at -20◦C or -80◦C for longer

storage until assayed. Blood was taken and serum obtained 48 hours following CPB for routine measurement of sCreat.

4. Methods

Urinary KIM-1 was measured using sandwich ELISA. The wells coated with specific antibodies were incubated with 50 µL of dilution buffer and 25 µL of urine at room temperature for 120 min. After 4 washes with 300 µL of washing buffer 100 µL of biotinylated anti-KIM-1 conjugate was added to each well followed by 60 min of incubation at room temperature, 4 washes, and 100 µL of tetramethylbenzidine substrate was added for a final incubation for 20 min. Immediately after adding 100 µL of Stop-solution absorbance was read at 405 nm with 490 nm filter. Concentrations were calculated by a standard curve in pg/mL.

Urinary creatinine was routinely measured with automatic biochemical analyzer using an enzymatic method. GFR (glomerular filtration rate) was calculated using MDRD (Modification of Diet in Renal Disease) formula (Levey et al., 2000). Measurement data was protocolled strictly. In addition, the results for urinary KIM-1 were normalized to urinary creatinineand expressed in ng/mL.

The statistical analysis was performed using SPSS 19.0 (IBM Corporation).

5. Results

A total of 160 patients were enrolled in the study and their demographic and clinical characteristics are displayed in Table 1.The mean age was 65 years, 44% were females, pre-operative mean eGFR was 91 mL/min/1.73 m^2. Serial preoperative sCreat values were stable and none of the participants had preoperative AKI. Mean CPB perfusion was 134 min. Cardioplegia was achieved after external aortic cross-clamping, through ante-/retrograde cold blood diastolic cardioplegic arrest. Cardiac function was regained either spontaneously by warm reperfusion, or through defibrillation with 20 joule. 44 (27.5%) patients had >50% increase in sCreat levels 48 hours post CPB and defined as AKI. Mean preoperative eGFR was insignificantly lower in patients who developed AKI. All AKI patients had prolonged hospital stay by mean of 11 days. Dialysis was required in six cases.

Table 1: Patients demographic and clinical characteristics

	AKI	no AKI	p
Total number	44 (27.5%)	116 (72.5%)	-
Males	21/90 (23.3%)	69/90 (76.7%)	-
Females	23/70 (32.9%)	47/70 (67.1%)	-
Age	67.5 (±8.5)	64 (±5.4)	<0.001
Mean CPB time (min)	134 (±26)	110 (±18)	<0.0001
Mean preoperative eGFR (MDRD)	89*	92*	<0.001
ΔsCreat% (T=48 hours)	97	13	<0.001
Prolonged hospital stay (days)	11.2 ± 3.6	0	<0.001
Dialysis	6	0	<0.0001
In-hospital death	4	0	<0.0001

** eGFR calculated using MDRD formulamL/min/1.73m²*

KIM-1 diagnostic performance

ROC (receiver operator characteristics) analysis revealed 2-6 hours post-CPB urinary KIM-1 AUC of 0.84 ($p<0.001$). For calculated urinary KIM-1 to urinary creatinine ratio the ROC analysis revealed an enhanced performance with AUC 0.85 ($p<0.001$) giving ΔAUC of 0.01. The results are displayed in Figure 1. In addition, a medium positive correlation between age and urinary KIM-1 levels, and high positive correlation between CPB time and urinary KIM-1 levels were found using bivariate correlation analysis. The results are displayed in Table 2.

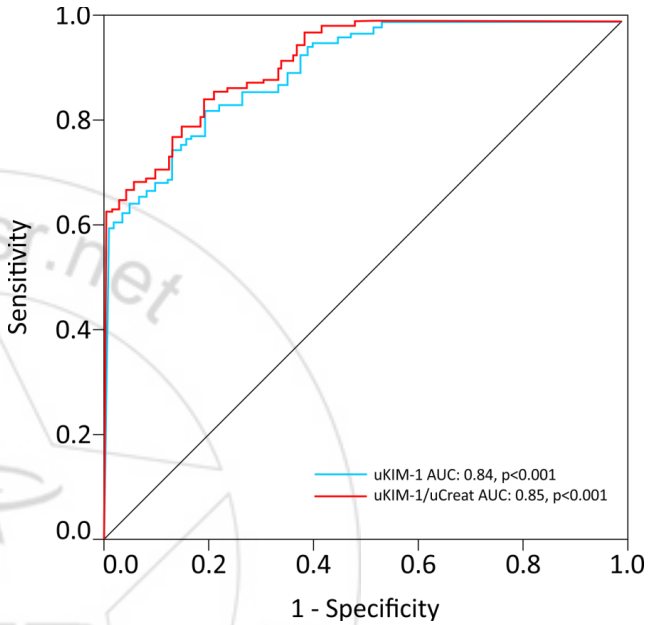

Figure 1: ROC-AUC of 2-6 hours post-CPB urinary KIM-1 and urinary KIM-1 to urinary KIM-1 to urinary creatinine ratio.

Table 2: Pearson Correlation between age, CPB time and urinary KIM-1

		uKIM1 (T=2-6 hours)
Age (years)	Pearson Correlation	,433**
	Sig. (2-tailed)	,003
	N	44
CPB (min)	Pearson Correlation	,774**
	Sig. (2-tailed)	,000
	N	44
		** *p<0.01*

6. Discussion

The current study among adults undergoing major cardiac surgery including CPB explored the predictive value of urinary KIM-1 and urinary KIM-1 to urinary KIM-1 to urinary creatinine ratio measured 2-6 hours following CPB, for early detection of AKI. Urinary KIM-1 as a marker of tubular dedifferentiation that is upregulated in proximal tubules after ischemic injury (Ichimuraet al., 1998) emerged sensitive and highly specific for early detection of AKI in the patients cohort enrolled in the study. We normalized urinary KIM-1 levels to urinary creatinine in order to account for differences in relative amounts of water extracted along the nephron.

Usually frequent measurements of urinary markers in the first 12 hours after CPB have better predictive performance, but we focused on single-point measurement during a very early post-operative periodconsidered to be relevant, since potentially successful therapeutic strategies for AKI can be applied in this very early point.

In the course of our study 27.5% of 160 subjects included developed AKI, defined as acute change in serum creatinine levels compared to baseline. We found higher incidence in patients with prolonged CPB time and advanced age. Urinary KIM-1 measured in the very early post-operative period predicted AKI with AUC 0.84 ($p<0.001$) and urinary KIM-1 to urinary creatinine ratio outperformed with AUC 0.85 ($p<0.001$). Better performance of normalized values is probably due to minimizing the influence of some effective modifiers of absolute values such as volume infusions, or drug interferences in the course of therapy in concrete patients situations.

This study was the first to compare the diagnostic performance of absolute single-point levels of urinary KIM-1 with normalized values for early detection of AKI in Bulgarian adult patients cohort undergoing major on-pump cardiac surgery. It is also the first one to suggest using normalized values as optimal allowing better comparability of results and minimizing the effect of extrarenal variables. A larger multi-center study of adults undergoing CPB is required to confirm both the predictive value of early post-operative levels of urinary KIM-1, and the enhanced diagnostic performance of urinary KIM-1 to urinary creatinine ratio in AKI cases.

7. Acknowledgements

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8. Conflict of Interests

The authors declare that there is no conflict of interests.

References

[1] Moran SM, Myers BD. Course of acute kidney failure studied by a model of creatinine kinetics.-Kidney Int. 1985;27(6):928-937.
[2] Bailly V, Zhang Z, Meier W, et al. Shedding of Kidney Injury Molecule-1, a Putative Adhesion Protein Involved in Renal Regeneration, - The Journal of Biological Chemistry, 277, 2002, 39739-39748.
[3] Bonventre JV, Weinberg JM. Recent advances in pathophysiology of ischemic acute renal failure.-J Am SocNephrol. 2003;14(8):2199-2210.
[4] Bonventre JV. Kidney injury molecule-1 (KIM-1): a urinary biomarker and much more.-Nephrol Dial Transplant. 2009;24:3265-3268.
[5] FDA News. FDA, European medicines agency to consider additional test results when assessing new drug safety collaborative effort by FDA and EMEA expected to yield additional safety data. – FDA News, 2008.
[6] Goldstein SL, Woo JG, et al. Temporal relationship and predictive value of urinary acute kidney injury biomarkers after pediatric cardiopulmonary bypass.-J Am CollCardiol. 2011;58(22):2301-2309.
[7] Han WK, Wagener G, Zhu Y, et al. Urinary biomarkers in the early detection of acute kidney injury after cardiac surgery.-Clin J Am SocNephrol. 2009;4(5):873-882.
[8] Ichimura T, Bonventre JV, Bailly V, et al. Kidney injury molecule-1 (KIM-1), a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury.-J Biol Chem. 1998;273(7):4135-4142.
[9] Levey AS, Greene T, Kusek JW, et al. A simplified equation to predict glomerular filtration rate from serum creatinine.-J Am SocNephrol. 2000;11:155A.
[10] Liangos O, Tighiouart H, Perianayagam MC, et al. Comparative analysis of urinary biomarkers for early detection of acute kidney injury following cardiopulmonary bypass.-Biomarkers. 2009;14(6):423-431.
[11] Van Timmeren MM, van den Heuvel MC, Bailly V, Bakker SJL, van Goor H, Stegeman CA, Tubular kidney injury molecule-1 (KIM-1) in human renal disease.-The Journal of Pathology. 2007;212(2):209-217.