BJA Advance Access published December 3, 2014

British Journal of Anaesthesia Page 1 of 9
doi:10.1093/bja/aeu382

BJA

Predictive value of urine interleukin-18 in the evolution and outcome of acute kidney injury in critically ill adult patients

S. Nisula[1]*, R. Yang[3], M. Poukkanen[4], S. T. Vaara[1], K. M. Kaukonen[1], M. Tallgren[5], M. Haapio[2], J. Tenhunen[6], A. M. Korhonen[1] and V. Pettilä[1], The FINNAKI Study Group

[1] Intensive Care Units, Division of Anaesthesia and Intensive Care Medicine, Department of Surgery and [2] Department of Medicine, Division of Nephrology, Helsinki University Central Hospital, Box 340, Helsinki 00029, Finland
[3] Critical Care Medicine Research Group, Department of Intensive Care Medicine, Tampere University Hospital, Tampere, Finland
[4] Department of Anaesthesia and Intensive Care Medicine, Lapland Central Hospital, Rovaniemi, Finland
[5] Department of Anesthesia and Intensive Care Medicine, Turku University Hospital, Turku, Finland
[6] Department of Surgical Sciences/Anaesthesiology and Intensive Care, University of Uppsala, Uppsala, Sweden

* Corresponding author. E-mail: sara.nisula@hus.fi

Editor's key points

- Acute kidney injury (AKI) is common in the critically ill.
- Concentrations of interleukin-18 (IL-18) in urine have been proposed as a new biomarker for AKI.
- In this large study, there was only a weak association between urinary IL-18 concentrations within 24 h of ICU admission and the development of AKI.
- These data do not support the use of urine IL-18 as a predictor of significant AKI in critically ill adults.

Background. Interleukin-18 (IL-18) is a pro-inflammatory protein, which mediates ischaemic tubular injury, and has been suggested to be a sensitive and specific biomarker for acute kidney injury (AKI). The predictive value of IL-18 in the diagnosis, evolution, and outcome of AKI in critically ill patients is still unclear.

Methods. We measured urine IL-18 from critically ill patients at intensive care unit (ICU) admission and 24 h. We evaluated the association of IL-18 with developing new AKI, renal replacement therapy (RRT), and 90-day mortality. We calculated areas under receiver operating characteristics curves (AUCs), best cut-off values, and positive likelihood ratios (LR+) for IL-18 concerning these endpoints. Additionally, we compared the predictive value of IL-18 at ICU admission to that of urine neutrophil gelatinase-associated lipocalin (NGAL).

Results. In this study population of 1439 patients the highest urine IL-18 during the first 24 h in the ICU associated with the development of AKI with an AUC [95% confidence interval (CI)] of 0.586 (0.546–0.627) and with the development of Stage 3 AKI with an AUC (95% CI) of 0.667 (0.591–0.774). IL-18 predicted the initiation of RRT with an AUC (95% CI) of 0.655 (0.572–0.739), and 90-day mortality with an AUC (95% CI) of 0.536 (0.497–0.574).

Conclusions. IL-18 had poor-to-moderate ability to predict AKI, RRT, or 90-day mortality in this large cohort of critically ill patients. Thus, it should be used with caution for diagnostic or predictive purposes in the critically ill.

Keywords: acute kidney injury; critical illness; interleukin-18; intensive care; long-term outcome; renal replacement therapy

Accepted for publication: 5 August 2014

Acute kidney injury (AKI) is a frequent organ dysfunction in critically ill patients, and it increases both short- and long-term mortality.[1–4] Current diagnosis and staging of AKI are based on changes in serum creatinine and urine output despite known shortcomings in these variables.[5] More specific, sensitive, and rapid biomarkers to identify and monitor AKI are needed.[6]

Interleukin-18 (IL-18) is a pro-inflammatory protein that acts as an immunoregulatory agent. It has been associated with many autoimmune diseases, ischaemic heart disease, emphysema, metabolic syndrome, and sepsis.[7] Regarding AKI, studies first showed that IL-18 mediates tubular injury in mice predisposed to ischaemia,[8] and that the lack of IL-18 protects from tubular damage.[9] Thereafter, data from humans indicated that urine IL-18 levels are higher in patients with kidney injury compared either with patients with transient functional renal dysfunction or with healthy controls.[10]

Based on pathophysiological plausibility urine IL-18 has been suggested as a new biomarker for AKI. However, only few studies have explored the value of urine IL-18 in the diagnosis,[11] evolution,[12] and outcome of AKI.[13] In paediatric patients undergoing cardiac surgery the predictive value of IL-18 to detect AKI has been good with AUCs exceeding 0.8,[14 15] but in adult patients,[16] and especially critically ill adult patients[12 17] the studies have reported discouraging results. In addition, no adequately powered clinical studies exist regarding renal replacement therapy (RRT).[18] Studies evaluating IL-18 in the prediction of mortality have been either too small[13] or used clinically too short observation periods.[11 12]

Accordingly, we tested the value of IL-18 separately in prediction of new AKI, RRT, and 90-day mortality in a large cohort of critically ill adult patients. We hypothesized that IL-18 would bring additional benefit to prediction of these outcomes and be useful in clinical practice.

Methods

Patients

The Ethics Committee of the Department of Surgery in Helsinki University Hospital gave approval for this study. We collected a written, informed consent from all study patients or proxy. This was a substudy of the prospective, observational, multicentre FINNAKI study.[3] The study included consecutive emergency intensive care unit (ICU) admissions and postoperative patients admitted for more than 24 h. The study excluded (i) patients <18 years of age, (ii) readmitted patients, who received RRT during their previous admission, (iii) patients electively admitted with an ICU length of stay of <24 h if discharged alive, (iv) patients on chronic dialysis, (v) organ donors, (vi) patients without permanent residency in Finland or without sufficient language skills, (vii) patients transferred between study ICUs if included in the study for 5 days already, and (viii) patients receiving intermediate care. As a result of logistic and economic reasons and to avoid futility we included a convenience sample of patients from the first half of the FINNAKI study (1.9–1.12.2011) for this substudy by taking complete sample boxes of consecutive patients out of storage by random blinded for any patient characteristics or studied outcomes.

Definitions

We used the KDIGO (kidney disease: improving global outcomes) guidelines[5] with both daily creatinine (Cr) and hourly urine output measurements to define AKI. We defined progression of AKI as worsening of KDIGO stage during Day 2 or 3 in the ICU or new onset of AKI on Day 2 or 3. For baseline creatinine we used the latest value from the previous year excluding the week before admission. In patients lacking a baseline Cr, we estimated it by the modification of diet in renal disease (MDRD) equation assuming a glomerular filtration rate of 75 ml min^{-1} 1.73 m^{-2} as recommended.[19 20] We defined sepsis with the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) guidelines.[21] The observation period for AKI and RRT was 3 days from admission because of the known kinetics of IL-18.[14] For analyses of AKI and RRT as endpoints, we excluded patients that fulfilled these endpoints already on Day 1.

Data collection

To obtain patient characteristics, severity scores, length of stay, and physiological data, we used a prospective study-specific database utilizing the platform of the Finnish Intensive Care Consortium database (Tieto Ltd, Helsinki, Finland). We created a daily case report form (CRF) to record additional patient information such as RRT and sepsis status. The Finnish Population Register Centre provided the 90-day mortality data.

Laboratory samples

We collected urine samples from all eligible patients on admission and 24 h later. We aliquoted and stored the samples at −80°C. We used the (Cusabio Biotech® Wuhan, China) ELISA kit for the IL-18 analyses. One author (R.Y., Tampere University Hospital, Tampere, Finland) assayed the samples according to the instructions, and he was blinded to patient data. For IL-18, the measurable range was 3.9–250 pg $litre^{-1}$. This ELISA method used shows good intra- and inter-assay precision [median coefficient of variation (CV%) <8% (intra), and <10% (inter)].

We had urine neutrophil-gelatinase associated lipocalin (NGAL) assayed from a cohort of patients from the FINNAKI study. Urine NGAL was analysed with the (Bioporto® NGAL Rapid) ELISA kit. We have previously published NGAL results[22] with patient cohorts for IL-18 and NGAL partly (59.4%) overlapping.

Statistical analyses

We compared non-parametric data with the Mann–Whitney *U*-test and categorical variables with the χ^2 test or Fisher's exact test. We present data as medians with interquartile ranges (IQRs) or as absolute numbers [percentage with 95% confidence intervals (CIs)]. We calculated areas under receiver operating characteristics curves (AUCs) with 95% CIs. We defined an AUC of 0.5–0.75 as poor, AUC of 0.75–0.9 as good, and AUC of >0.9 as excellent as suggested.[23] We identified the best cut-off points for IL-18 with the Youden index and calculated sensitivity, specificity, and positive likelihood ratios (LR+), using these cut-off points.

We separately tested the following variables: (a) the highest (admission or 24 h) IL-18 concentration (IL-18max), (b) the change in IL-18 concentration from admission to 24 h. Finally we compared (c) admission IL-18 to the admission NGAL, and (d) the combination (IL-18×NGAL) to admission IL-18 and NGAL. We tested the independent predictive value of IL-18max concerning AKI and 90-day mortality by logistic regression analysis. We constructed multivariable models by testing variables in univariable models and selecting significant values ($P<0.2$) to the multivariable models. Furthermore, we added *post hoc* analysis regarding extension of observation period to 5 days regarding new AKI and RRT. We performed all analyses with SPSS version 20 and 21 (SPSS, Chicago, IL, USA).

Results

Altogether 1439 patients had a urine IL-18 sample available on ICU admission. Of these, 1080 (75.1%) also had an IL-18 sample at 24 h available. The study flow chart is shown in Figure 1. The characteristics of the included study patients are presented in Table 1.

IL-18 and development of new AKI

The incidence of AKI in this study population was 497/1439 (34.5%). Of the 497 AKI patients, 229 (46.1%) had AKI on admission day and, thus, we excluded those patients from the analysis regarding new AKI. Of the remaining 1210 patients