Research Article

Combining Serum Cystatin C and Urinary N-Acetyl-Beta-D-Glucosaminidase Improves the Precision for Acute Kidney Injury Diagnosis after Resection of Intracranial Space-Occupying Lesions

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Keywords

Acute kidney injury · Cystatin C · Intracranial space-occupying lesion · Neurosurgery · N-acetyl-β-D-glucosaminidase

Abstract

Background: Postoperative acute kidney injury (AKI) is frequent and associated with adverse outcomes. Unfortunately, the early diagnosis of AKI remains a challenge. Combining functional and tubular damage biomarkers may provide better precision for AKI detection. However, the diagnostic accuracy of this combination for AKI after neurosurgery is unclear. Serum cystatin C (sCysC) and urinary albumin/creatinine ratio (uACR) are considered functional bio-

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markers, while urinary N-acetyl- β -D-glucosaminidase (uNAG) represents tubular damage. We aimed to assess the performances of these clinical available biomarkers and their combinations for AKI prediction after resection of intracranial space-occupying lesions. **Methods:** A prospective study was conducted, enrolling adults undergoing resection of intracranial space-occupying lesions and admitted to the neurosurgical intensive care unit. The discriminative abilities of postoperative sCysC, uNAG, uACR, and their combinations in predicting AKI were compared using the area under the receiver operating characteristic curve (AUC-ROC), continuous net reclassification index (cNRI), and incremental discrimination improvement (IDI). **Results:** Of 605 enrolled patients, AKI occurred in 67 patients. The cutoff values of sCysC, uNAG, and uACR to predict postoperative AKI were 0.72 mg/L, 19.98 U/g creatinine, and 44.21 mg/g creatinine, respectively. For predicting AKI, the composite of sCysC and uNAG (AUC-ROC = 0.785) outperformed either individual biomarkers or the other two panels (uNAG plus uACR or sCysC plus uACR). Adding this panel to the predictive model improved the AUC-ROC to 0.808. Moreover, this combination significantly improved risk reclassification over the clinical model alone, with cNRI (0.633) and IDI (0.076). Superior performance of this panel was further confirmed with bootstrap internal validation. **Conclusions:** Combination of functional and tubular damage biomarkers improves the predictive accuracy for AKI after resection of intracranial space-occupying lesions.

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Introduction

Acute kidney injury (AKI) is a frequent complication in the postsurgical population and associated with longer length of stay, significantly higher costs, and increased rates of mortality and morbidity [1, 2]. Early identification of AKI is crucial to guide management. Unfortunately, AKI represents a multifactorial and complex clinical condition, and thus early diagnosis of postoperative AKI remains a challenge. Accordingly, the Acute Dialysis Quality Initiative (ADQI) working group recommended a combination of functional and tubular damage biomarkers for detecting AKI, which reflects different underlying pathological processes of AKI [3]. Recently, combining functional and tubular damage biomarkers was reported as an effective clinical strategy for detecting AKI, including patients after cardiac surgery [4, 5] or patients suffering from heart failure [6]. However, limited data are available regarding the prognostic utility of the abovementioned composite in predicting AKI after neurosurgery, which is a well-known high-risk surgery.

Urinary N-acetyl- β -D-glucosaminidase (uNAG) is a tubular damage biomarker [7, 8], while serum cystatin C (sCysC) and urinary albumin/creatinine ratio (uACR) are glomerular filtration biomarkers [7]. Besides, these clinically available biomarkers are considered markers for AKI detection worldwide [7–13]. On this ground, we conducted a prospective, observational study in an adult neurological intensive care unit (ICU) to assess the performance of combinations of these biomarkers for AKI prediction in patients undergoing resection of intracranial space-occupying lesions.

Patients and Methods

Patient Population

The prospective observational study was conducted in a neurosurgical ICU of a tertiary care hospital. All patients (aged 18 years or older) who underwent resection of intracranial space-occupying lesions and were admitted to the neurosurgical ICU between October 2014

and July 2016 were included. The exclusion criteria included presence of AKI before surgery, preexisting end-stage renal disease or renal dysfunction requiring renal replacement therapy before operation, preexisting renal transplantation, preexisting nephrectomy, pregnancy, and refusal of consent or missing admission data.

Data Collection

Each patient's clinical data were prospectively collected from electronic patient medical records and laboratory databases. The following variables were recorded: age, sex, body mass index, smoking, preexisting clinical conditions, previous resection of intracranial space-occupying lesions, American Society of Anesthesiologists classification, preoperative use of nephrotoxic drugs, preoperative administration of radiographic contrast or mannitol, and diagnostic group (intracranial hematoma, meningioma, glioma, pituitary tumor, schwannoma, craniopharyngioma, metastatic carcinoma, and others). Blood and urinary samples were measured at the central laboratory of our hospital using the same standard protocol. Laboratory values included level of baseline serum creatinine (sCr), preoperative hemoglobin, as well as postoperative sCr and hemoglobin. sCr was also measured after operation at ICU admission and thereafter at least once a day as part of routine clinical care during ICU hospitalization. We also recorded the hourly urine output of each patient from enrollment to ICU discharge. The baseline estimated glomerular filtration rate (eGFR) was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation [14]. The pre- and postoperative Glasgow Coma Scale (GCS) score and the postoperative Acute Physiology and Chronic Health Evaluation (APACHE II) score were used to evaluate disease severity. They were assessed immediately after patients had recovered from anesthesia. Reoperation within 3 days after first operation was recorded. Additionally, we collected the levels of pre- and postoperative serum sodium and potassium and calculated the changes in serum sodium concentration from first post- to preoperative check (Δ serum sodium) and the changes in serum potassium concentration from first post- to preoperative check (Δ serum potassium).

Surgical data were recorded, including duration of surgery, lowest mean arterial pressure (i.e., lowest mean arterial pressure for at least five continuous minutes) during anesthesia, estimated amount of intraoperative blood loss, and amount and type of intraoperative fluids administered (crystalloid, artificial colloid, red blood cells, plasma, and mannitol). Outcome variables, including duration of postoperative mechanical ventilation, incidence of postoperative tracheotomy, total ICU and in-hospital costs, ICU and in-hospital mortality, and length of stay in hospital and ICU, were also recorded.

Clinical symptoms and the requirement of neurosurgical technique vary between infra- and supratentorial space-occupying lesions [15–17]. The infratentorial region includes the cerebellum, the brain stem, and the fourth ventricle, while the supratentorial region includes the cerebral hemispheres, the lateral ventricle, the pineal region, the sella region, and the third ventricle. According to the brain region involved in the surgery, patients were classified into two groups: an infratentorial region group and a supratentorial region group.

Biomarker Assays

Postoperative sCysC, uNAG, and urinary albumin were measured once at ICU admission, using the UniCel DxH 800 Synchron System (Beckman Coulter, Brea, CA, USA) in the central laboratory of our hospital. The inter- and intra-assay coefficients of variation for urinary albumin were <10%, respectively, the coefficients of inter- and intra-assay variation for uNAG $\leq$ 10%, respectively. The coefficients of inter- and intra-assay variation in sCysC were <5% and $\leq$ 10%, respectively. Both the values of urinary albumin and uNAG were normalized to urinary creatinine concentration. The personnel measuring the biomarkers were blinded to each patient's clinical characteristics. According to previous studies, urinary albumin will not

degrade obviously within short-term storage [18, 19], and the stability of uNAG and sCysC has been displayed [20–22]. Therefore, pre-analysis of the samples regarding the influence of cooling or freezing was not conducted.

Outcome and Definitions

The outcome was the occurrence of AKI within 72 h after surgery. AKI was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for AKI [23] as any of the following: increase in sCr by ≥ 0.3 mg/dL (≥ 26.5 μ mol/L) within 48 h, or increase in sCr to ≥ 1.5 times baseline within 1 week, or urine output < 0.5 mL/kg/h for 6 h. AKI is staged according to the following KDIGO criteria. Stage 1: increase of sCr to 1.5–1.9 times from baseline, or ≥ 0.3 mg/dL (≥ 26.5 μ mol/L) increase of sCr, or urine output < 0.5 mL/kg/h for 6–12 h. Stage 2: increase of sCr to 2.0–2.9 times from baseline or urine output < 0.5 mL/kg/h for ≥ 12 h. Stage 3: increase of sCr to 3.0 times from baseline, or ≥ 4.0 mg/dL (≥ 353.6 μ mol/L) increase of sCr, or initiation of renal replacement therapy, or urine output < 0.3 mL/kg/h for ≥ 24 h, or anuria for ≥ 12 h.

Baseline creatinine was determined by using the following rules ranked in descending order of preference as previously described [24]: (1) the most recent pre-ICU value between 30 and 365 days before ICU admission ($n = 52$); (2) a stable pre-ICU value > 365 days for patients aged < 40 years (stable defined as within 15% of the lowest ICU measurement) before ICU admission ($n = 3$); (3) pre-ICU value > 365 days before ICU admission and less than the initial sCr on ICU admission ($n = 12$); (4) pre-ICU value (between 3 and 39 days before ICU admission) less than or equal to the initial on-admission sCr to ICU and not obviously in AKI ($n = 351$); (5) the lowest initial on-admission sCr to ICU ($n = 81$), the last ICU value ($n = 56$), or the minimum value at follow-up to 365 days ($n = 50$).

Statistical Analysis

We calculated that the postoperative AKI rate in patients who underwent resection of intracranial space-occupying lesion was 12%, which we determined in a chart review (unpublished). Based on a previous study described by Hanley and McNeil [25], we estimated that a sample size of 573 patients was required, with a two-sided test (α error = 5%; power = 90%). Considering a possible dropout rate of 10%, we would need approximately 630 cases.

SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA), R version 3.3.0 for Windows (R Foundation for Statistical Computing, Vienna, Austria), and MedCalc version 12.5.0 for Windows (MedCalc Software, Ostend, Belgium) were used to complete the analysis. Continuous variables were expressed as medians with interquartile range or mean $\pm$ standard deviation. Categorical variables were expressed as number (percentage). To compare the nonnormally distributed continuous variables, the Wilcoxon rank-sum test was used. The categorical variables were compared by the χ^2 or the Fisher exact test. The renal biomarkers displayed nonnormal distributions, and thus the Spearman correlation was used to assess the correlation. Based on a previous report [26], we described the correlation coefficient using the following values: 0.90–1.0 = very strong, 0.70–0.89 = strong, 0.40–0.69 = moderate, 0.10–0.39 = weak, and 0.00–0.09 = negligible correlation. The receiver operating characteristic (ROC) curves with their area under the ROC curve (AUC-ROC) were calculated. The comparison of AUC-ROC between the groups was conducted with the method of DeLong et al. [27], and the combination with the highest AUC-ROC was included in the subsequent analyses. The sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratios of the biomarkers were also analyzed. The optimal cutoff values for AKI detection were defined for individual biomarkers and their combinations according to the Youden index [28]. We conducted uni- and multivariate logistic regression to construct the clinical model for postoperative AKI. The clinical perioperative variables with $p < 0.10$ in univariate

Fig. 1. Flowchart for patient selection. AKI, acute kidney injury; ESRD, end-stage renal disease; RRT, renal replacement therapy.

analysis were all included in the multivariate analysis. Logistic multivariate forward stepwise (likelihood ratio) regression was then used to construct the clinical risk prediction model. The odds ratio and 95% confidence interval were calculated. The performance of the optimal panel combining with the clinical model was assessed by AUC-ROC, incremental discrimination improvement (IDI), and net reclassification index (NRI), as described previously [29, 30]. The NRI and IDI are the extensions of the reclassification idea [30, 31]. The NRI [30] mainly focuses on reclassification tables which are constructed separately for patients with and without event. The NRI calculates the correct movement in the categories “upwards” for patients with event and “downwards” for patients without event. For patients with event, any “upward” movement indicates improved reclassification, whereas any “downward” movement implies worse reclassification. For patients without event, the interpretation is opposite. Thus, the NRI is the sum of the improvement in reclassification. Here, the continuous NRI (cNRI) was calculated. On the other hand, IDI mainly focuses on the differences between integrated (average) sensitivities and “one minus specificities” for risk models with and without adding new markers. Thus, IDI is the value to integrate all the NRI possible cutoffs for the event’s probability. The performance of the optimal panel for AKI prediction was internally validated by a bootstrap method with 1,000 replications [32]. All tests were two-tailed, and $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics and Outcomes of Patients

Of the 648 consecutive patients who were screened for inclusion in the study, 43 (6.6%) were excluded (Fig. 1). For the analyses, 605 patients were enrolled. The baseline characteristics and outcomes of patients are summarized in Table 1. Overall, AKI based on the KDIGO criteria occurred in 67 patients (11.1%) within the first 72 h after surgery. Of these AKI patients, 60 (89.6%) were at stage 1 and 7 (10.4%) at stage 2. Compared with the non-AKI patients, the AKI patients were older. Emergency surgery was done most in the AKI group (16.4 vs. 1.7%, $p < 0.001$). Additionally, patients with AKI had higher American Society of Anesthesiologists classification scores and were treated with more mannitol preoperatively compared to patients without AKI. However, AKI patients did not take more nephrotoxic

Table 1. Baseline characteristics and outcomes of patients with and without postoperative AKI

Characteristics	All patients (n = 605)	Non-AKI (n = 538)	AKI (n = 67)	p value
Age, years	52 (39–60)	51 (38–60)	59 (47–68)	<0.001
Male	300 (49.6%)	260 (48.3%)	40 (59.7%)	0.079
Body mass index	22.2 (20.8–23.4)	22.2 (20.8–23.5)	22.1 (21.4–23.3)	0.801
Smoking	31 (5.1%)	30 (5.6%)	1 (1.5%)	0.237
Preexisting clinical conditions				
Hypertension	62 (10.2%)	51 (9.5%)	11 (16.4%)	0.077
Diabetes mellitus	31 (5.1%)	25 (4.6%)	6 (9.0%)	0.140
Chronic kidney disease	5 (0.8%)	3 (0.6%)	2 (3.0%)	0.097
Cerebrovascular disease	22 (3.6%)	17 (3.2%)	5 (7.5%)	0.085
Coronary artery disease	6 (0.8%)	5 (0.7%)	1 (1.5%)	0.445
Malignancy	71 (11.7%)	63 (11.7%)	8 (11.9%)	0.956
Previous resection of ICSOL	53 (8.8%)	46 (8.6%)	7 (10.4%)	0.604
Baseline serum creatinine, mg/dL	0.70 (0.61–0.84)	0.71 (0.61–0.84)	0.67 (0.55–0.79)	0.066
Baseline eGFR, mL/min/1.73 m ²	106 (95–118)	106 (95–118)	103 (95–115)	0.269
Preoperative medication				
Radiographic contrast	16 (2.6%)	13 (2.4%)	3 (4.5%)	0.405
Nephrotoxic drugs ^a	14 (2.2%)	12 (2.3%)	2 (3.0%)	0.666
Accumulative doses of mannitol, mL	0 (0.0–0.0)	0 (0.0–0.0)	0 (0–250)	0.019
Baseline hemoglobin, g/L	134 (124–145)	135 (124–144)	132 (119–150)	0.700
ASA classification				0.012
I	170 (28.1%)	156 (29.0%)	14 (20.9%)	
II	386 (63.8%)	346 (64.3%)	40 (59.7%)	
III	40 (6.6%)	30 (5.6%)	10 (14.9%)	
IV	9 (1.5%)	6 (1.1%)	3 (4.5%)	
V	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Preoperative serum sodium, mmol/L	139.8 (138.1–141.4)	139.7 (138.1–141.4)	140.1 (138.3–142.2)	0.256
Preoperative serum potassium, mmol/L	3.9 (3.7–4.1)	3.9 (3.7–4.1)	3.9 (3.6–4.1)	0.352
Preoperative GCS score	15 (15–15)	15 (15–15)	15 (15–15)	<0.001
Emergency surgery	20 (3.3%)	9 (1.7%)	11 (16.4%)	<0.001
Diagnostic group				0.001
Intracranial hematoma	20 (3.3%)	9 (1.7%)	11 (16.4%)	
Meningioma	178 (29.4%)	156 (29.0%)	22 (32.8%)	
Glioma	102 (16.9%)	94 (17.5%)	8 (11.9%)	
Pituitary tumor	84 (13.9%)	78 (14.5%)	6 (9.0%)	
Schwannoma	64 (10.6%)	61 (11.3%)	3 (4.5%)	
Craniopharyngioma	20 (3.3%)	17 (3.2%)	3 (4.5%)	
Metastatic carcinoma	56 (9.3%)	49 (9.1%)	7 (10.4%)	
Others ^b	81 (13.4%)	74 (13.8%)	7 (10.4%)	
Outcomes				
Duration of mechanical ventilation, h	3 (1–5)	3 (1–5)	5 (2–13)	<0.001
Tracheotomy	15 (2.5%)	7 (1.3%)	8 (11.9%)	<0.001
ICU mortality	3 (0.5%)	0 (0%)	3 (4.5%)	0.001
Hospital mortality	8 (1.3%)	4 (0.7%)	4 (6.0%)	0.007
Postoperative length of ICU stay, days	2 (2–3)	2 (2–3)	3 (2–5)	0.004
Postoperative length of hospital stay, days	10 (8–15)	10 (8–15)	13 (9–20)	0.005
Total ICU costs, CNY	8,881 (7,213–12,785)	8,573 (7,030–12,388)	10,889 (8,917–17,662)	<0.001
Postoperative hospital costs, CNY	21,703 (16,655–31,225)	20,859 (16,539–28,617)	28,062 (20,546–62,263)	<0.001

Continuous variables are expressed as mean ± standard deviation or median (25th to 75th percentile, interquartile range). Categorical variables are expressed as a n (%). AKI, acute kidney injury; ASA, American Society of Anesthesiologists; CNY, Chinese yuan; eGFR, estimated glomerular filtration rate; GCS, Glasgow Coma Scale; ICSOL, intracranial space-occupying lesion; ICU, intensive care unit. ^a Includes any of the following medications administered within 5 days before operation: angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, nonsteroidal anti-inflammatory drug, immunosuppressant, aminoglycoside, vancomycin, acyclovir, amphotericin, allopurinol, or colistin. ^b Includes hemangioblastoma, cavernous hemangioma, embryonal dysplastic neuroepithelial tumor, primitive neuroectodermal tumor brain, abscess, cyst, or cholinoma.

drugs preoperatively than non-AKI patients. There was no significant difference in preoperative application of radiographic contrast between patients with and without AKI. Baseline sCr and eGFR were similar for the two groups.

Notably, patients who experienced AKI were more likely to suffer adverse outcomes. AKI occurrence was associated with a higher rate of ICU and in-hospital mortality, postoperative tracheotomy, higher costs, longer ICU and hospital length of stay, and prolonged duration of postoperative mechanical ventilation.

Table 2. Intra- and postoperative characteristics of patients with and without postoperative AKI

Characteristics	All patients (n = 605)	Non-AKI (n = 538)	AKI (n = 67)	p value
Intraoperative				
Duration of anesthesia, min	350 (255–435)	350 (255–435)	360 (255–445)	0.657
Duration of surgery, min	320 (230–415)	320 (230–405)	330 (230–425)	0.617
Brain region involved in operation				0.028
Infratentorial region	147 (24.3%)	138 (25.7%)	9 (13.4%)	
Supratentorial region	458 (75.7%)	400 (74.3%)	58 (86.6%)	
Estimated blood loss/100 mL	3.0 (2.0–6.0)	3.0 (2.0–5.6)	3.0 (2.0–6.0)	0.378
Minimum mean arterial pressure, mm Hg	75 (70–80)	75 (70–80)	75 (71–80)	0.818
Intraoperative fluids				
Crystalloid/500 mL	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–3.2)	0.710
Artificial colloid/500 mL	2.0 (2–3.0)	2.0 (1.5–3.0)	2.0 (2.0–3.0)	0.378
Mannitol, mL	0.0 (0.0–250)	0.0 (0.0–250)	0.0 (0.0–250)	0.845
Red blood cells, >4 units	60 (9.9%)	49 (9.1%)	11 (16.4%)	0.059
Plasma	59 (9.8%)	52 (9.7%)	7 (10.4%)	0.839
Postoperative				
APACHE II score	9 (7–12)	9 (7–11)	11 (9–16)	<0.001
GCS score	15 (15–15)	15 (15–15)	15 (10–15)	<0.001
Δ GCS score	0 (0–0)	0 (0–0)	0 (–1–0)	<0.001
Serum sodium, mmol/L	140.9 (138.9–143.2)	140.8 (138.9–143.1)	141.2 (139.1–144.9)	0.097
Δ serum sodium, mmol/L	1.2 (–0.8–3.9)	1.2 (–0.8–3.7)	1.8 (–1.0–5.2)	0.395
Serum potassium, mmol/L	3.6 (3.4–3.9)	3.6 (3.3–3.9)	3.8 (3.5–3.9)	0.002
Δ serum potassium, mmol/L	–0.29 (–0.56–0.03)	–0.31 (–0.58–0.01)	–0.11 (–0.42–0.18)	0.001
Serum creatinine, mg/dL	0.80 (0.68–0.96)	0.79 (0.67–0.94)	0.89 (0.76–1.12)	<0.001
sCysC, mg/L	0.78 (0.62–0.97)	0.75 (0.61–0.94)	0.97 (0.82–1.17)	<0.001
uNAG, U/g creatinine	21.56 (12.94–33.88)	19.89 (12.30–31.72)	29.74 (22.09–56.85)	<0.001
uACR, mg/g creatinine	18.14 (9.95–37.08)	17.43 (9.69–32.99)	29.81 (17.45–79.43)	<0.001
Hemoglobin, g/L	115 (104–127)	116 (104–126)	113 (99–131)	0.577
UP, mL/kg/h	2.20 (1.72–2.84)	2.21 (1.71–2.79)	2.22 (1.83–2.85)	0.738
Accumulative doses of mannitol, mL	500 (0–1,375)	375 (0–1,375)	910 (0–1,375)	0.034
Nephrotoxic drugs ^a	63 (10.4%)	55 (10.2%)	8 (11.9%)	0.664
Reoperation ^b	11 (1.8%)	7 (1.3%)	4 (6.0%)	0.025

Continuous variables are expressed as mean ± standard deviation or median (25th to 75th percentile, interquartile range). Categorical variables are expressed as a n (%). AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; GCS, Glasgow Coma Scale; sCysC, serum cystatin C; uACR, urinary albumin-creatinine ratio; uNAG, urinary N-acetyl-β-D-glucosaminidase; UP, urine production within the first 24 h after operation; Δ, change from first post- to preoperative check. ^a Includes any of the following medications administered within 3 days after operation: angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, nonsteroidal anti-inflammatory drug, immunosuppressant, aminoglycoside, vancomycin, acyclovir, amphotericin, allopurinol, or colistin. ^b Reoperation within 3 days after the first surgery.

Intra- and Postoperative Characteristics of the Patients

Table 2 depicts the intra- and postoperative characteristics of patients with and without AKI. Compared with patients without AKI, patients with AKI had higher postoperative APACHE II and GCS scores and higher concentrations of postoperative sCr, sCysC, uNAG, and uACR. In our cohort, patients with AKI were treated with more mannitol after operation compared to patients without AKI. AKI patients were more likely to undergo reoperation. The percentage of patients who received surgery involving the supratentorial region was significantly higher in the AKI than the non-AKI group ($p = 0.028$).

The median concentrations of pre- and postoperative serum sodium were 139.8 and 140.9 mmol/L, respectively, while the median concentrations of pre- and postoperative serum potassium were 3.9 and 3.6 mmol/L, respectively (Tables 1, 2). Compared to non-AKI patients, patients with AKI had higher levels of postoperative serum potassium ($p = 0.002$). Furthermore, the Δ serum potassium was significantly larger in the non-AKI group (–0.31 [–0.58, 0.01]) than that in the AKI group (–0.11 [–0.42, 0.18]) ($p = 0.001$). In addition, Δ serum potassium showed a significant but negligible correlation with baseline eGFR, while there was no significant correlation between Δ serum sodium and baseline eGFR (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000504599). Similarly, Δ serum potassium had a weak correlation with postoperative sCr ($r = 0.166$, $p < 0.01$).

Table 3. Detective characteristics of the three biomarkers and their possible combinations for postoperative AKI ($n = 67$)

Logistic regression models	AUC-ROC (95% CI)	Cutoff ^a	Sensitivity	Specificity	(+) LR	(-) LR	PPV	NPV
Univariate models								
sCysC	0.749 (0.696–0.801)*	0.72 mg/L	0.93	0.47	1.73	0.16	0.18	0.98
uNAG	0.718 (0.658–0.777)**	19.98 U/g Cre	0.88	0.50	1.77	0.24	0.18	0.97
uACR	0.645 (0.569–0.721)***	44.21 mg/g Cre	0.45	0.82	2.51	0.67	0.24	0.92
Multivariate models								
uNAG + sCysC	0.785 (0.737–0.833)****	0.06 ^b	0.99	0.51	2.00	0.03	0.20	1.00
uNAG + uACR	0.718 (0.658–0.777)**	0.08 ^b	0.88	0.50	1.75	0.24	0.18	0.97
uACR + sCysC	0.750 (0.699–0.802)*	0.07 ^b	0.94	0.46	1.75	0.13	0.18	0.98

(-) LR, negative likelihood ratio; (+) LR, positive likelihood ratio; AKI, acute kidney injury; AUC-ROC, area under the receiver operating characteristic curve; CI, confidence interval; Cre, creatinine; NPV, negative predictive value; PPV, positive predictive value; sCysC, serum cystatin C; uACR, urinary albumin-creatinine ratio; uNAG, urinary N-acetyl- β -D-glucosaminidase. ^a Ideal cutoff value according to the Youden index. ^b Cutoff points of the biomarker panels were the predicted probability generated from the multiple logistic regression model. * $p < 0.05$ vs. uACR and sCysC + uNAG; ** $p < 0.05$ vs. sCysC + uNAG; *** $p < 0.05$ vs. sCysC, sCysC + uACR, and sCysC + uNAG; **** $p < 0.05$ vs. sCysC, uNAG, uACR, uNAG + uACR, and sCysC + uACR.

Fig. 2. ROC analysis of three biomarkers and their combinations for AKI prediction. Among 605 patients, 67 were diagnosed as AKI. AKI, acute kidney injury; AUC, area under the receiver operating characteristic curve; CI, confidence interval; ROC, receiver operating characteristic; sCysC, serum cystatin C; uACR, urinary albumin-creatinine ratio; uNAG, urinary N-acetyl- β -D-glucosaminidase.

Predictive Abilities of Individual Biomarkers and Their Combinations for Postoperative AKI Development

Among the three biomarkers, the correlation between sCysC and baseline eGFR was strongest ($r = -0.308$, $p < 0.01$) (online suppl. Table 2). Similarly, sCysC displayed a moderate correlation with postoperative sCr ($r = 0.470$, $p < 0.01$).

The ROC curve analysis demonstrated that the three clinical biomarkers predicted postoperative AKI with statistical significance (Table 3). There was no significant difference in AUC-ROC between sCysC and uNAG or between uNAG and uACR, but the AUC-ROC was statistically higher for sCysC than uACR ($p = 0.028$). We then developed the possible panels consisting of these biomarkers to assess their predictive ability (sCysC plus uNAG, uNAG plus

Table 4. Clinical risk factors for AKI in patients undergoing resection of intracranial space-occupying lesions

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	p value	OR	95% CI	p value
<i>Preoperative variables</i>						
Age	1.041	1.020–1.062	<0.001	1.035	1.013–1.057	<0.001
Male sex	1.584	0.945–2.655	0.081			
Preexisting hypertension	1.876	0.924–3.807	0.082			
Preexisting cerebrovascular disease	2.472	0.881–6.932	0.086			
Preexisting chronic kidney disease	5.487	0.900–33.449	0.065			
Emergency craniotomy	11.546	4.587–29.058	<0.001			
ASA classification			0.006			
I		reference				
II	1.288	0.681–2.436	0.436			
III	3.714	1.509–9.142	0.004			
IV	5.571	1.256–24.718	0.024			
Diagnostic group			<0.001			
Intracranial hematoma		reference				
Meningioma	0.155	0.043–0.310	<0.001			
Glioma	0.070	0.022–0.217	<0.001			
Pituitary tumor	0.063	0.019–0.211	<0.001			
Schwannoma	0.040	0.009–0.173	<0.001			
Craniopharyngioma	0.144	0.032–0.654	0.012			
Metastatic carcinoma	0.117	0.036–0.382	0.001			
Others ^a	0.077	0.024–0.250	<0.001			
Preoperative GCS score	0.793	0.719–0.876	<0.001			
<i>Intraoperative variables</i>						
Brain region involved in operation	2.223	1.073–4.606	0.032			
Infratentorial region		reference				
Intraoperative fluids						
Red blood cells >4 units	1.960	0.964–3.987	0.063			
<i>Postoperative variables</i>						
APACHE II score	1.167	1.109–1.227	<0.001			
Reoperation ^b	4.816	1.372–16.911	0.014			
Postoperative GCS score	0.795	0.738–0.856	<0.001	0.817	0.755–0.884	<0.001
Δ GCS score	0.830	0.751–0.917	<0.001			
Serum sodium	1.097	1.031–1.168	0.003			
Δ serum sodium	1.049	0.994–1.107	0.081			
Serum potassium	2.849	1.587–5.114	<0.001			
Δ serum potassium	2.485	1.521–4.059	<0.001			
Accumulative doses of mannitol	1.000	1.000–1.001	0.061			
Serum creatinine	16.093	5.273–49.117	<0.001	11.425	3.562–36.643	<0.001

AKI, acute kidney injury; APACHE, Acute Physiology and Chronic Health Evaluation; ASA, American Society of Anesthesiologists; CI, confidence interval; GCS, Glasgow Coma Scale; OR, odds ratio; Δ, change from first post- to preoperative check. ^aHemangioblastoma, cavernous hemangioma, embryonal dysplastic neuroepithelial tumor, primitive neuroectodermal tumor brain, abscess, cyst, or cholinoma. ^bReoperation within 3 days after the first surgery.

uACR, and sCysC plus uACR). The AUC-ROC for postoperative AKI yielded superior performance by the panel of sCysC plus uNAG than by either the individual biomarkers or the other two panels (uNAG plus uACR and sCysC plus uACR) (Table 3; Fig. 2). Consequently, the combination of sCysC plus uNAG was chosen for the subsequent analyses.

In addition, the AUC-ROC of the combination of uNAG and sCysC for predicting postoperative AKI within the first 24 h after operation was 0.828 (0.765–0.890), its AUC-ROC within

Table 5. AUC-ROC, cNRI, and IDI analyses of postoperative AKI

Variables	AUC-ROC	p value ^a	IDI (95% CI)	p value	cNRI (95% CI)	p value ^a
Clinical model ^b	0.759 (0.697–0.822)					
+ sCysC	0.789 (0.736–0.843)	0.060	0.033 (0.006–0.061)	0.018	0.436 (0.187–0.685)	<0.001
+ uNAG	0.787 (0.727–0.848)	0.070	0.057 (0.025–0.090)	<0.001	0.580 (0.331–0.830)	<0.001
+ sCysC + uNAG	0.808 (0.756–0.861)	0.007	0.076 (0.035–0.117)	<0.001	0.633 (0.386–0.880)	<0.001

AKI, acute kidney injury; AUC-ROC, area under the receiver operating characteristic curve; CI, confidence interval; cNRI, continuous net reclassification index; IDI, incremental discrimination improvement; sCysC, serum cystatin C; uNAG, urinary N-acetyl-β-D-glucosaminidase. ^a Biomarker + clinical model versus clinical model. ^b The clinical model for detecting AKI is composed of age, postoperative serum creatinine, and postoperative Glasgow Coma Scale score.

48 h after operation was 0.787 (0.737–0.836), and its AUC-ROC within 72 h was 0.785 (0.737–0.833) (online suppl. Table 3).

The performance of sCysC plus uNAG was further confirmed by bootstrap internal validation, in which the average AUC-ROC value for predicting postoperative AKI was 0.787 (0.739–0.836).

Relative Contribution of the Combination of sCysC and uNAG to the Clinical Model for Postoperative AKI Prediction

To determine the added contribution of the combination of sCysC and uNAG to the clinical model for postoperative AKI prediction, logistic regression analysis was performed. The clinical model for AKI prediction included age, postoperative sCr concentration, and postoperative GCS score (Table 4).

The panel of sCysC plus uNAG was then added to the abovementioned model (Table 5). The clinical model could predict postoperative AKI with reasonable certainty (AUC-ROC = 0.759). The AUC-ROC of this clinical model was significantly improved to 0.808 with the addition of sCysC plus uNAG ($p = 0.007$). To determine whether the panel of sCysC plus uNAG can materially improve risk reclassification, we used IDI and the cNRI in this analysis. Addition of sCysC plus uNAG significantly improved the risk reclassification of AKI over the clinical model alone, with the largest cNRI (0.633) and IDI (0.076).

To further confirm the improvement in risk classification with this panel to the clinical risk model, bootstrap internal validation was conducted and demonstrated comparable cNRI (0.638) and IDI (0.079).

Discussion

In this study, we demonstrated that the combination of functional and tubular damage biomarkers (sCysC plus uNAG) presents an effective clinical strategy for predicting AKI after resection of intracranial space-occupying lesions. To our knowledge, this is the first study that prospectively evaluated the diagnostic accuracy of combining functional and tubular damage biomarkers for AKI prediction in patients undergoing neurosurgery.

Resection of intracranial space-occupying lesions is one of the most common neurosurgical procedures [2, 33, 34]. Development of AKI after neurosurgery is a frequent complication and associated with adverse outcomes [1, 2, 35]. In the present study, postoperative AKI prevalence was 11.1% and was associated with higher rate of mortality, prolonged hospital length of stay, and higher costs. A recent large retrospective study on 1,656 patients

undergoing craniotomy [1] showed that the incidence of postoperative AKI was 9.9%, similar to the result found in our cohort, and indicated that occurrence of AKI was a risk factor for postoperative mortality.

Potential biomarkers have been explored for an early recognition of AKI including, but not limited to, urinary matrix metalloproteinase-7 [36], urinary angiotensinogen [9], tissue inhibitor of metalloproteinase-2, insulin-like growth factor binding protein 7 [37], neutrophil gelatinase-associated lipocalin [38], kidney injury molecule-1 [39], NAG [8, 40], CysC [7, 40], and urinary albumin [7]. However, AKI is a heterogeneous syndrome, and individual biomarkers cannot reflect its multiple pathophysiological processes [41]. Therefore, the ADQI working group recommended combining functional and tubular damage AKI biomarkers, which can reflect different underlying pathological processes of AKI [3]. sCysC and uACR are considered functional biomarkers [7], while uNAG represents tubular damage [7, 8]. Of note, these biomarkers are clinically available worldwide. Hence, we selected these biomarkers to conduct our investigation based on the hypothesis that renal markers can be classified as those representing tubular damage and those reflecting changes in renal function [3, 7]. Similar to previous studies [40, 42–44], the three biomarkers showed poor to moderate AUC-ROC values for AKI prediction in our cohort. Excitingly, the composite of sCysC (functional biomarker) plus uNAG (tubular damage biomarker) was more robust than either the individual biomarkers or the other two combinations. Additionally, we found that the combination of sCysC and uNAG yielded the highest AUC-ROC for predicting AKI within the first 24 h after operation. This combination of sCysC and uNAG measured at ICU admission seems to have relatively different predictive ability for AKI occurring at different times after operation. The possible reason may be that the predictive power of the biomarkers becomes weaker at longer time intervals.

On the one hand, sCysC, produced in all nucleated cells and freely filtered in glomeruli and completely absorbed [8], is considered a better marker of glomerular filtration rate [8] and a potential biomarker for AKI detection [7, 45]. Increased concentration of urinary albumin indicates increased permeability of the basal membrane of glomerular injury [46] and reflects glomerular structure and function change. Thus, urinary albumin is considered a functional marker for AKI detection [47, 48]. On the other hand, uNAG, produced in proximal and distal tubular cells and nonrenal cells, is too large to undergo glomerular filtration and released into urine after tubular damage. Hence, uNAG is a quite sensitive marker for renal tubule damage [41, 49]. In this study, the combination of uNAG plus sCysC, which includes two markers indicative of different AKI pathophysiological conditions, yielded fairly good performance in predicting AKI. The improved performance of combining functional and tubular damage biomarkers (sCysC and uNAG) in this cohort is in keeping with previous studies in patients undergoing cardiac surgery or suffering from heart failure [4–6]. Basu et al. [4] showed that a combination of a tubular injury biomarker (urinary neutrophil gelatinase-associated lipocalin) and a functional glomerular damage biomarker (plasma CysC) had additive ability to predict AKI in 345 children undergoing cardiopulmonary bypass surgery. A previous research on 103 adults with acute decompensated heart failure found that combining functional and tubular damage markers (sCysC and urinary kidney injury molecule-1) improved the discriminatory power for AKI detection [6].

Nevertheless, use of a biomarker composite do not always improve predictive precision. Han et al. [50] found that a composite of tubular injury biomarkers (urinary kidney injury molecule-1 and uNAG) did not enhance diagnostic performance for AKI in children after cardiopulmonary bypass surgery. Similarly, in our cohort, the composite of uNAG plus uACR and the composite of sCysC plus uACR failed to yield additive ability to predict postoperative AKI. One possible explanation is that the former combination included the same source of

specimens and the latter included two biomarkers, both indicating glomerular damage and sharing the same mechanism [51].

Our study has several limitations. First, the study was conducted in a single center, and hence our conclusions have limited generalizability. Additional multicenter cohorts are warranted to verify the efficacy of using these biomarkers to predict postoperative AKI. Second, only one measurement of these biomarkers was used. Repeat measurements may improve the accuracy of assessment. Nevertheless, the ADQI cannot recommend a serial measurement schedule [3], as it is not practical and cost-effective for a series of sample collecting and measuring. We speculate that our findings are not debilitated by this limitation. Third, there may be a certain link between brain dysfunction and kidney disease [52]. A recent report indicated that AKI was associated with impaired cognition in children with severe malaria [53]. In our department we did not routinely evaluate the cognitive ability by the Mini-Mental State Examination or the Montreal Cognitive Assessment. We will discuss the association between AKI and cognitive ability impairment in future study. Additionally, the GCS score was reported to be an independent risk factor for AKI in previous study [54]. Hence, we included preoperative GCS score, postoperative GCS score, and change in GCS score from first post- to preoperative check in logistic regression for AKI prediction. In the present study, the postoperative GCS score was the independent risk factor for postoperative AKI. Last but not least, statistical power to detect the effect of AKI on mortality was limited due to a small number of events.

In conclusion, the present study demonstrates that combining functional and tubular damage biomarkers (sCysC plus uNAG) is a reasonable strategy to improve the discriminative performance for AKI prediction in patients undergoing resection of intracranial space-occupying lesions. This study was conducted in patients who underwent resection of intracranial space-occupying lesions, which is one of the most common neurosurgical procedures. Moreover, these clinically available biomarkers (sCysC, uNAG, and uACR) could be used as routine diagnostic tools in clinical practice. Thus, this study could have significant clinical implications for similar cohorts at risk of AKI.

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Statement of Ethics

All experiments were performed in accordance with approved protocols, guidelines, and regulations. The protocol was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [55]. This study was approved by the ethics committee of Guangdong General Hospital. All procedures were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written informed consent was obtained from each patient or from appropriate surrogates for patients unable to consent.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Y. Deng, J. Ma, N. Tan, and C. Chen contributed equally to the design of the research and the interpretation of the data and finalized the manuscript. Y. Deng participated in project development, data collection, management of data analysis, and manuscript writing/editing. J. Ma participated in project development, data collection, management of data analysis, and manuscript writing. Y. Hou, D. Zhou, T. Hou, J. Li, and S. Liang participated in data collection and management of data analysis. N. Tan participated in project development, management of data analysis, and manuscript editing. C. Chen participated in project development, management of data analysis, and manuscript editing. All authors contributed to the acquisition and analysis of the data, drafted the manuscript, and agree to be fully accountable for ensuring the integrity and accuracy of the work. All authors read and approved the final manuscript.

References

- Kovacheva VP, Aglio LS, Boland TA, Mendu ML, Gibbons FK, Christopher KB. Acute Kidney Injury After Craniotomy Is Associated With Increased Mortality: A Cohort Study. *Neurosurgery*. 2016 Sep;79(3):389–96.
- Deng Y, Yuan J, Chi R, Ye H, Zhou D, Wang S, et al. The Incidence, Risk Factors and Outcomes of Postoperative Acute Kidney Injury in Neurosurgical Critically Ill Patients. *Sci Rep*. 2017 Jun;7(1):4245.
- McCullough PA, Shaw AD, Haase M, Bouchard J, Waikar SS, Siew ED, et al. Diagnosis of acute kidney injury using functional and injury biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol*. 2013;182:13–29.
- Basu RK, Wong HR, Krawczeski CD, Wheeler DS, Manning PB, Chawla LS, et al. Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. *J Am Coll Cardiol*. 2014 Dec;64(25):2753–62.
- Prowle JR, Calzavacca P, Licari E, Ligabo EV, Echeverri JE, Bagshaw SM, et al. Combination of biomarkers for diagnosis of acute kidney injury after cardiopulmonary bypass. *Ren Fail*. 2015 Apr;37(3):408–16.
- Yang CH, Chang CH, Chen TH, Fan PC, Chang SW, Chen CC, et al. Combination of Urinary Biomarkers Improves Early Detection of Acute Kidney Injury in Patients With Heart Failure. *Circ J*. 2016;80(4):1017–23.
- Charlton JR, Portilla D, Okusa MD. A basic science view of acute kidney injury biomarkers. *Nephrol Dial Transplant*. 2014 Jul;29(7):1301–11.
- Ostermann M, Joannidis M. Acute kidney injury 2016: diagnosis and diagnostic workup. *Crit Care*. 2016 Sep;20(1):299.
- Yang X, Chen C, Tian J, Zha Y, Xiong Y, Sun Z, et al. Urinary Angiotensinogen Level Predicts AKI in Acute Decompensated Heart Failure: A Prospective, Two-Stage Study. *J Am Soc Nephrol*. 2015 Aug;26(8):2032–41.
- Schanz M, Pannes D, Dippon J, Wasser C, Alscher MD, Kimmel M. The Influence of Thyroid Function, Inflammation, and Obesity on Risk Prediction of Acute Kidney Injury by Cystatin C in the Emergency Department. *Kidney Blood Press Res*. 2016;41(5):604–13.
- Zhang D, Gao L, Ye H, Chi R, Wang L, Hu L, et al. Impact of thyroid function on cystatin C in detecting acute kidney injury: a prospective, observational study. *BMC Nephrol*. 2019 Feb;20(1):41.
- Wang L, Deng Y, Zhai Y, Xu F, Li J, Zhang D, et al. Impact of blood glucose levels on the accuracy of urinary N-acetyl-β-D-glucosaminidase for acute kidney injury detection in critically ill adults: a multicenter, prospective, observational study. *BMC Nephrol*. 2019 May;20(1):186.
- Deng Y, Wang L, Hou Y, Ma J, Chi R, Ye H, et al. The influence of glycemic status on the performance of cystatin C for acute kidney injury detection in the critically ill. *Ren Fail*. 2019 Nov;41(1):139–49.
- Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009 May;150(9):604–12.

- 15 Stein KP, Wanke I, Forsting M, Oezkan N, Huetter BO, Sandalcioğlu IE, et al. Associated Aneurysms in Infratentorial Arteriovenous Malformations: Role of Aneurysm Size and Comparison with Supratentorial Lesions. *Cerebrovasc Dis*. 2016;41(5–6):219–25.
- 16 Lou X, Gui QP, Sun L, Wu NZ, Lyu JH, Ma L. Comparisons of MR Findings Between Supratentorial and Infratentorial Gangliogliomas. *Clin Neuroradiol*. 2016 Mar;26(1):65–71.
- 17 Demaerel R, van Loon J, Van Calenbergh F. Outcome after surgery in supratentorial and infratentorial solitary brain metastasis. *Acta Neurochir (Wien)*. 2019 May;161(5):1047–53.
- 18 Lambers Heerspink HJ, Nauta FL, van der Zee CP, Brinkman JW, Gansevoort RT, de Zeeuw D, et al. Alkalization of urine samples preserves albumin concentrations during prolonged frozen storage in patients with diabetes mellitus. *Diabet Med*. 2009 May;26(5):556–9.
- 19 Innanen VT, Groom BM, de Campos FM. Microalbumin and freezing. *Clin Chem*. 1997 Jun;43(6 Pt 1):1093–4.
- 20 Han WK, Wagener G, Zhu Y, Wang S, Lee HT. Urinary biomarkers in the early detection of acute kidney injury after cardiac surgery. *Clin J Am Soc Nephrol*. 2009 May;4(5):873–82.
- 21 Zhang Z, Lu B, Sheng X, Jin N. Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. *Am J Kidney Dis*. 2011 Sep;58(3):356–65.
- 22 Filler G, Bökenkamp A, Hofmann W, Le Bricon T, Martínez-Brú C, Grubb A. Cystatin C as a marker of GFR – history, indications, and future research. *Clin Biochem*. 2005 Jan;38(1):1–8.
- 23 Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl*. 2012;2:1–138.
- 24 Endre ZH, Walker RJ, Pickering JW, Shaw GM, Frampton CM, Henderson SJ, et al. Early intervention with erythropoietin does not affect the outcome of acute kidney injury (the EARLYARF trial). *Kidney Int*. 2010 Jun;77(11):1020–30.
- 25 Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982 Apr;143(1):29–36.
- 26 Schober P, Boer C, Schwarte LA. Correlation Coefficients: Appropriate Use and Interpretation. *Anesth Analg*. 2018 May;126(5):1763–8.
- 27 DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988 Sep;44(3):837–45.
- 28 Youden WJ. Index for rating diagnostic tests. *Cancer*. 1950 Jan;3(1):32–5.
- 29 Cook NR. Statistical evaluation of prognostic versus diagnostic models: beyond the ROC curve. *Clin Chem*. 2008 Jan;54(1):17–23.
- 30 Pencina MJ, D’Agostino RB Sr, D’Agostino RB Jr, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. *Stat Med*. 2008 Jan;27(2):157–72; discussion 207–12.
- 31 Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology*. 2010 Jan;21(1):128–38.
- 32 Efron B, Tibshirani RJ. *An introduction to the bootstrap*. Boca Raton (FL): Chapman & Hall/CRC Press; 1994.
- 33 Fry DE, Nedza SM, Pine M, Reband AM, Huang CJ, Pine G. Inpatient and postdischarge outcomes following elective craniotomy for mass lesions. *Neurosurgery*. 2019 Jul;85(1):E109–15.
- 34 Sherrod BA, Rocque BG. Morbidity associated with 30-day surgical site infection following nonshunt pediatric neurosurgery. *J Neurosurg Pediatr*. 2017 Apr;19(4):421–7.
- 35 Ahmed M, Sriganesh K, Vinay B, Umamaheswara Rao GS. Acute kidney injury in survivors of surgery for severe traumatic brain injury: Incidence, risk factors, and outcome from a tertiary neuroscience center in India. *Br J Neurosurg*. 2015;29(4):544–8.
- 36 Yang X, Chen C, Teng S, Fu X, Zha Y, Liu H, et al. Urinary Matrix Metalloproteinase-7 Predicts Severe AKI and Poor Outcomes after Cardiac Surgery. *J Am Soc Nephrol*. 2017 Nov;28(11):3373–82.
- 37 Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, Demuth GE, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. *Am J Respir Crit Care Med*. 2014 Apr;189(8):932–9.
- 38 de Geus HR, Bakker J, Lesaffre EM, le Noble JL. Neutrophil gelatinase-associated lipocalin at ICU admission predicts for acute kidney injury in adult patients. *Am J Respir Crit Care Med*. 2011 Apr;183(7):907–14.
- 39 Han WK, Bailly V, Abichandani R, Thadhani R, Bonventre JV. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. *Kidney Int*. 2002 Jul;62(1):237–44.
- 40 Deng Y, Chi R, Chen S, Ye H, Yuan J, Wang L, et al. Evaluation of clinically available renal biomarkers in critically ill adults: a prospective multicenter observational study. *Crit Care*. 2017 Mar;21(1):46.
- 41 Sprenkle P, Russo P. Molecular markers for ischemia, do we have something better than creatinine and glomerular filtration rate? *Arch Esp Urol*. 2013 Jan–Feb;66(1):99–114.
- 42 Royakkers AA, Korevaar JC, van Suijlen JD, Hofstra LS, Kuiper MA, Spronk PE, et al. Serum and urine cystatin C are poor biomarkers for acute kidney injury and renal replacement therapy. *Intensive Care Med*. 2011 Mar;37(3):493–501.
- 43 Katagiri D, Doi K, Honda K, Negishi K, Fujita T, Hisagi M, et al. Combination of two urinary biomarkers predicts acute kidney injury after adult cardiac surgery. *Ann Thorac Surg*. 2012 Feb;93(2):577–83.
- 44 Ralib AM, Pickering JW, Shaw GM, Than MP, George PM, Endre ZH. The clinical utility window for acute kidney injury biomarkers in the critically ill. *Crit Care*. 2014 Nov;18(6):601.

- 45 Bell M, Granath F, Mårtensson J, Löfberg E, Ekblom A, Martling CR; KING (Karolinska Intensive care Nephrology Group). Cystatin C is correlated with mortality in patients with and without acute kidney injury. [Nephrol Dial Transplant](#). 2009 Oct;24(10):3096–102.
- 46 Zheng J, Xiao Y, Yao Y, Xu G, Li C, Zhang Q, et al. Comparison of urinary biomarkers for early detection of acute kidney injury after cardiopulmonary bypass surgery in infants and young children. [Pediatr Cardiol](#). 2013 Apr;34(4):880–6.
- 47 Ware LB, Johnson AC, Zager RA. Renal cortical albumin gene induction and urinary albumin excretion in response to acute kidney injury. [Am J Physiol Renal Physiol](#). 2011 Mar;300(3):F628–38.
- 48 Tziakas D, Chalikias G, Kareli D, Tsigalou C, Risgits A, Kikas P, et al. Spot urine albumin to creatinine ratio outperforms novel acute kidney injury biomarkers in patients with acute myocardial infarction. [Int J Cardiol](#). 2015 Oct;197:48–55.
- 49 Vaidya VS, Ferguson MA, Bonventre JV. Biomarkers of acute kidney injury. [Annu Rev Pharmacol Toxicol](#). 2008;48(1):463–93.
- 50 Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, et al. Urinary biomarkers in the early diagnosis of acute kidney injury. [Kidney Int](#). 2008 Apr;73(7):863–9.
- 51 Siew ED, Ware LB, Bian A, Shintani A, Eden SK, Wickersham N, et al. Distinct injury markers for the early detection and prognosis of incident acute kidney injury in critically ill adults with preserved kidney function. [Kidney Int](#). 2013 Oct;84(4):786–94.
- 52 Viggiano D, Wagner CA, Blankestijn PJ, Bruchfeld A, Fliser D, Fouque D, et al. Mild cognitive impairment and kidney disease: clinical aspects. [Nephrol Dial Transplant](#). doi: 10.1093/ndt/gfz051 [Epub ahead of print].
- 53 Conroy AL, Opoka RO, Bangirana P, Idro R, Ssenkusu JM, Datta D, et al. Acute kidney injury is associated with impaired cognition and chronic kidney disease in a prospective cohort of children with severe malaria. [BMC Med](#). 2019 May;17(1):98.
- 54 Sjøvik S, Isachsen MS, Nordhuus KM, Tveiten CK, Eken T, Sunde K, et al. Acute kidney injury in trauma patients admitted to the ICU: a systematic review and meta-analysis. [Intensive Care Med](#). 2019 Apr;45(4):407–19.
- 55 von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. [Ann Intern Med](#). 2007 Oct;147(8):573–7.