Editorial

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New Issues With Neutrophil Gelatinase-associated Lipocalin in Acute Kidney Injury

Acute kidney injury (AKI) is a syndrome characterized by an increase in the serum creatinine level, a decrease in urine output, or both [1]. AKI is not a single disease but a heterogeneous syndrome with a broad spectrum of etiologies, pathophysiologies, and clinical presentations [1]. The pathophysiological mechanisms of AKI include kidney hypoperfusion, cardiac dysfunction, nephrotoxicity, sepsis, and intra-abdominal hypertension [1, 2]. AKI has a stage-dependent worsening prognosis [3, 4]. Hoste, *et al.* [5] reported that increasing AKI severity was associated with hospital mortality when adjusted for other variables, with an odds ratio of 1.679 (P=0.109) in stage 1, 2.945 (P=0.005) in stage 2, and 6.884 (P<0.001) in stage 3. Therefore, early detection of AKI is essential as it negatively impacts clinical outcomes, and subclinical kidney cell injury can be reversible when recognized early [6]. However, conventional kidney markers such as serum creatinine or urine output occasionally delay AKI diagnosis and treatment because they are considerably affected only late in the course of AKI [1, 4].

AKI detection is undergoing a dynamic revolution; biomarker technology allows better, earlier, and more accurate determination of diagnosis and prognosis, with powerful implications for disease management. There has been considerable progress in the standardization of the AKI definition according to the Risk, Injury, Failure, Loss, End-Stage; Acute Kidney Injury Network; Kidney Disease Improving Global Outcomes; and European Renal Best Practice criteria [7]. Early and accurate diagnosis of AKI is gaining additional value, and the role of biomarkers is increasing. Tubular damage markers can be used to detect AKI before functional marker levels are increased, and new biomarkers have revealed a new subset of AKI termed “subclinical AKI” [8]. Conventional functional and emerging damage biomarkers can be combined to expand the diagnosis of AKI to subclinical AKI. Recently, a refined staging system for the diagnosis of AKI was published, in which patients with AKI with damage biomarker positivity without an increase in the serum creatinine level and not reaching urine output criteria were classified as stage 1S [9].

Neutrophil gelatinase-associated lipocalin (NGAL) is an intensely studied kidney biomarker reflecting early damage and prognosis [1, 3]. NGAL is expressed in multiple human tissues, including kidney tubular epithelial cells in the basal state [2]. Upon acute injury, NGAL expression in the kidneys is promptly upregulated multiple folds [2, 3]. For the exact diagnosis of AKI in various clinical situations, several cutoffs for blood and urine NGAL have been suggested. Di Somma, *et al.* [10] reported that blood NGAL levels in AKI increase as early as at 6 hours, which is nearly 2 days earlier than when serum creatinine levels increase at 48 hours. Based on international analysis, they suggested cutoffs of 150 ng/mL as a high-sensitivity threshold for AKI prediction and 400 ng/mL as a high-specificity threshold for AKI diagnosis [10]. NGAL values at admission predict in-hospital mortality at a threshold of 400 ng/mL, with an odds ratio of 8.3 [10, 11]. A recent meta-analysis of 52 observational studies to inves-

tigate the predictive ability of NGAL levels in 13,040 patients at risk of AKI revealed that NGAL cutoffs for AKI in adults ranged from ≥105 to ≥350 ng/mL for various clinical laboratory platforms [3]. For severe AKI, cutoffs with 95% specificity were >580 ng/mL for urinary NGAL, with 27% sensitivity, and >364 ng/mL for plasma NGAL, with 44% sensitivity [3].

The other novel kidney damage marker test, the NephroCheck Test the NephroCheck Test (Astute Medical Inc., San Diego, CA, USA), which is a rapid test for the quantitative measurement of tissue inhibitor of metalloproteinase 2 (TIMP2) and insulin-like growth factor binding protein 7 (IGFBP7), uses a high specificity cutoff (2.0) to identify patients who are at the highest risk of AKI and therefore may be eligible for more active interventions [12]. However, as mentioned above, the NGAL cutoff for AKI diagnosis has not yet been standardized.

Various methods have been used to determine study-specific optimal NGAL cutoffs to define NGAL-positivity or -negativity [13]. In this issue of *Annals of Laboratory Medicine*, Albert, *et al.* [13] explore to what extent differences among methods and classification systems impact the calculated risk of adverse outcomes in two independent prospective cardiac surgery cohorts. They conclude that the magnitude of the attributed risk of adverse events varies according to the NGAL cutoff selection method and AKI classification system (including subclinical AKI) used [13]. In future, prospective studies are required to evaluate alternative methods and the advantages and limitations of the different approaches for NGAL cutoff selection and AKI classification system application.

AUTHOR CONTRIBUTIONS

Hur M and Cho SY drafted the editorial and read and approved its final version.

CONFLICTS OF INTEREST

None declared.

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REFERENCES

1. Ronco C, Bellomo R, Kellum JA. Acute kidney injury. Lancet 2019;394:1949-64.
2. Marakala V. Neutrophil gelatinase-associated lipocalin (NGAL) in kidney injury - a systematic review. Clin Chim Acta 2022;536:135-41.
3. Albert C, Zapf A, Haase M, Röver C, Pickering JW, Albert A, et al. Neutrophil gelatinase-associated lipocalin measured on clinical laboratory platforms for the prediction of acute kidney injury and the associated need for dialysis therapy: a systematic review and meta-analysis. Am J Kidney Dis 2020;76:826-41.e1.
4. Albert C, Haase M, Albert A, Zapf A, Braun-Dullaeus RC, Haase-Fielitz A. Biomarker-guided risk assessment for acute kidney injury: time for clinical implementation? Ann Lab Med 2021;41:1-15.
5. Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, et al. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study. Intensive Care Med 2015;41:1411-23.
6. Yang HS, Hur M, Lee KR, Kim H, Kim HY, Kim JW, et al. Biomarker rule-in or rule-out in patients with acute diseases for validation of acute kidney injury in the emergency department (BRAVA): a multicenter study evaluating urinary TIMP-2/IGFBP7. Ann Lab Med 2022;42:178-87.
7. Vanmassenhove J, Van Biesen W, Vanholder R, Lameire N. Subclinical AKI: ready for primetime in clinical practice? J Nephrol 2019;32:9-16.
8. Zou C, Wang C, Lu L. Advances in the study of subclinical AKI biomarkers. Front Physiol 2022;13:960059.
9. Ostermann M, Zarbock A, Goldstein S, Kashani K, Macedo E, Murugan R, et al. Recommendations on acute kidney injury biomarkers from the acute disease quality initiative consensus conference: a consensus statement. JAMA Netw Open 2020;3:e2019209.
10. Di Somma S, Magrini L, De Berardinis B, Marino R, Ferri E, Moscatelli P, et al. Additive value of blood neutrophil gelatinase-associated lipocalin to clinical judgement in acute kidney injury diagnosis and mortality prediction in patients hospitalized from the emergency department. Crit Care 2013;17:R29.
11. Cruz DN, de Cal M, Garzotto F, Perazella MA, Lentini P, Corradi V, et al. Plasma neutrophil gelatinase-associated lipocalin is an early biomarker for acute kidney injury in an adult ICU population. Intensive Care Med 2010;36:444-51.
12. 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;189:932-9.
13. Albert A, Radtke S, Blume L, Bellomo R, Haase M, Stieger P, et al. Neutrophil gelatinase-associated lipocalin cutoff value selection and acute kidney injury classification system determine phenotype allocation and associated outcomes. Ann Lab Med 2023;43:539-53.

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