TBX21 as an early immune biomarker of sepsis and septic shock: development of a prognostic immune risk score model

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The early detection of sepsis onset, progression to septic shock, and accurate prognosis are critical for effective management, yet reliable biomarkers for diagnostic and prognostic assessments remain lacking. The present study aims to identify a potential biomarker, explore its relationship with immune function, and develop an immune-related risk score (IRS) prognostic model. Adult sepsis and septic shock datasets from the GEO database were screened. Through differential gene expression analysis, weighted gene coexpression network analysis, and STRING-Cytoscape analysis, hub genes associated with the trend of sepsis onset and progression to septic shock were identified. Among these, reduced *TBX21* was associated with increased 28-day mortality in sepsis patients after prognostic analysis. Enzyme-linked immunosorbent assay (ELISA) further confirmed that serum TBX21 progressively decreased in healthy volunteers, septic patients and patients with septic shock. GSEA showed that *TBX21* functioned primarily through immune signalling pathways. Immunoscore and immune infiltration analyses were used to evaluate immune scores and immune cell changes in septic shock and sepsis patients with low *TBX21* expression. The proportion of M0 macrophage infiltration was significantly increased; however, CD8(+) T-cell infiltration was decreased in both septic shock patients and sepsis patients with low *TBX21* expression. External validation of flow cytometry also found that patients with septic shock had significantly fewer CD8(+) T cells in their peripheral blood compared to patients with sepsis. Based on *TBX21* expression, prognostic signatures were identified (*CEACAM6*, *PTGDS*, and *CX3CR1*) to develop an IRS model, validated for stability and predictive ability internally. Expression trends of these signatures across healthy volunteers, sepsis, and septic shock groups were characterised. In conclusion, *TBX21* was identified as a potentially protective gene that may regulate the onset and progression of sepsis to septic shock at early stages, predominantly through immune pathways. Early reduced *TBX21* expression correlated with increased 28-day mortality in sepsis patients, and the developed IRS prognostic model had high stability and predictive ability. *TBX21* may be a potential immunotherapeutic target for sepsis.

Keywords: Bioinformatics, immune-related risk score, prognostic signatures, sepsis, septic shock, *TBX21*

SEPSIS, a life-threatening systemic inflammatory response syndrome caused by various infections, represents a major global health challenge with a high annual incidence worldwide and a substantial economic burden on healthcare systems, particularly when progressing to septic shock. Despite improvements in diagnostic and therapeutic techniques in developed countries, mortality rates, particularly in patients with septic shock, remain high[1,2]. In clinical practice, sepsis may rapidly deteriorate into life-threatening septic shock, resulting in significantly worse clinical outcomes. The dominant methods currently used for sepsis prognosis and severity assessment rely on clinical scoring systems (the SOFA score, APACHE II score, SAPS II score, etc.)[3,4] and classical biomarkers (interleukin 6, C-reactive protein, procalcitonin, etc)[5,6]. However, these approaches lack disease specificity and do not adequately reflect the immune changes that occur during sepsis progression. In recent years, early immune suppression in sepsis patients has been shown to be an important contributor to the development of septic shock[7], and early immune dysfunction can be further exacerbated in patients with septic shock[8]. Several studies have been dedicated to identifying sepsis-specific immune biomarkers[9–11]; however, research has yet to confirm the reliability of these novel biomarkers.

As septic shock is associated with poorer clinical outcomes, there is an urgent need for reliable and easily detectable biomarkers to predict the risk of sepsis development, progression and prognosis. Early identification of high-risk patients would enable the timely implementation of aggressive and effective interventions to improve patient outcomes. Furthermore, exploring the role of biomarkers in the dysregulation of the immune system during sepsis

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