Characterisation of host-response heterogeneity in the sepsis transcriptome using two immune axis scores

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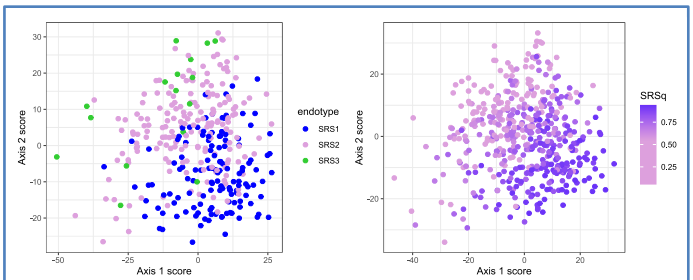
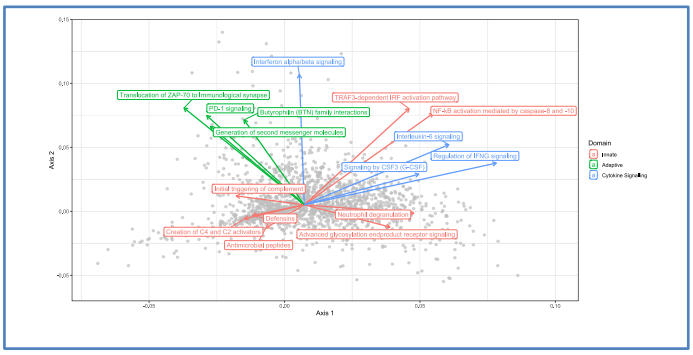
Background

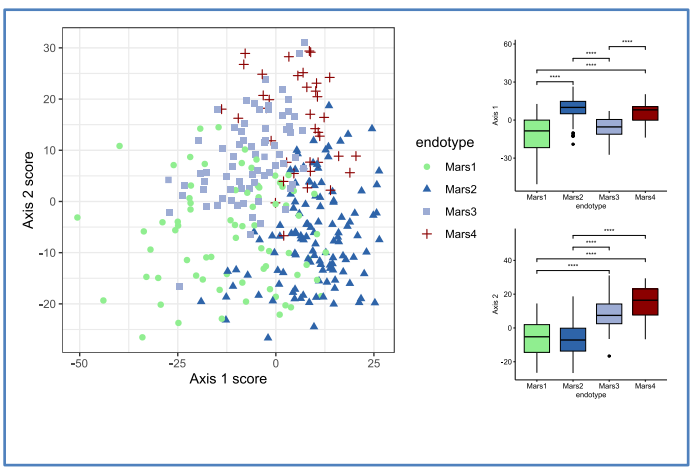
Host responses during sepsis are highly heterogeneous, complicating the identification of patients at risk of mortality or those potentially benefitting from targeted therapies. Previous studies have identified transcriptomic endotypes to assist with this challenge, to classify patients into categories. Here we introduce a two-dimensional framework for measuring patients' immune system heterogeneity using two continuous "immune-axis" scores.

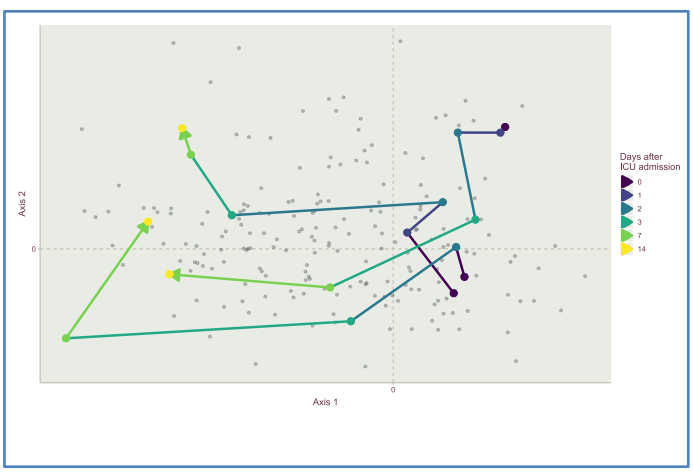
Methods

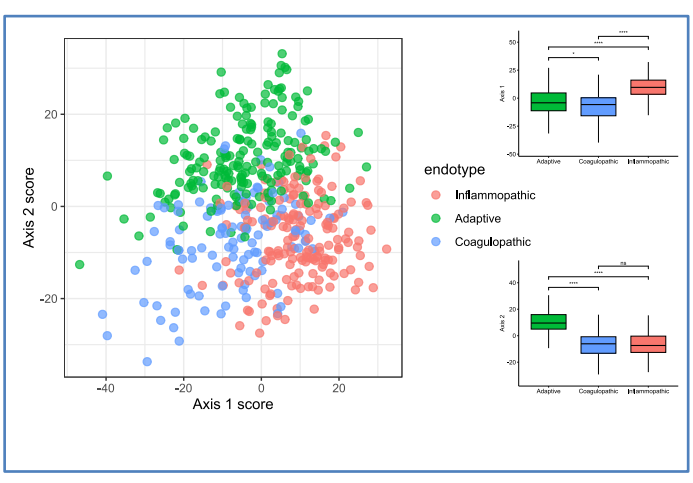
Whole-blood transcriptome was measured in 479 patients with sepsis at ICU admission using microarray (U219). Genes related to the immune system were selected and principal component analysis (PCA) analysis was performed. The first two PC scores are taken as the immune-axes scores. Upon these axes the scatter plot was coloured separately for each of the three existing sepsis endotype systems (Davenport et al., Scicluna et al. and Sweeney et al). Immune system pathway directionality was determined using the centroid of the constituent gene loadings within each Reactome pathway in the "Immune System" domain. A 20-gene signature was developed to enable axis scores to be calculated on different RNA platforms (e.g. RNAseq). Finally the axes scores were calculated for 39 CAP sepsis patients from the placebo arm of an RCT, in which whole-blood transcriptome was measured at multiple time-points (0,1,2,3,7 and 14±2 days after ICU admission) using RNAseq. Individual trajectories were plotted on the two axes and an average trajectory was estimated using linear mixed modelling.

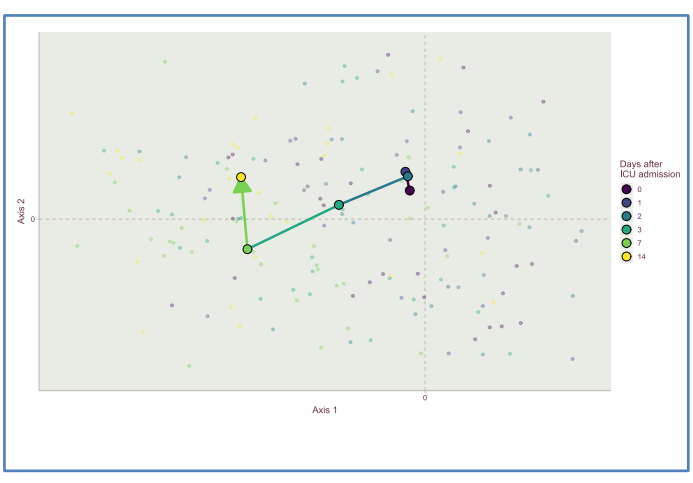












CONCLUSIONS

- By accurately accounting for time-dependent exposure and confounding factors, our study demonstrates that the onset of ICU-acquired AKI is independently associated with a higher case fatality rate.
- Next steps include to model the attributable effect of persistence of AKI versus patients with a transient-AKI course on ICU mortality.