Proline-specific enzymes as potential biomarkers in septic shock patients (sepsis-2)

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Introduction & Materials and Methods

To date, there is no standard diagnostic test to identify septic patients, although early identification is necessary to improve their outcome [1]. We sought to identify novel biomarkers by studying the enzymatic activity of the proline-specific peptidases dipeptidyl peptidase 4 (DPP4), prolyl carboxypeptidase (PRCP), fibroblast activation protein α (FAP) and prolyl oligopeptidase (PREP) in EDTA-plasma of 22 intensive care controls and 40 patients with septic shock (sepsis-2) on days 1, 3, 5 and 7. DPP4 activity was measured using the colorigenic substrate Gly-Pro-pNA, PRCP using a RP-HPLC technique, measuring the hydrolysis of Z-Pro-Phe and FAP and PREP activity was determined by cleavage of the fluorogenic substrate Z-Gly-Pro-AMC. On the same days, inflammatory (e.g. TNFα, IL-6), hemodynamic (e.g. mean arterial pressure, pulse) and metabolic parameters (e.g. bilirubin, lactate) were also measured to identify possible associations.

Enzymatic activities
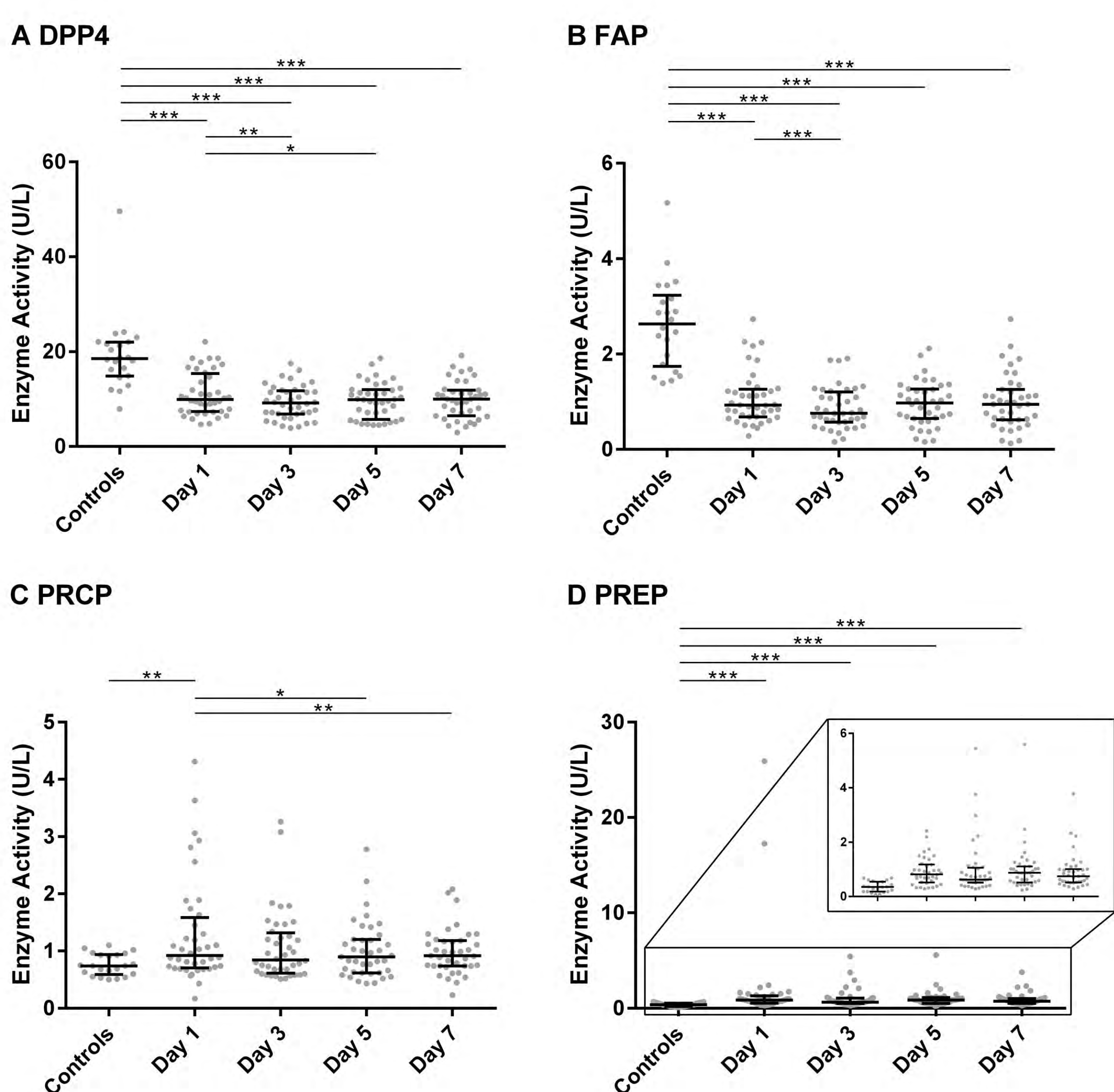
Between control group and different days: linear mixed models, post-hoc Dunnet's correction. Within cases: linear mixed models, post-hoc Tukey's correction. Data are presented as median with interquartile range. * p≤0.05; ** p≤0.01; *** p≤0.001.

ROC-curves
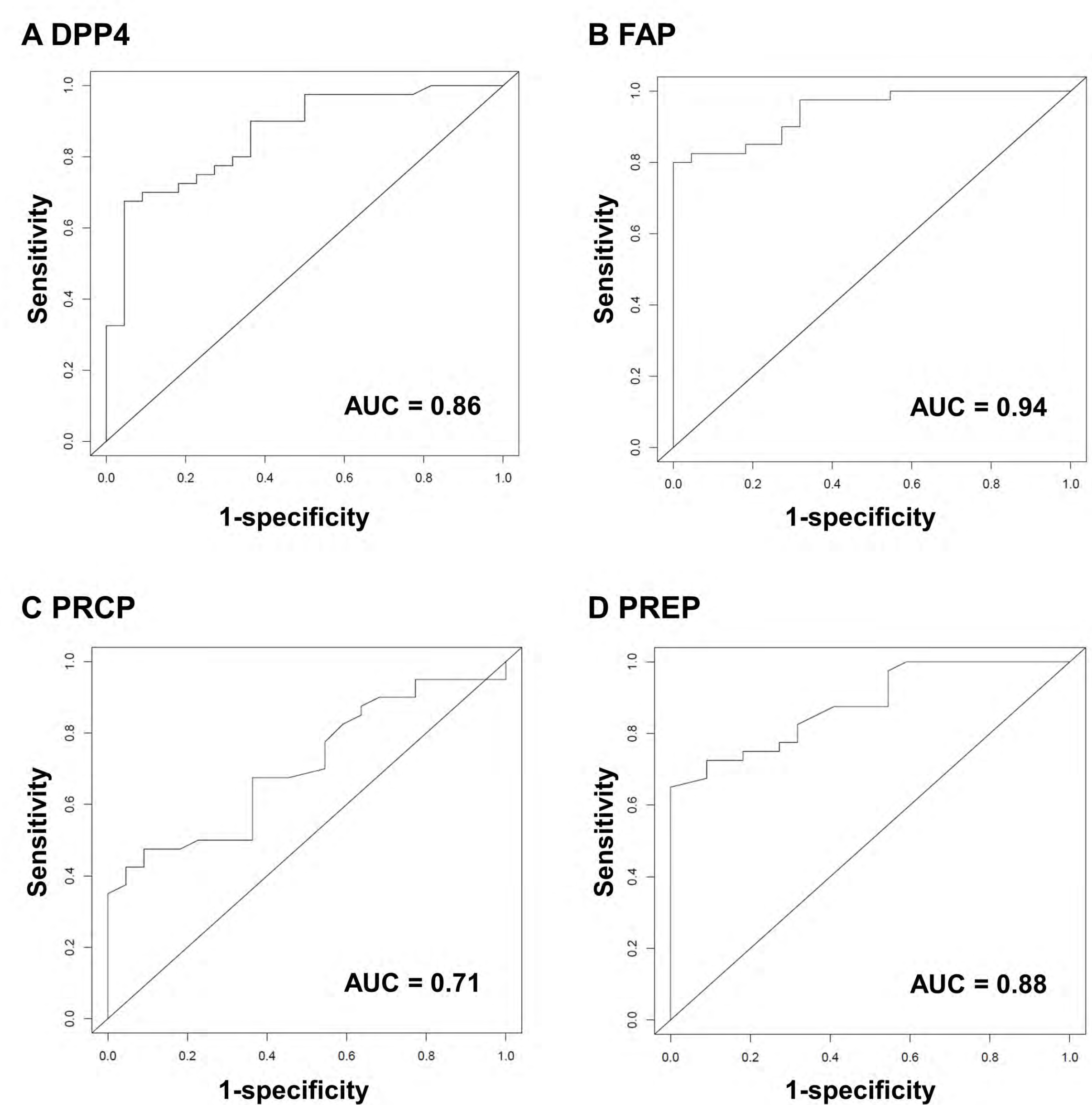
Abbreviations: ROC: receiver operating characteristics; AUC: area under the curve.

Associations

Abbreviations: I-FABP, intestinal fatty acid-binding protein; IFNγ, interferon γ; IL, interleukin; IL-1RA, IL-1 receptor antagonist; MAP, mean arterial pressure; NIR, noradrenalin infusion rate; PaO$_2$/FiO$_2$ ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen; TNFα, tumor necrosis factor α.
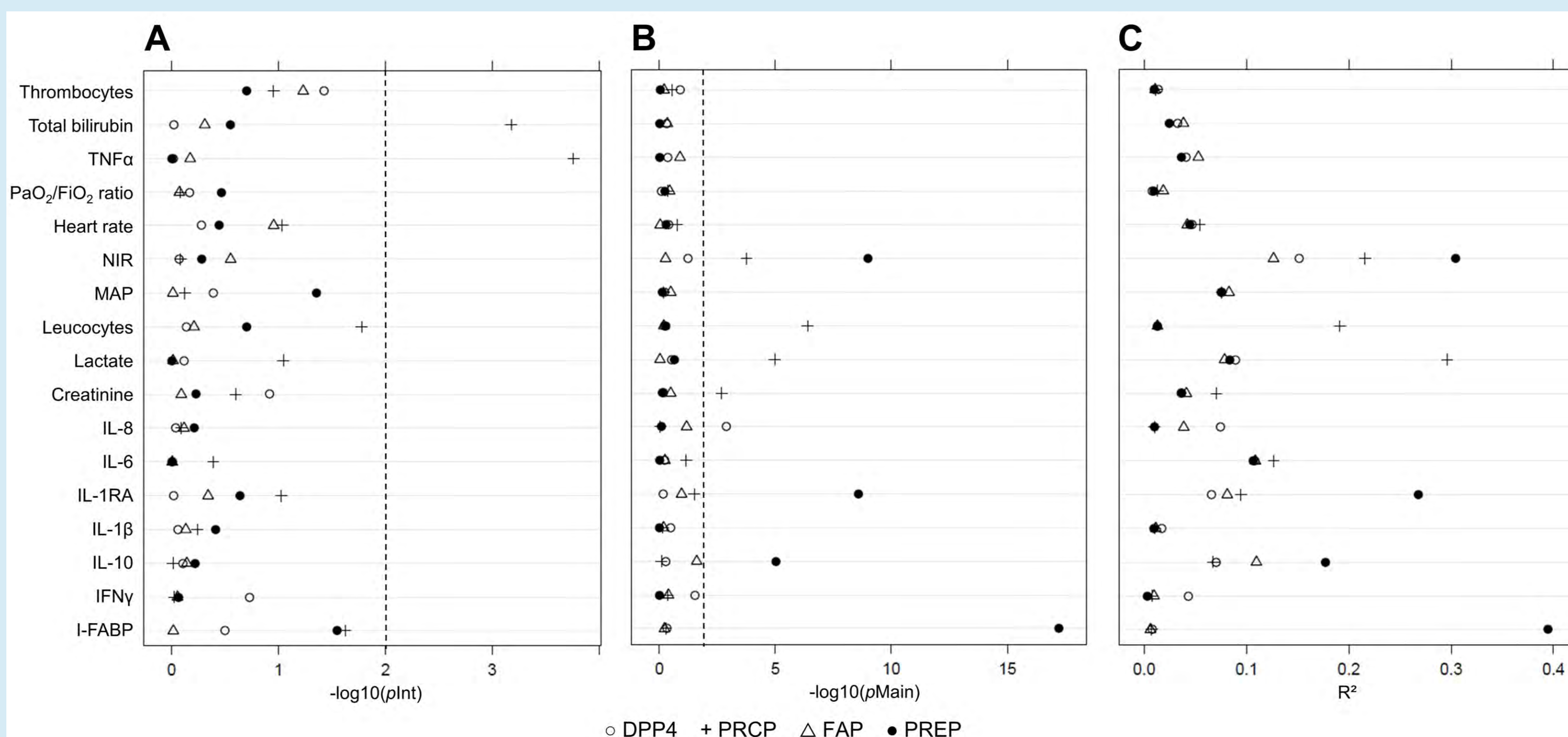
pInt: Log-transformed p-value for the interaction of the longitudinally measured parameters; **pMain:** Log-transformed p-value for the main effect for the longitudinally measured parameters; The dotted line indicates p≤0.01. Linear mixed models were used. In case of a significant interaction between time and the parameter, no main effect p-value is shown in the dot plot. R² is only depicted when pInt>0.01.

Conclusions

Large differences in the enzymatic activities of the enzymes could be seen between controls and patients over the 4 days. Especially DPP4, FAP and PREP are good at discriminating between controls and cases. Further research should specify if they are also good in discriminating between sepsis and other conditions. Several interesting associations, such as between **PRCP and PREP with noradrenalin, PRCP with lactate and PREP with IL-1RA and I-FABP** were identified. Some of these associations can, possibly partly, be explained by already known mechanisms. The association between PREP and IL-1RA and PREP and I-FABP on the other hand is new and unexplored and warrants further research.

References:
1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. American Medical Association; 2016;315:801.