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Journal of the Chinese Medical Association 79 (2016) 411−412

www.jcma-online.com

Editorial

Neutrophil gelatinase-associated lipocalin: Still a good predictive marker of acute kidney injury in severe septic patients?

Serum creatinine (sCr) is considered a lagging indicator of acute kidney injury (AKI), and reliance on sCr as a marker for AKI may delay initiation of appropriate therapy. Novel biomarkers including plasma or urine keratinocyte-derived chemokine/Gro-α, plasma or urine neutrophil gelatinase-associated lipocalin (NGAL), urine kidney injury molecule-1, and urine cytokines interleukin-6 (IL-6), IL-8, and IL-18 have been investigated as early markers of AKI prior to elevation of sCr.[1−6] Mishra et al[3] demonstrated that both plasma and urine NGAL concentration 2 hours after surgery are powerful independent predictors of AKI within 72 hours in children undergoing cardiopulmonary bypass. However, serum NGAL has been shown to increase in response to acute infections, pancreatitis, heart failure, systemic inflammatory syndrome, severe sepsis, and septic shock.[7−10] It means NGAL may be less specific to predict AKI under these circumstances. Using NGAL as an early marker of AKI in intensive care patients showed heterogeneous results in several studies.[9,11−13] De Geus et al[11] reported serum NGAL measured at intensive care unit (ICU) admission is not superior to sCr-derived estimated glomerular filtration rate in predicting the development of severe AKI in 632 adult critically ill patients, but serum NGAL adds significant accuracy in combination with estimated glomerular filtration rate. Martensson et al[9] also demonstrated that plasma NGAL is a poor predictor for AKI in 45 septic shock patients because peak plasma NGAL is not significantly different between septic shock patients with and without AKI. On the contrary, Cruz et al[12] found good correlation between the peak plasma NGAL concentration with AKI severity, and that plasma NGAL was also an early marker to predict AKI development within the next 48 hours and the necessity of renal replacement therapy in ICU patients. Constantin et al[13] showed high sensitivity and specificity (82% and 97%) to predict AKI by using plasma NGAL higher than a cutoff value of 155 nmol/L. Since these studies found plasma NGAL could predict the need for renal replacement therapy, NGAL could be still regarded as an early marker of severe AKI in ICU patients.[11−13] However, plasma NGAL poorly predicted mortality in the studied groups.[11,12]

Recently, Huang et al[14] investigated the utilization of the traditional biomarker sCr in comparison with novel biomarkers, including plasma NGAL, IL-6, and IL-10 within 24 hours after admission, to predict the development of AKI within 7 days among severe septic patients in ICU. When the cutoff values of sCr > 1.5 mg/dL and plasma NGAL > 150 ng/mL were used, the study showed better predictive value of AKI by sCr than by plasma NGAL. In comparison with the previously mentioned studies that enrolled patients without pre-existing chronic kidney disease and excluded patients with admission due to AKI, the enrollment criteria of this study include nine patients with end-stage renal disease and possibly some patients with chronic kidney disease among the eight patients without previous data of sCr. In addition, the values of mean and standard deviation of plasma NGAL of patient with Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease (RIFLE)-failure are 217.2 ng/mL and16.8 ng/mL, respectively, which means >97.5% of patients in this group had a value of plasma NGAL > 183.6 ng/mL ($217.2-16.8\times 2=183.6$), thus, almost all patients in this group have plasma NGAL > 150 ng/mL. This indicates that a cutoff value of 150 ng/mL for NGAL is too low to have good specificity for the prediction of development of RIFLE-failure in the study patients. Furthermore, they used impaired renal function of sCr > 1.5 mg/dL as an early marker of AKI within 7 days after ICU admission in the current study. It may lead to potential bias if there is a lagging period between arrival at the emergency department and admission to the ICU, and some AKI episodes developed even several days before visiting the hospital. The study selected an observation period of 7 days after admission to the ICU, but the development of AKI may appear 7 days after NGAL sampling and result in lower sensitivity of plasma NGAL in predicting an acute renal insult. Cruz et al[12] also had shown decline in the area under receiver operating characteristic curve with longer observation period. Furthermore, most patients in the study had higher plasma NGAL concentration owing to underlying severe sepsis, and it contributed to lower specificity of plasma NGAL in predicting development of AKI due to a lower cutoff value of plasma NGAL.

Indeed, we usually do not know the exact onset of AKI in severely septic patients, and thus it is difficult to define a proposed time of NGAL measurement in these patients. The

http://dx.doi.org/10.1016/j.jcma.2016.02.005

superiority of plasma NGAL as an early biomarker of AKI may be restricted to the cases with known timing of renal insult, such as major surgical procedures, cardiopulmonary bypass, or sudden onset of shock or sepsis during hospitalization. Therefore, it should be sampled as early as possible after the patient's arrival at medical facilities. A higher cutoff value of plasma NGAL concentration and repeated measurement may reasonably increase the predictive value of plasma NGAL for AKI, allowing appropriate treatment as early as possible for AKI patients in the ICU.

Conflict of interests

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

Acknowledgments

This work was supported by intramural grants (V104C-050, V105C-075) from Taipei Veterans General Hospital, and the Ministry of Science and Technology (MOST 104-2314-B-010 -032 -MY3) in Taiwan.

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