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Clinical Utility of Novel Biomarkers in the Perioperative Acute Kidney Injury

Summary

Introduction: Acute kidney injury (AKI) is a common and clinically significant postoperative complication (1). Particularly high risk of AKI occurs in procedures related to vascular surgery. It is estimated that in patients undergoing endovascular aortic repair (EVAR), nearly 40% develop AKI (2). Early recognition of postoperative AKI is crucial for implementing effective treatment and potential therapy modification to prevent further kidney damage. According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, traditional biomarkers of kidney injury such as serum creatinine (sCr) and hourly urine output (UOP) are the gold standards for diagnosis (3,4). Diagnosis of AKI based on these classic biomarkers is only possible in the later stages, when a significant portion of nephrons are damaged. Serum creatinine levels depend on many individual factors as well as disease-related factors: gender, age, muscle mass, diet, and current pharmacotherapy. Factors influencing hourly urine output include, among others: fluid balance, pharmacotherapy, ongoing inflammatory processes, and electrolyte disturbances. For several decades, intensive search has been conducted for early and independent biomarkers of AKI (5). Proenkephalin A119-159 (PENK) is one of the molecules undergoing intensive research in this area. PENK is a monopeptide filtered in the glomeruli, not subjected to secretion, with a concentration independent of age and muscle mass. A 2023 meta-analysis demonstrated that PENK has a significant potential as an early detection marker for AKI (6). A group of particular interest in the context of using PENK for early AKI detection were patients treated in Intensive Care Units (ICU) due to septic shock (7). Previous studies also showed that this biomarker was an independent predictor of successful discontinuation of renal replacement therapy (RRT) (8). Existing studies regarding the use of PENK in the perioperative period involved small patient groups undergoing both cardiac surgery and vascular procedures, as well as liver transplantation(9–11). Therefore, an interesting area for further research is the verification of the potential of clinical utility of new biomarkers in diagnosing acute kidney injury in groups of patients with multi-factorial risk factors to develop this syndrome.

Aim of the study: The aim of this study was to assess the clinical value of the novel biomarker proenkephalin A119-159 for the early perioperative detection of acute kidney injury (Publications 2. and 3.), as well as a summary of previous research publications on the application of PENK in various clinical contexts (publication 1.).

Methodology: Publications 2. and 3. are based on results from a single-centre, prospective, observational, cross-sectional study conducted from April 2022 to June 2024 at the Central Clinical Hospital of the Medical University of Warsaw. The research project titled "New biomarker panels and machine learning in early detection of acute kidney injury" aimed to assess the clinical applicability of newly selected kidney injury biomarkers. A total of 68 patients scheduled for planned EVAR procedures were included. The procedure and postoperative care were conducted according to standard operating procedures (SOP). Blood samples for biomarker analysis were collected preoperatively and for up to three subsequent days. Serum PENK levels were measured immediately after collection using POCT in the Post-Anesthesia Care Unit (PACU). Remaining blood samples were centrifuged and frozen immediately at -80°C, and after completing the cohort, other biomarkers, including PENK, were analyzed using ELISA. Demographic, anthropometric, medical history data, including current pharmacotherapy and laboratory results, were collected. The risk of death on the day of surgery was calculated based on the Sequential Organ Failure Assessment (SOFA) scale and the Simplified Acute Physiology Score (SAPS). During the hospital stay in PACU up to 72 hours post-surgery, standard continuous monitoring of vital functions and laboratory parameters was performed. Postoperative data included the occurrence of AKI, need for pharmacological circulatory support, and transfusion of blood products. Follow-up was conducted via telephone survey six months after inclusion to estimate early and late mortality.

Results:

Publication 2. was based on a pilot study of 34 patients initially qualified for the research project. AKI was diagnosed postoperatively in 12 patients (35%). The level of proenkephalin A119-159 measured by POCT correlated with serum sCr levels. No earlier perioperative increase in penKid levels compared to sCr was observed.

Publication 3. is based on results from a group of 68 patients. AKI according to KDIGO criteria was diagnosed in 18 patients (26.5%). Significant risk factors for developing AKI

included age and perioperative transfusions of blood products. No statistically significant correlation was found between AKI and early mortality ($p = .071$), whereas six-month mortality was significantly higher in the AKI group (50%) compared to the non-AKI group (11.9%) ($p = .006$). PenKid levels measured by POCT showed moderate agreement with KDIGO AKI criteria (Gwet's $AC1 = 0.52$, $p < .001$), whereas PENK measured by ELISA showed minimal agreement (Gwet's $AC1 = 0.10$, $p < .428$). PenKid demonstrated high diagnostic sensitivity up to 80%, with moderate specificity of 51%, while positive predictive value remained low and negative predictive value high throughout the measurement period. Subclinical AKI (sAKI), indicated by postoperative increases in penKid above 80 pmol/L, was more frequently detected than the actual incidence of later AKI at all time points.

Conclusions:

Publications 2. and 3.: The results presented in Publications 2. and 3. suggest that penKid has potential utility in the diagnosis of perioperative AKI. However, it was not confirmed that penKid allows earlier diagnosis of AKI compared to sCr levels. The high sensitivity and strong negative predictive value (NPV) imply that penKid could be useful for identifying patients at low risk of AKI. Conversely, moderate specificity and low positive predictive value (PPV) indicate that caution should be exercised when using penKid for AKI prognosis, especially considering its tendency to overestimate risk. The limited sample size in the studies from Publications 2. and 3., typical for research on highly specialised procedures, restricts the statistical power of the findings. A strength of the study is the homogeneity of the group, resulting from: a uniform type of procedure, involvement of one surgical team, and standardised perioperative care.

Publication 1.: A comprehensive review of current scientific literature assessing the application of proenkephalin A119-151 as a biomarker in the diagnosis of acute kidney injury (AKI) has yielded the following key findings:

Research supports the applicability of proenkephalin A 119-159 as a biomarker across various clinical scenarios, notably among patients admitted to intensive care units (ICUs). Regarding the use of PENK for diagnosing perioperative acute kidney injury (AKI), additional studies are warranted due to limited cohort sizes, the necessity of methodological validation across diverse patient populations, and reported inconsistencies in PENK's predictive accuracy for early AKI detection.