Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Tissue inhibitor metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) best predicts the development of acute kidney injury

Samuel Asamoah Sakyi [a,*], Richard K. Dadzie Ephraim [b], Prince Adoba [a], Benjamin Amoani [c], Tonnies Buckman [a], Richard Mantey [a], Benjamin A. Eghan [d]

[a] Department of Molecular Medicine, School of Medical Sciences, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Ghana
[b] Department of Medical Laboratory Science, School of Allied Health Sciences, College of Health and Allied Sciences, University of Cape Coast, Cape Coast, Ghana
[c] Department of Biomedical Sciences, College of Health and Allied Sciences, School of Allied Health Sciences, University of Cape Coast, Cape Coast, Ghana
[d] Department of Medicine, School of Medical Sciences, Komfo Anokye Teaching Hospital, College of Health Sciences, Kwame Nkrumah University of Science and Technology, Ghana

ABSTRACT

Background: Acute kidney injury (AKI) is routinely diagnosed by creatinine-based guidelines, which is sub-optimal marker after injury due to renal and non-renal factors. This has necessitated the need for more specific and sensitive biomarkers for early detection of AKI in at risk patients. This prospective cross-sectional study used the biomarkers of cell cycle arrest and Neutrophil Gelatinase Associated Lipocalin (NGAL) to assess AKI among hospitalized patients.
Methods: We conveniently enrolled 151 in-patients at the Trauma and Specialist Hospital, Winneba in Ghana. Socio-demographic and clinical information were collected using structured questionnaires. Blood samples were collected for the estimation of serum creatinine, and AKI diagnosed and staged using the KDIGO guideline. Fresh urine samples were collected and urinary NGAL, TIMP-2 (tissue inhibitor metalloproteinase 2) and IGFBP-7 (insulin-like growth factor binding protein 7) were estimated using ELISA kits.
Results: The cell cycle arrest biomarkers and NGAL were significantly (P < 0.001) higher among participants with AKI than those without AKI. [TIMP-2]*[IGFBP-7] showed the best diagnostic performance (AUC = 0.94, CI = 0.90–0.98) followed by [IGFBP-7]*NGAL] (AUC = 0.93, CI = 0.87–0.99), with NGAL having the least (AUC = 0.62, CI = 0.46–0.78). The cut-off for [TIMP-2]*[IGFBP-7] showed the best predictive ability (95.8% sensitivity, 77.2% specificity, 44.2% PPV and 99% NPV). The cut-off for NGAL, on the other hand, showed the least predictive ability (62.5% sensitivity, 42.5% specificity, 17.0% PPV and 85.7% NPV).
Conclusion: Tissue inhibitor metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) best predicts the development of AKI, and can be used in high risk patients for early diagnosis of AKI.

1. Introduction

Acute kidney injury (AKI) is a major complication that contributes to morbidity and mortality especially in critically ill people. The burden of AKI is most significant in developing countries with limited resources for the care of patients once the disease progresses to chronic kidney disease (CKD) or kidney failure necessitating renal replacement therapy [1]. It is therefore crucial to address the case of developing countries in the detection of AKI in its early and potentially reversible stages. Routinely, AKI is diagnosed by the creatinine-based guidelines, which

solely rely on an increase in serum creatinine or decrease in urine volume guidelines [2, 3]. Unfortunately, creatinine is a sub-optimal marker after injury, since levels are often not reflective of glomerular filtration rate (GFR) due to renal and non-renal factors that affect creatinine levels [4]. The diagnosis of AKI may also be delayed or missed in persons with significant fluid shifts or fluid overload [5, 6]. Furthermore, these guidelines require baseline kidney function which is not always available and has led to use of various surrogate estimates such as admission creatinine or back-calculating a baseline creatinine in patients. These methods can, however, inflate or reduce the incidence of

---

AKI in hospitalized patients [2]. There is therefore the need for more specific and sensitive biomarkers for early diagnosis of AKI and prediction of severity of injury. Highly sensitive biomarkers will help physicians initiate early treatment and also help pharmaceutical industries develop better drugs to manage the condition. Also, knowledge on the aetiology of the injury will improve management of affected patients [7].

Several new biomarkers have been developed that enables detection of subtle changes in kidney function before serum creatinine increases and identifies sub-clinical AKI. Tissue inhibitor metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) are markers of cell cycle arrest, depicting stress (before injury) that proceeds the development of AKI [8]. NGAL gene is also known to be up-regulated more than tenfold during the first few hours following ischemic kidney injury in an animal study [9]. Though significant progress has been made in the discovery and validation of these biomarkers, their clinical use is uncertain. In addition, most of the studies which examined the clinical utility of these biomarkers were conducted in developed countries with few studies done in Africa. Also, to the best of our knowledge, this study is the first study to use the cell cycle arrest biomarkers to examine AKI in Ghana, and Sub-Saharan Africa to a larger extent. It is therefore, imperative to evaluate biomarkers of cell cycle arrest (TIMP-2 and IGFBP-7) and NGAL to assess AKI among general hospitalized patients in Ghana.

2. Materials and methods

2.1. Study design and site

This hospital-based prospective cross-sectional study was conducted from June, 2017 to February, 2018 at the Trauma and Specialist Hospital in the Effutu municipality of Ghana. According to the 2010 Population and Housing Census, the Effutu Municipality has a population of 68,592 representing 3.1% of the region's total population. Most (93.3%) of the population in the municipality live in urban communities [10]. The hospital serves as the Central Regional hospital providing Trauma, Orthopedic and general healthcare to people in Winneba and the region as a whole.

2.2. Study participants

Participants for this study included both males and females admitted to the various wards of the hospital. One hundred and eighty (180) in-patients were initially enrolled into the study using convenience sampling. However, blood samples after 48-hours of admission were not obtained from 29 of them, hence withdrawn from the study. Finally, one hundred and fifty-one (151) consenting in-patients admitted at the various wards of the hospital were used for the study.

2.2.1. Exclusion criteria

Patients who did not consent to participating in the study, those with chronic kidney disease and patients with baseline end stage renal disease (ESRD) were excluded from the study.

2.2.2. Ethical consideration

Ethical approval was sought from the Ethics Committee of the hospital and The Committee on Human Research, Publication and Ethics, School of Medical Sciences, Kwame Nkrumah University of Science and Technology (CHRPE/AP/464/17) before commencing the study. Informed written consent was sought from each participant before collecting their data and samples. Participants were informed that they are free to withdraw from the study at any time without affecting their patient care. Figure 1 denote the schematic representation of study.

2.3. Socio-demographic data and clinical history

Information on age, gender, ethnicity, occupation, medication used, diagnosis, co-morbidities, and length of hospital stay and outcome were obtained through interview and from patient's medical records using a structured pre-tested questionnaire.

2.4. Measurement of blood pressure

Blood pressure of the participants were measured by trained personnel using a mercury sphygmomanometer (ACCOSON, England) after patients have rested for 5 min [11]. The mean values of duplicate measurements were recorded.
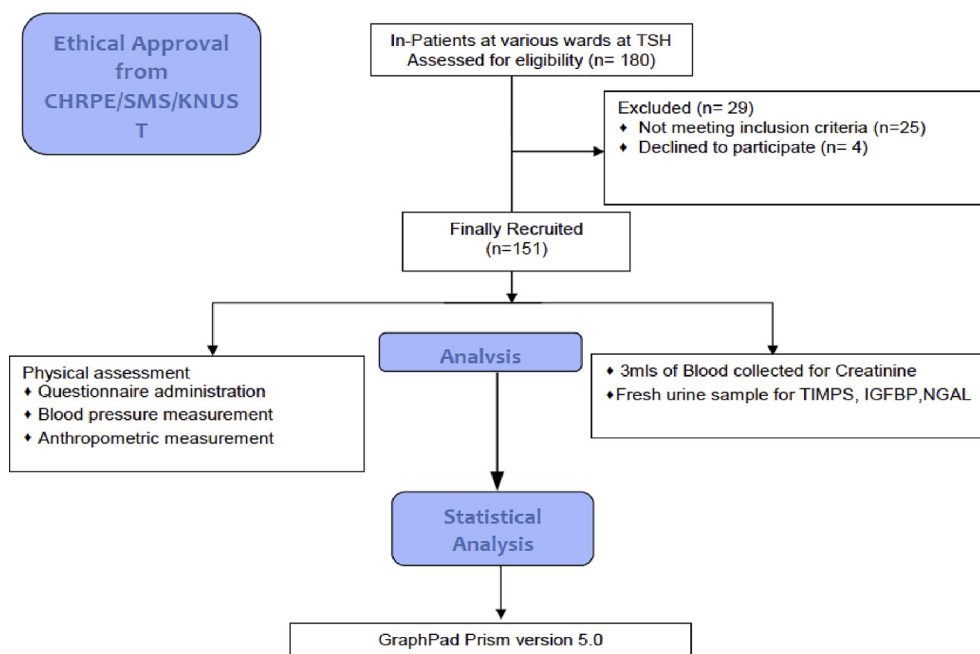

Figure 1. Schematic representation of study.

2.5. Blood sample collection

Three (3) ml of venous blood sample was collected from each participant within 7 days into a serum gel separator tube (Micropoint Diagnostics; Reference KJ040AS). After centrifugation of samples at 1500 g for 5 min, the serum was stored in cryovials at −80 °C (Thermo Scientific™ Revco™ UxF -Ultra-Low Temperature Freezers, USA) until assayed.

2.5.1. Diagnosis and staging of AKI

The serum creatinine levels of the serum samples were measured using Pentra C200 automated chemistry analyzer (Horiba ABX SAS, 34184 Montpellier Cedex 4, France). For participants without preadmission serum creatinine concentration, baseline serum creatinine was calculated using the MDRD equation assuming a GFR of 75 ml/min/1.73m^2. AKI was diagnosed and staged using the KDIGO guideline [12].

2.6. Estimation of biomarkers

Fresh urine samples were collected within 24 h of admission from each patient, centrifuged and the supernatant stored at -80 °C until assayed. Commercially available sandwich ELISA kits were used to estimate urinary NGAL, TIMP-2 and IGFBP-7 using microplate reader (Mindray MR-96A; Shenzhen Mindray Bio-medical electronics Co., Ltd, China) using commercial.

A combination of the biomarkers ([TIMP-2]*[IGFBP-7]; [TIMP-2]*[NGAL]; [IGFBP-7]*[NGAL] in (ng/ml)^2/1000) was calculated by multiplying the biomarkers and dividing by 1000.

2.7. Statistical analysis

Collected data were stored in Microsoft Excel and analyzed using GraphPad prism version 5.0 (GraphPad software, San Diego California USA, www.graphpad.com) and the Statistical Package for Social Sciences (SPSS) Version 21.0 (Chicago IL, USA). Categorical data were expressed in numbers and percentages while continuous data were expressed as Mean ± SD. Chi square test was used to compare proportions of categorical variables. Independent sample t-test was used to compare mean biomarker levels between participants with AKI and those without AKI. Mean biomarker levels among the various AKI stages were represented by mean plots and multiple comparison of means performed using Tukey's Post-Hoc test. Pearson's correlation was used to test the association between the various biomarker levels. Receiver operating characteristics (ROC) curve analysis was used to assess the diagnostic performance of the biomarkers in predicting moderate to severe AKI (KDIGO stage 2 and 3). The optimal cutoffs of the biomarkers were set at the best accuracy (area under the curve) value based on the ROC curve analysis, and their sensitivity, specificity, positive predictive value and negative predictive value for the optimal cutoff value recorded. The multivariate logistic regression was used to determine independent association between cell arrest markers and AKI. A *p*-value less than 0.05 was considered statistically significant for all comparisons.

3. Results

A total of 151 participants were included in the statistical analysis. There was no significant difference in age between males and females (*p* = 0.854). Majority of the participants were within 20–34 years (46.4%). Most (29.8%) of them were admitted to the female ward with the maternity ward having the least number of participants (13.2%). A significant difference was found between the proportions of males and females with respect to ward of admission (P < 0.001). A greater proportion (61.6%) had an optimal blood pressure, 7.3% had pre-hypertension, 9.9% had hypertension and 4% had isolated systolic hypertension (ISH) on admission. No significant difference was found in the mean systolic and diastolic blood pressure between males and females (P > 0.05). Baseline serum creatinine, however, was significantly higher among the males than the females (P < 0.001) (Table 1).

Table 1. General characteristics of study participants.

Parameters	Total (N = 151)	Male (N = 66)	Female (N = 85)	P-value
	n (%)	n (%)	n (%)	
Age (years) (Mean ± SD)	38.00 ± 13.31	37.78 ± 14.78	38.18 ± 12.14	0.854
Age group (years)				0.153
20–34	70 (46.4)	33 (50.0)	37 (43.5)	
35–49	51 (33.8)	21 (31.8)	30 (35.3)	
50–64	24 (15.9)	7 (10.6)	17 (20.0)	
65–79	2 (1.3)	2 (3.0)	0 (0.0)	
≥80	4 (2.6)	3 (4.5)	1 (1.2)	
Ward				**<0.001***
A/E	29 (19.2)	15 (22.7)	14 (16.5)	
Maternity	20 (13.2)	3 (4.5)	17 (20.0)	
Male ward	36 (23.8)	36 (54.5)	0 (0.0)	
Female ward	45 (29.8)	0 (0.0)	45 (52.9)	
Trauma & Orthopedic	21 (13.9)	12 (18.2)	9 (10.6)	
BP				0.685
Optimal	93 (61.6)	45 (68.2)	48 (56.5)	
Normal	26 (17.2)	10 (15.2)	16 (18.8)	
Pre-hypertension	11 (7.3)	4 (6.1)	7 (8.2)	
Hypertension	15 (9.9)	5 (7.6)	10 (11.8)	
ISH	6 (4.0)	2 (3.0)	4 (4.7)	
SBP	116.49 ± 16.58	114.70 ± 15.81	119.18 ± 18.53	0.119
DBP	76.05 ± 11.40	75.20 ± 9.58	78.00 ± 13.32	0.151
Baseline Creatinine (μmol/l)	76.05 ± 11.40	111.87 ± 27.93	92.35 ± 13.91	**<0.001***

Values are presented as frequency, n (%) or Mean ± SD. Chi-square was used to compare between males and females; *p < 0.05 is considered statistically significance difference; A/E: Accident and Emergency; BP: Blood Pressure; ISH: Isolated systolic hypertension; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; p<0.005.

Table 2. Demographic and Clinical Characteristics of Study Participants Stratified by AKI status.

Parameters	KDIGO		
	AKI (N = 44)	No AKI (N = 107)	P-value
Age (years)	36.84 ± 13.13	38.48 ± 13.42	0.495
Age group (years)			0.171
20–34	25 (56.8)	45 (42.1)	
35–49	9 (20.5)	42 (39.3)	
50–64	9 (20.5)	15 (14.0)	
65–79	0 (0.0)	2 (1.9)	
≥80	1 (2.3)	3 (2.8)	
Sex			0.420
Male	17 (38.6)	49 (45.8)	
Female	27 (61.4)	58 (54.2)	
BP			**0.020***
Optimal	20 (45.5)	73 (68.2)	
Normal	7 (15.9)	19 (17.8)	
Pre-hypertension	6 (13.6)	5 (4.7)	
Hypertension	8 (18.2)	7 (6.5)	
ISH	3 (6.8)	3 (2.8)	
SBP (mmHg)	125.45 ± 23.37	113.83 ± 13.08	**<0.001***
DBP (mmHg)	80.11 ± 15.64	75.40 ± 9.69	**0.026***

BP = Blood Pressure; DBP = Diastolic Blood Pressure; SBP = Systolic Blood Pressure; ISH = Isolated Systolic Hypertension.; p<0.005.

Table 3. Reason for admission of participants in relation to AKI status.

Reason for admission	Total	AKI	No AKI
Diabetes mellitus	14 (9.3)	4 (9.1)	10 (9.3)
Hypertension	18 (11.9)	10 (22.7)	8 (7.5)
Trauma	21 (13.9)	8 (18.2)	13 (12.1)
Malignancy	4 (2.6)	1 (2.3)	3 (2.8)
Hepatitis B	12 (7.9)	8 (18.2)	4 (3.7)
HIV/AIDS	6 (4.0)	0 (0.0)	6 (5.6)
Hepatitis C	2 (1.3)	0 (0.0)	2 (1.9)
Obstetrics & Gynaecological	20 (13.2)	6 (13.6)	14 (13.1)
Unknown	54 (35.8)	7 (15.9)	47 (43.9)

Table 4. Mean biomarker levels among participants stratified by AKI status.

| Parameters	AKI (N = 44)	No AKI (N = 107)	P-value
TIMP-2 (ng/ml)	36.52 ± 35.19	9.99 ± 13.90	<0.001
IGFBP-7 (ng/ml)	106.75 ± 93.76	25.05 ± 43.63	<0.001
NGAL (ng/ml)	87.98 ± 114.37	41.57 ± 12.31	<0.001
[TIMP-2][IGFBP-7]/1000 $(ng/ml)^2$	5.02 ± 7.12	0.40 ± 1.08	<0.001
[TIMP-2][NGAL]/1000 $(ng/ml)^2$	4.15 ± 7.80	0.36 ± 0.44	<0.001
[IGFBP-7][NGAL]/1000 $(ng/ml)^2$	14.37 ± 32.67	0.84 ± 1.35	<0.001

Table 2 shows the demographic and clinical characteristics of study participants in relation to AKI status. Majority (56.8%) of the participants with AKI were within 20–34 years. AKI was present in 61.4% of the females and 38.6% of the males. Among the participants with AKI, 13.6% had pre-hypertension, 18.2% had hypertension and 6.8% had ISH. A significant difference was found in blood pressure between proportion of participants with AKI and those without AKI (P = 0.020). Mean systolic (P < 0.001) and diastolic (P = 0.026) blood pressure were also significantly higher among participants with AKI than those without AKI (Table 2).

Table 3 expatiates on the causes of admission of study participants. Diabetes mellitus and hypertension were present in 9.3% and 11.9% respectively of the participants. The diagnosis of majority of them (35.8%) were unknown. AKI was commonest among participants with hypertension (22.7%) followed by hepatitis B (18.2%) and trauma (18.2%). None of the participants with HIV (0.0%) and hepatitis C infections (0.0%) had AKI (Table 3).

Figure 2 illustrates the AKI stage among participants when KDIGO guideline and RIFLE criteria were used respectively. Stage 1 AKI was found in 13.2% of the participants, followed by stage 2 (9.3%) and stage 3 (6.6%) (Figure 2).

Table 4 presents mean biomarker levels among participants stratified by AKI status. The level of biomarkers TIMP-2, IGFBP-7, NGAL, [TIMP-2]*[IGFBP-7], [TIMP-2]*[NGAL], [IGFBP-7]*[NGAL], were significantly increased in participants with AKI compared to those without AKI (P < 0.001).

Figure 3 illustrates mean biomarker levels in relation to AKI stages. Mean levels of TIMP-2, IGFBP-7, [TIMP-2]*[IGFBP-7], [TIMP-2]*[NGAL], [IGFBP-7]*[NGAL] increased with increasing AKI severity stage (Stage 3 > Stage 2 > Stage 1 > No AKI). On the contrary, NGAL level decreased in Stage 2 AKI with a subsequent rise in Stage 3.
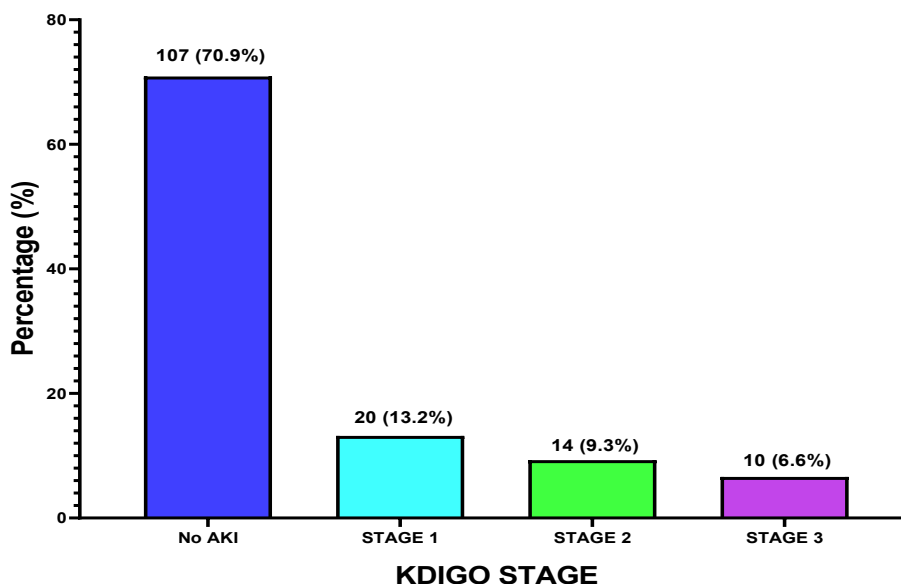
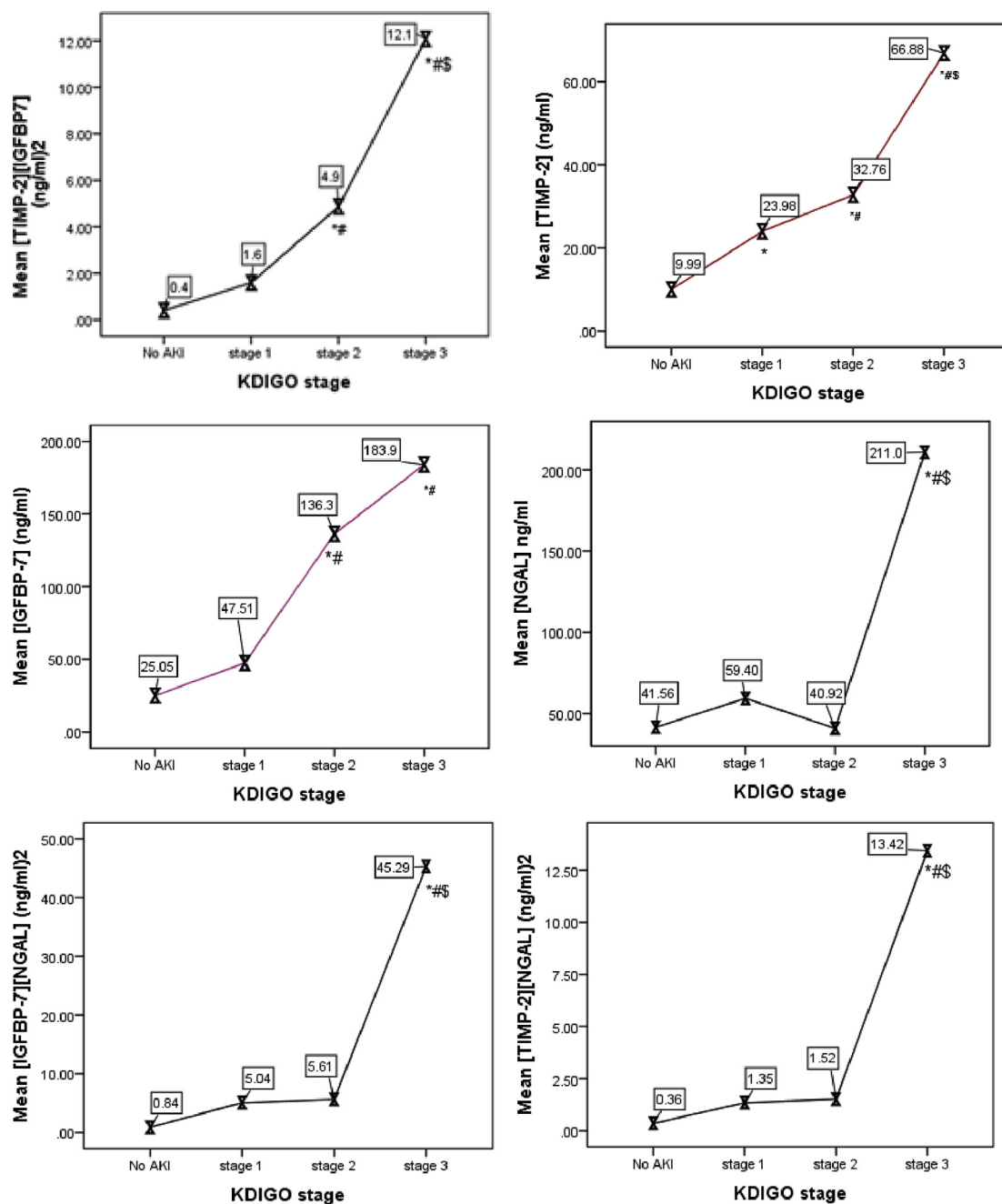**Figure 2.** AKI stages among study participants using KDIGO guidelines.

Figure 3. Mean biomarker levels in relation to KDIGO AKI stage. Graphs present mean plots of biomarkers among various AKI stages. Multiple comparison was performed using Tukey's Post-hoc test; *: represents statistical difference from No AKI group; #: represents statistical difference from Stage 1; $: represents statistical difference from Stage 2.

Table 5. Association between biomarkers and AKI.

Biomarker	aOR	95% CI	P-value
TIMP-2	1.57	1.35–3.92	**0.021**
IGFBP-7	4.09	1.32–12.72	**<0.001**
NGAL	0.82	0.36–1.20	0.802
[TIMP-2]*[IGFBP-7]	7.26	1.64–32.20	**<0.001**
[TIMP-2]*[NGAL]	1.93	1.46–4.89	**<0.001**
[IGFBP-7][*NGAL]	2.82	1.93–8.60	**0.033**

aOR: Adjusted odd's ratio. p <0.005.

After adjusting for sex and age in a multivariate logistic regression, increasing TIMP2 [aOR (95% CI) = 1.57 (1.35–3.92), $p = 0.021$], IGFBP [aOR (95% CI) = 4.09 (1.32–12.72), $p < 0.001$], [TIMP-2]*[IGFBP-7] [aOR (95% CI) = 7.26 (1.64–32.20), $p < 0.001$], [TIMP-2]*[NGAL] [aOR (95% CI) = 1.93 (1.46–4.89), $p < 0.001$], [IGFBP-7][*NGAL] [aOR (95% CI) = 2.82 (1.93–8.60), $p < 0.033$] were significantly associated with increased odds of AKI. However, NGAL was not associated with AKI (Table 5).

Figure 4 and Table 6 presents the ROC curves and diagnostic performance of biomarkers in predicting AKI stages 2 and 3. [TIMP-2]*[IGFBP-7] showed the best diagnostic performance (AUC = 0.94, CI = 0.90–0.98) followed by [IGFBP-7]*NGAL] (AUC = 0.93, CI = 0.87–0.99), IGFBP-7 (AUC = 0.91, CI = 0.4–0.98), [TIMP-2]*[NGAL] (AUC = 0.88,
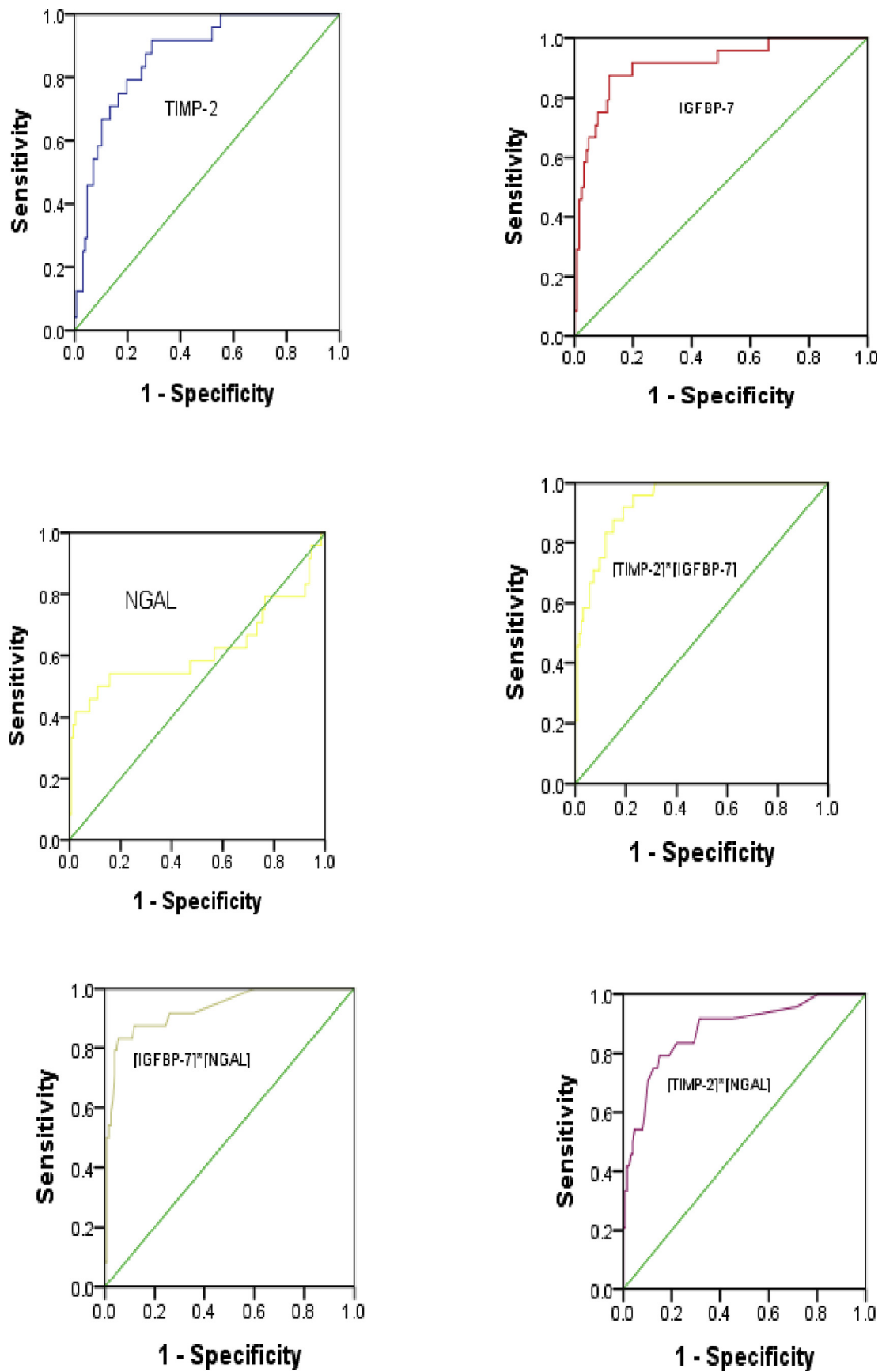
Figure 4. Receiver Operating Characteristics (ROC) curves of biomarkers in predicting AKI stages 2 and 3.

Table 6. Diagnostic performance of biomarkers in predicting KDIGO AKI stage 2 and 3.

Biomarkers	cut-off	AUC	Sens (%)	Spec (%)	PPV (%)	NPV (%)	P-value
TIMP-2	15.59	0.87 (0.80–0.94)	83.3	74.8	38.5	96.0	<0.001
IGFBP-7	40.68	0.91 (0.4–0.98)	91.7	80.3	46.8	98.1	<0.001
NGAL	39.20	0.62 (0.46–0.78)	62.5	42.5	17.0	85.7	0.065
[TIMP-2]* [IGFBP-7]	0.30	0.94 (0.90–0.98)	95.8	77.2	44.2	99.0	<0.001
[TIMP-2]* [NGAL]	0.65	0.88 (0.80–0.96)	83.3	78.0	41.7	96.1	<0.001
[IGFBP-7]* NGAL]	0.75	0.93 (0.87–0.99)	91.7	74.0	40.0	97.9	<0.001

AUC: Area under Curve; Sens: Sensitivity; Spec: Specificity; PPV: Positive Predictive Value; NPV: Negative Predictive Value. p< 0.005.

CI = 0.80–0.96), TIMP-2 (AUC = 0.87, CI = 0.80–0.94) and NGAL (AUC = 0.62, CI = 0.46–0.78).

The best predictive cut-off values of the biomarkers were 15.59 for TIMP-2, 40.68 for IGFBP-7, 39.20 for NGAL, 0.30 for [TIMP-2]*[IGFBP-7], 0.65 for [TIMP-2]*[NGAL] and 0.75 for [IGFBP-7]*[NGAL]. The cut-off for [TIMP-2]*[IGFBP-7] showed the best predictive ability (95.8% sensitivity, 77.2% specificity, 44.2% PPV and 99% NPV). The cut-off for NGAL, on the other hand, showed the least predictive ability (62.5% sensitivity, 42.5% specificity, 17.0% PPV and 85.7% NPV).

4. Discussion

This study assessed the use of cell cycle arrest biomarkers and NGAL in diagnosis of AKI and prediction of moderate to severe AKI (KDIGO stages 2 and 3) among hospitalized patients. Moderate to severe AKI was chosen rather than all AKI because this severity has been associated with significant increase in incidence of clinically important outcomes such as need for renal replacement therapy, hospital mortality, and persistent renal dysfunction [13, 14, 15]. Urinary [TIMP-2]*[IGFBP-7] had the best diagnostic performance in predicting KDIGO AKI stage 2 and 3, with a best cut-off value of 0.3.

In a discovery and validation study by Kashani et al. [13] in the United States of America (USA), two cell cycle arrest markers (TIMP-2 and IGFBP-7) were found to better predict AKI, and increased significantly in patients with AKI. This is consistent with the significantly higher TIMP-2 and IGFBP-7 among participants who had AKI than those without AKI in our study. Combination of these cell cycle arrest biomarkers ([TIMP-2]* [IGFBP-7]) by [13] was also higher in patients with AKI than those without AKI, and increased with increasing AKI severity stage. This is also similar to the finding of higher [TIMP-2]*[IGFBP-7] level in participants who had AKI in this study than those without AKI. Also, mean level of [TIMP-2]* [IGFBP-7] increased as AKI stage increased in this study. Honore et al. [16] also observed a higher concentration of [TIMP-2]*[IGFBP-7] among sepsis patients who developed AKI than those who did not. Wetz et al. [17] found levels of urinary [TIMP-2]*[IGFBP7] to be higher in the patients who developed AKI after cardiac surgery than those that did not. TIMP2 and IGFBP7 play a role in the G1 cell-cycle arrest phase during the very early phases of cellular stress. Renal tubular cells also go through this G1 cell-cycle arrest phase after stress due to a variety of insults. Cell-cycle arrest signaling is a protective response by multiple cells, but is only detectable in urine following AKI [18].

NGAL has been found to be expressed on the apical epithelial membranes of the distal nephron following AKI, and excreted in the urine through exocytosis [19]. NGAL production has been shown to be dramatically upregulated following renal injury. In this study, urine NGAL significantly increased in participants with AKI compared to those without AKI. De Geus et al. [20] also reported a higher urine NGAL level among ICU patients who developed AKI than those who did not. Zweirs et al. [21] found significantly higher urine NGAL levels among critically ill children who developed AKI. A combination of each of the cell cycle arrest biomarkers and NGAL ([TIMP-2]*[NGAL] and [IGFBP-7]* [NGAL]) were significantly increased in participants with AKI compared to those without AKI. The levels also increased with in increasing AKI

severity, indicating its probable use in monitoring progression of the condition.

Urinary [TIMP-2]*[IGFBP-7] showed the best diagnostic performance in predicting moderate to severe AKI (KDIGO stage 2 and 3) within 24 h of admission, with an AUC of 0.94. A cut-off value of 0.3 was also found to predict moderate to severe AKI. A study by Hoste et al. [15] and Kashani et al. [13] also found a cut-off of 0.3 to best predict AKI stage 2 and 3. Kimmel et al. [22] and Gunnerson et al. [23] also obtained a cut-off of 0.3. However, Honore et al. [16] among sepsis patients, Dusse et al. [24] among patients who have undergone aortic valve transplantation, Pilarczyk [25] after coronary artery bypass surgery found higher cut-off values.

In the study by Kashani et al. [13] among intensive care unit patients in the United States of America (USA), IGFBP7 and TIMP-2 showed an AUC of 0.76 and 0.79 respectively. However, IGFBP-7 had a higher AUC (0.91) than TIMP-2 (AUC = 0.87) in this study. Yamashita et al. [26] observed urinary [TIMP-2] to perform well in predicting severe AKI in critically ill patients with and without sepsis with a ROC AUC range of 0.81–0.84. The findings in this study indicates a better ability of IGFBP-7 in predicting KDIGO AKI stage 2 and 3 than TIMP-2 in our setting.

Urinary NGAL had the least predictive ability with an AUC of 0.62. Kashani et al. [13] also found NGAL to have the least predictive ability when compared to the cell cycle arrest biomarkers [27]. The better predictive ability of the cycle arrest biomarkers compared to urine NGAL could be explained by the fact that the cell cycle arrest biomarkers are stress markers which signal cells of impending injury. Hence the stress markers increase before injury occurs while NGAL increases after tubular injury has occurred [18]. A cut-off of 39.2 was found to predict AKI stage 2 and 3 among our participants.

The predictive ability of a combination of a stress biomarker with a tubular biomarker (NGAL) was also examined. A combination of NGAL and IGFBP-7 ([IGFBP-7]*NGAL]) was the second best marker in predicting AKI stage 2 and 3 (AUC = 0.93). A cut-off of 0.75 was obtained with a sensitivity of 91.7% and a specificity of 74%. This shows [IGFBP-7]*[NGAL] as another biomarker which needs to be further investigated for early prediction of AKI. Hence, a combination of stress biomarker and injury biomarker may be of diagnostic importance in predicting AKI.

This study has strength in it being the first study to use the cell cycle arrest biomarkers to assess AKI among patients in Sub-Saharan Africa, to the best of our knowledge. However it is limited by the small sample size, non-availability of preadmission serum creatinine and 24-hour urine output, and inability to examine other novel biomarkers.

5. Conclusion

Urinary Tissue inhibitor metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) best predicts the development of AKI, and can be used in high risk patients for early diagnosis of AKI among hospitalized patients. Urinary [TIMP-2] *[IGFBP-7] is an early marker for AKI and had the best diagnostic performance in predicting KDIGO AKI stage 2 and 3. A combination of NGAL and IGFBP-7 ([IGFBP-7]*NGAL]) was the second best marker in predicting AKI stage 2 and 3. NGAL had the least predictive ability.

References

[1] D.E. Yousif, A.R. Topping, M.F. Osman, et al., Acute kidney injury in sub-sahara Africa: a single-center experience from khartoum, Sudan, Blood Purif. 45 (2018) 201–207.

[2] M.E. Thomas, C. Blaine, A. Dawnay, et al., The definition of acute kidney injury and its use in practice, Kidney Int. 87 (2015) 62–73.

[3] A.K. Roy, C. Mc Gorrian, C. Treacy, et al., A comparison of traditional and novel definitions (RIFLE, AKIN, and KDIGO) of acute kidney injury for the prediction of outcomes in acute decompensated heart failure, Cardiorenal Med. 3 (2013) 26–37.

[4] M. Schetz, J. Gunst, G. Van den Berghe, The impact of using estimated GFR versus creatinine clearance on the evaluation of recovery from acute kidney injury in the ICU, Intensive Care Med. 40 (2014) 1709–1717.

[5] K.D. Liu, B.T. Thompson, M. Ancukiewicz, et al., Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes, Crit. Care Med. 39 (2011) 2665–2671.

[6] E. Macedo, J. Bouchard, S.H. Soroko, et al., Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients, Crit. Care 14 (2010) R82.

[7] V.S. Vaidya, M.A. Ferguson, J.V. Bonventre, Biomarkers of acute kidney injury, Annu. Rev. Pharmacol. Toxicol. 48 (2008) 463–493.

[8] C. Ronco, Acute kidney injury: from clinical to molecular diagnosis, Crit. Care 20 (2016) 201.

[9] J. Mishra, Q. Ma, A. Prada, et al., Identification of neutrophil gelatinase-associated lipocalin as a novel early urinary biomarker for ischemic renal injury, J. Am. Soc. Nephrol.: JASN (J. Am. Soc. Nephrol.) 14 (2003) 2534–2543.

[10] Ghana Statistical Service, 2010 Population & Housing Census. Ghana, 2014.

[11] T.G. Pickering, J.E. Hall, L.J. Appel, et al., Recommendations for blood pressure measurement in humans and experimental animals: Part 1: blood pressure measurement in humans: a statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research, Hypertension 45 (2005) 142–161.

[12] KDIGO. Kidney Disease, Improving Global Outcomes (KDIGO) clinical practice guideline for acute kidney injury, Kidney Int. 2 (2012) 1–138.

[13] K. Kashani, A. Al-Khafaji, T. Ardiles, et al., Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury, Crit. Care 17 (2013) R25.

[14] A. Bihorac, L.S. Chawla, A.D. Shaw, et al., Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication, Am. J. Respir. Crit. Care Med. 189 (2014) 932–939.

[15] E.A. Hoste, P.A. McCullough, K. Kashani, et al., Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers, Nephrol. Dial. Transplant. 29 (2014) 2054–2061.

[16] P.M. Honore, H.B. Nguyen, M. Gong, et al., Urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 for risk stratification of acute kidney injury in patients with sepsis, Crit. Care Med. 44 (2016) 1851–1860.

[17] A.J. Wetz, E.M. Richardt, S. Wand, et al., Quantification of urinary TIMP-2 and IGFBP-7: an adequate diagnostic test to predict acute kidney injury after cardiac surgery? Crit. Care 19 (2015) 3.

[18] J.A. Kellum, F.E. Sileanu, R. Murugan, et al., Classifying AKI by urine output versus serum creatinine level, J. Am. Soc. Nephrol.: JASN (J. Am. Soc. Nephrol.) 26 (2015) 2231–2238.

[19] K.M. Schmidt-Ott, Neutrophil gelatinase-associated lipocalin as a biomarker of acute kidney injury-where do we stand today? Nephrol. Dial. Transplant. 26 (2006) 762–764.

[20] H.R. de Geus, J. Bakker, E.M. Lesaffre, et al., Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients, Am. J. Respir. Crit. Care Med. 183 (2011) 907–914.

[21] A.J. Zwiers, S.N. de Wildt, J. van Rosmalen, et al., Urinary neutrophil gelatinase-associated lipocalin identifies critically ill young children with acute kidney injury following intensive care admission: a prospective cohort study, Crit. Care 19 (2015) 181.

[22] M. Kimmel, J. Shi, J. Latus, et al., Association of renal stress/damage and filtration biomarkers with subsequent AKI during hospitalization among patients presenting to the emergency department, Clin. J. Am. Soc. Nephrol.: CJASN 11 (2016) 938–946.

[23] K.J. Gunnerson, A.D. Shaw, L.S. Chawla, et al., TIMP2*IGFBP7 biomarker panel accurately predicts acute kidney injury in high-risk surgical patients, J. Traum. Acute Care Surg. 80 (2016) 243–249.

[24] F. Dusse, M. Edayadiyil-Dudasova, M. Thielmann, et al., Early prediction of acute kidney injury after transapical and transaortic aortic valve implantation with urinary G1 cell cycle arrest biomarkers, BMC Anesthesiol. 16 (2016) 76.

[25] K. Pilarczyk, M. Edayadiyil-Dudasova, D. Wendt, et al., Urinary [TIMP-2]*[IGFBP7] for early prediction of acute kidney injury after coronary artery bypass surgery, Ann. Intensive Care 5 (2015) 50.

[26] T. Yamashita, K. Doi, Y. Hamasaki, et al., Evaluation of urinary tissue inhibitor of metalloproteinase-2 in acute kidney injury: a prospective observational study, Crit. Care 18 (2014) 716.

[27] M. Haase, A. Haase-Fielitz, Can novel biomarkers complement best possible clinical assessment for early acute kidney injury diagnosis? J. Am. Coll. Cardiol. 58 (2011) 2310–2312.