47

Performance of Urine TIMP-2 in An Adult Mixed Intensive Care Unit

Tetsushi Yamashita, Kent Doi, Maki Tsukamoto, Masaomi Nangaku, Eisei Noiri
The University of Tokyo

Objectives

Tissue inhibitor of metalloproteinases-2 (TIMP-2), which inhibits not only metalloproteinases but also endothelial cell proliferation by binding the integrin alpha3 beta1, was recently reported as a novel biomarker for predicting severe AKI in critical ill patients.

This study was conducted to evaluate the performance of urine TIMP-2 in our adult mixed intensive care unit (ICU) by comparing with other biomarkers. We also evaluated the influence of sepsis on each biomarker.

Methods

Participants and study design

All patients in this study were older than 20 years and had been admitted to ICUs other than the coronary care unit (CCU) of The University of Tokyo Hospital. This study enrolled consecutive 100 ICU cases from July 2011 to October 2011. One Patient with end-stage renal disease and 1 patient who had several hemodiafiltration sessions before liver transplantation were excluded from this cohort. One patient experienced 2 episodes of ICU admission and we analyzed both cases. Therefore, 98 cases in 97 patients were analyzed. The study protocol was approved by The University of Tokyo Institutional Review Board. Informed consent was obtained from each participant or the participant's family.

Biomarker measurement

Paired urine and blood samples were collected at enrollment (within 24 hours after ICU admission) by standard methods and centrifuged. Plasma (EDTA) and urine supernatants were frozen, shipped on dry ice, stored at a -80˚ C and thawed immediately prior to biomarker measurement. We measured urine TIMP-2, plasma neutrophil gelatinase-associated lipocain (NGAL), and plasma interleukin-6 (IL-6) as biomarkers. Urine TIMP-2 was measured with research assays based on ELISA (R&D Systems, Minneapolis, MN, USA).

Results

Table 1. Baseline characteristics (Median [IQR])

	Non-AKI (n=56)	AKI (n=42)	P-value
Age	63 [43 – 75.8]	69 [60 – 75.3]	0.0463
Sex(Male)	66.1%	81.0%	0.1158
Sepsis	26.8%	61.9%	0.0008
Number of positive SIRS criteria	2 [2 – 3]	3 [2.8 – 4]	0.0037
Baseline Cre (mg/dl)	0.65 [0.46 – 0.79]	0.68 [0.49 - 0.91]	0.2347
Cre on ICU admission (mg/dl)	0.70 [0.52 – 0.89]	1.46 [0.99 – 2.87]	<0.0001
APACHE II score	14.5 [10 – 22]	27 [18 – 33.3]	<0.0001
In-hospital mortality	7.1%	26.2%	0.0119
ICU length of stay (day)	5 [3 -8]	9 [5 – 17.3]	0.0013

Figure 1. AKI staging

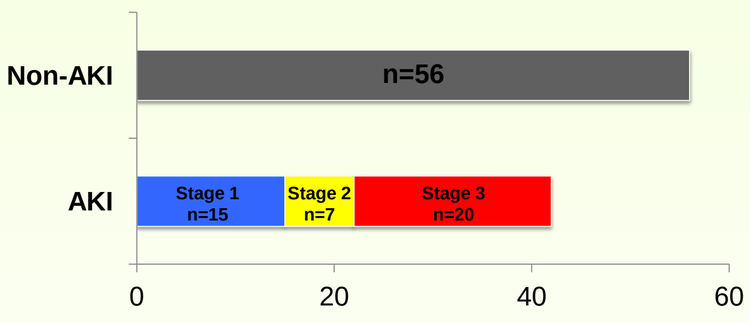
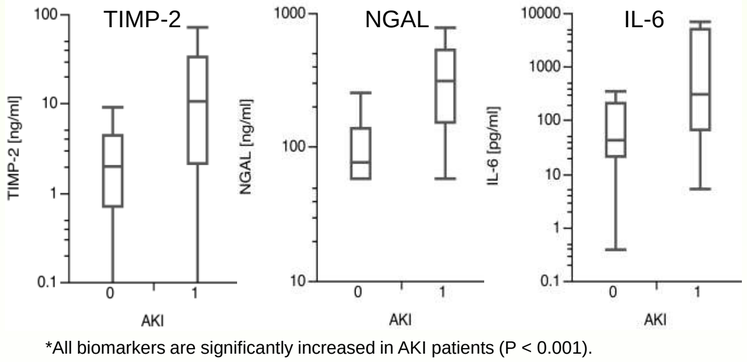


Figure 2. Biomarkers with and without AKI

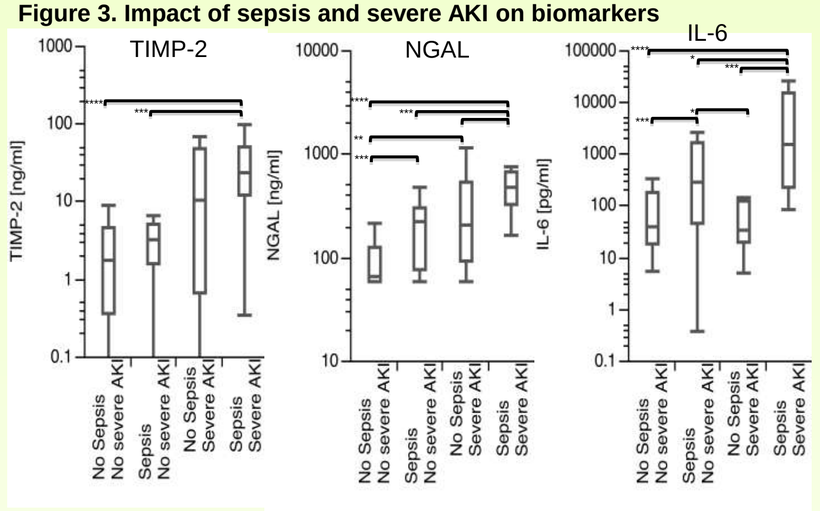


*All biomarkers are significantly increased in AKI patients (P < 0.001).

Table 2. Area under the receiver operating characteristic curve

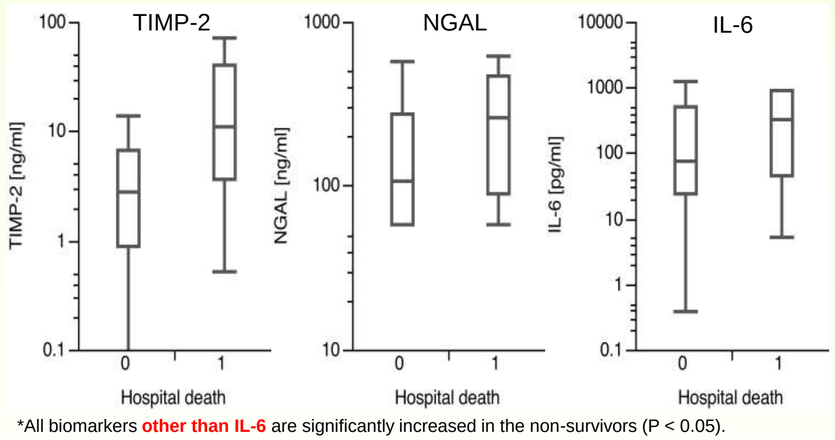
AUROC (95% CI)	TIMP-2	NGAL	IL-6	Cre
AKI	0.74 (0.63 – 0.83)	0.84 (0.74 – 0.91)	0.72 (0.60 – 0.81)	0.86 (0.77 – 0.92)
Severe AKI	0.80 (0.66 – 0.90)	0.87 (0.76 – 0.93)	0.69 (0.56 – 0.80)	0.85 (0.73 – 0.92)

Figure 3. Impact of sepsis and severe AKI on biomarkers



* p < 0.05 ** p < 0.01 *** p < 0.001 **** p < 0.0001

Figure 4. Biomarkers and in-hospital mortality



*All biomarkers **other than IL-6** are significantly increased in the non-survivors (P < 0.05).

Conclusions

A new urine biomarker of TIMP-2 is increased especially in severe AKI and associated with mortality. Sepsis appeared to have a smaller impact on urine TIMP-2 and NAG compared with plasma NGAL and IL-6.

References

1. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013;17:R25