Title: Dynamic Profile and Prognostic Value of microRNAs in Sepsis and Post-Sepsis: A Comprehensive Longitudinal Study

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Introduction: Sepsis is a life-threatening condition with high mortality during intensive care unit (ICU) stay, reaching up to 50%. Survivors also face elevated post-discharge mortality, often attributed to post-sepsis syndrome (PSS), whose etiology remains partially understood. Persistent inflammation is a key feature of PSS. In this context, extracellular vesicles (EVs) have gained attention for their role in intercellular communication during inflammation. The expression of microRNAs (miRNAs) via EVs during the acute phase of sepsis may persist long after recovery and contribute to PSS**.**

Objectives: To investigate the temporal expression profile and prognostic value of miRNAs in patients with sepsis over a long-term follow-up.

Methods: A prospective longitudinal study was conducted with 36 sepsis patients. Blood samples were collected at six time points (A–F) over a three-year follow-up. The expression of 15 selected miRNAs was quantified by RT-qPCR. Statistical analyses included non-parametric tests, mixed linear models, and survival analyses using Kaplan-Meier and Cox regression.

Results: The cohort had a mean age of 60 years, with a 61% mortality rate. In the initial phase, 14 out of 15 miRNAs showed differential expression between survivors and non-survivors, notably miR-191-5p and miR-27a-3p. Univariate survival analysis identified 14 miRNAs associated with prognosis, with miR-30d-5p and miR-191-5p showing the strongest associations. Multivariate analysis confirmed seven miRNAs and age as independent prognostic markers. Over time, miRNA expression patterns became increasingly synchronized, as shown by correlation analyses. Mixed linear models revealed a significant increase in several miRNAs across follow-up points.

Conclusion: This study demonstrates the dynamic nature of miRNA expression in sepsis and its prognostic relevance over time. Persistent alterations in miRNA levels, particularly in survivors, support their potential as biomarkers for risk stratification and long-term outcome prediction in sepsis. These findings underscore the need for further studies on the molecular mechanisms involved in systemic inflammation and PSS.