

Classification of sepsis patients as four blood genomic endotypes with prognostic and pathophysiological implications

- ▶ Allows for the risk stratification of sepsis patients, with patients classified as Mars1 endotype having the highest risk of mortality.
- ▶ Mars1-4 endotypes are characterized by shared and distinct biological mechanisms
- ▶ Tests can be performed within 4 hours of intensive care unit admission using whole blood

Sepsis | blood genomics | endotypes | risk stratification | precision medicine

Background

Sepsis remains a remarkable adversary to medicine, characterized by poor prognosis and high mortality rates. Despite the burden on patients, their families and the health care system, treatment remains mainly supportive. Unrecognized population substructures and the heterogeneity in the host response complicate the identification of high-risk patients who would benefit from specific adjuvant therapy. Blood transcriptional profiling has provided substantial advances in the context of sepsis.

Although promising new diagnostic biomarkers have emerged from the application of blood genomics to sepsis, patient selection for interventional trials and prognostication in sepsis continue to be driven by clinical criteria.

Invention

Gene expression data from 306 sepsis patients revealed that patients can be stratified as four molecular endotypes, designated Mars1-4. Importantly, Mars1-4 endotypes also stratified patients by risk of mortality, with the worst outcome at 28 days found for those patients classified as Mars1 with 39% mortality (n=35 out of 90); 22% (n=21 out of 105) for Mars2, 23% (n=16 out of 71) for Mars3 and 33% (n=13 out of 40) for Mars4 (Figure 1).

Mars1 patients were characterized as an immune paralyzed group of patients with dramatic depression of innate and adaptive immune functions. Mars2 was characterized by hyperinflammation, exemplified by high NF- κ B, Toll-like receptor and IL-6 signaling. Mars3 was characterized as a relatively lower risk

endotype with heightened adaptive immune functions, for example T cell receptor signaling and antigen presentation. Mars4 was characterized as a hyperinflammation endotype, specifically high in interferon signaling.

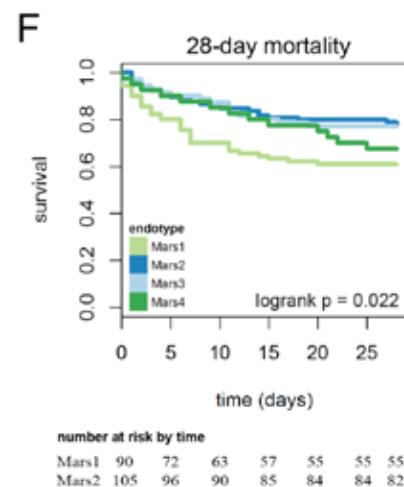


Figure 1. Unsupervised classification of sepsis patients and the association to clinical characteristics and outcome (discovery cohort). 28-day mortality by Kaplan-Meier survival analysis. X², chi-squared.

Robustness of invention

Gene expression data from an additional independent 216 sepsis patients also showed Mars1-4 blood genomic endotypes, again with Mars1 endotype having the highest risk of mortality. Moreover, robustness of the four endotype model was ascertained in another independent validation cohort from

the United Kingdom (GAINs cohort). Again, Mars1-4 endotypes were detected and Mars1 classified were at highest risk of mortality.

Biomarkers

A two gene ratio was derived for each endotype to enable clinical application as a PCR-based point-of-care test, with BPGM and TAP2 clearly classifying patients as the high-risk Mars1 endotype. Blood collected within the first 24hours of ICU admission as part of routine critical care can be used.

Applications

The four endotypes Mars1-4 allows for the stratification of sepsis patients, with varying risk of mortality. Blood collected from sepsis patients within the first 24 hours of ICU admission as part of routine critical care can be used. PCR technology allows for rapid screening, that is within 4 hours. Applicable to adult sepsis patients receiving critical care.

Intellectual property

A priority patent application covering this invention was filed in February 2017.

Inventor

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What are we looking for?

Licensing partner for this technique.

Key Publication

Scicluna BP, van Vught LA, Zwinderman AH, Wiewel MA, Davenport EE, Burnham KL, Nürnberg P, Schultz MJ, Horn J, Cremer OL, Bonten MJ, Hinds CJ, Wong HR, Knight JC, van der Poll T; MARS consortium. Classification of patients with sepsis according to blood genomic endotype: a prospective cohort study. *Lancet Respiratory Medicine*, Oct 2017