Value of single and combined inflammatory and kidney-dependent parameters for prediction of prognosis in septic shock

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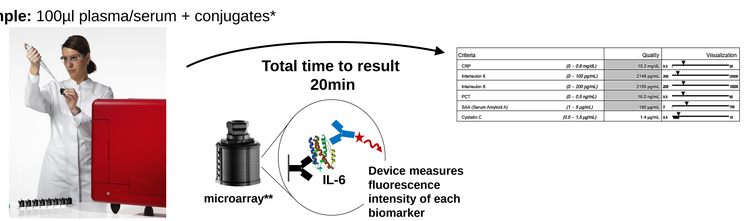
Background. Single inflammatory parameters like C-reactive protein (CRP), procalcitonin (PCT) and interleukin-6 (IL-6) are widely used in patients to diagnose sepsis. Aim of this study was to evaluate the prognostic value of inflammatory markers and new renal function parameters as single parameters in comparison to their combination in septic shock.

Methods. In a prospective study including 113 patients with septic shock *[1]*, CRP, PCT, IL-6, cystatin C and NGAL levels were quantified in 100 µL plasma by the multiplex hybcell technology (Fig.1; Cube Dx GmbH, Austria) on admission and day 1 of intensive care unit (ICU) stay. Informed consent was obtained from all patients or their legal representatives. Patients were followed up during ICU stay for death and acute kidney injury (AKI) *[2]*. To compare the groups, a two-tailed Mann Whitney U test was used, and a p-value < 0.05 was considered to be significant. In addition to single markers, combinations of two markers were derived by fitting logistic regression models including the two main effects and the interaction effect. For evaluation of the sensitivity and specificity of the single and combined markers, we constructed Receiver-Operating-Characteristics (ROC) curves and determined the cross-validated area under the curve (AUC) *[3]*.

[1] Bone et al. Chest 1992;101(6):1644-55. *[2]* Yong et al. Int J Nephrol 2011; 2011:762634. *[3]* Boule

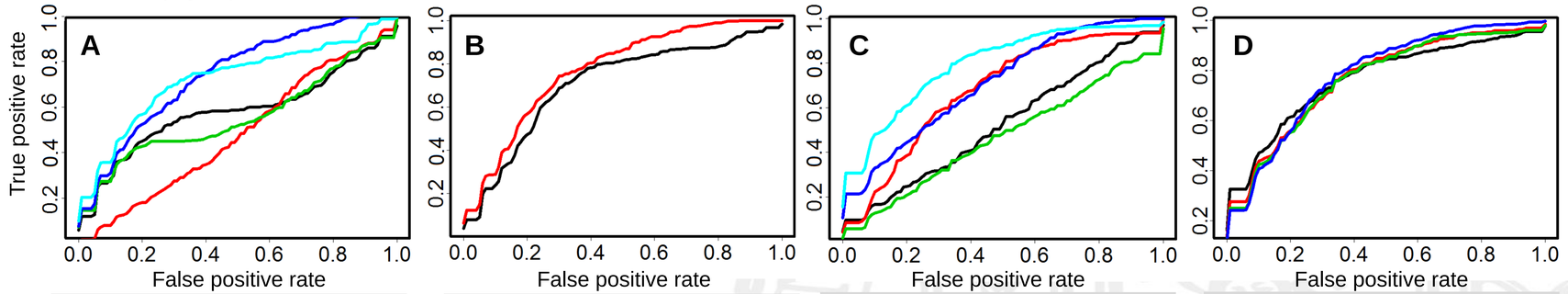


* conjugates; fluorescence labelled proteins (for competitive assay) and antibodies (for sandwich assay)
** microarray; during production antibody solutions are dispensed in array (grid) formation on the surface, immobilized antibodies capture labelled conjugates (e.g., CRP) or sample proteins (e.g., IL-6)

Figure 1[#]: Processing of samples

[#] with friendly permission of the Cube Dx GmbH, Austria.

Results. CRP, PCT and IL-6 on admission of patients showed no significant differences between patients who died and survivors. Patients with and without AKI had similar CRP and IL-6 values. Only PCT was significantly higher in AKI patients (p=0.01).
For prediction of death the AUC of the single inflammatory parameters ranged between 0.43 and 0.64 and was highest for CRP. The single kidney function parameters showed higher AUC values ranging between 0.65 and 0.75 with the highest value for NGAL on admission (Fig.2A). The combination of two inflammatory parameters to predict death reached AUC values between 0.38 and 0.59. In contrast, the combination of two kidney function parameters or of an inflammatory and a kidney function parameter on admission generally revealed AUC values higher > 0.65 with the highest AUC of 0.77 for CRP and cystatin C (Fig.2B). The AUCs for death prediction of these combined parameters were generally higher when calculated on admission than on day 1 of ICU stay.
For prediction of AKI the AUCs of the single kidney function parameters cystatin C and NGAL were higher (0.67-0.79) than that of inflammatory parameters ranging between 0.46 and 0.67 (Fig.2C). The combination of inflammatory parameters to predict an AKI showed AUC values between 0.46-0.65. In contrast, the combination of one inflammatory and one kidney function parameter on admission or on day 1 generally revealed AUC values higher than 0.61 with the highest AUCs for cystatin C combined with PCT (0.77), IL-6 (0.76) and CRP (0.75) on day 1, respectively. The combination of cystatin C with NGAL was similar with an AUC of 0.77 (Fig.2D).



Single markers on admission:
CRP (black), PCT (red), IL-6 (green), NGAL (blue), cystatin C (light blue).

Combined markers on admission:
NGAL * cystatin C (black), CRP * cystatin C (red).

Single markers on day 1:
CRP (black), PCT (red), IL-6 (green), NGAL (blue), cystatin C (light blue).

Combined markers on day 1:
CRP * cystatin C (black), PCT * cystatin C (red), IL-6 * cystatin C (green), NGAL * cystatin C (blue).

Figure 2: Cross-validated receiver-operating curves (ROC) for prediction of death (A, B) and acute kidney injury (C, D)

Summary and conclusions. Appropriate biomarkers for predicting prognosis in septic shock would be helpful for optimized management of septic shock and rational resource allocation in the intensive care unit. The main findings of our study in septic shock patients include 1) that single kidney function parameters tend to be more useful than single inflammatory parameters with regard to the prediction of poor clinical outcome including death and AKI, and 2) that the combination of two parameters seems to be a better predictor for death than levels of a single parameter.
The composition of inflammatory and new AKI parameters seems to provide an approach to a more accurate prognosis and identifies the septic shock patients with the worst clinical outcome. Since these parameters can all be obtained quickly by multiplex technology, our data support the adoption of a risk marker approach for mortality and AKI risk stratification in septic shock.