Differential Expression of miRNAs Involved in Shock Are Able to Characterise Mortality

Authors: *I. Rebollo-Mato,[1] A. García-Concejo,[2] L. Polo-Sánchez,[3] R. Prieto-Utrera,[3] P. Martínez-de Paz,[2] M. Álvarez-Bardón,[1] J. Matesanz-Isabel,[3] H. Gonzalo-Benito,[3] R. Cobo-Zubia,[4] E. Gómez-Sánchez,[5] M. Martín-Fernández,[1] E. Tamayo-Gómez[5]

1. University of Valladolid, Spain
2. Center for Biomedical Research Network on Infectious Diseases, Madrid, Spain
3. Institute of Health Sciences of Castile and León, Soria, Spain
4. Carlos III Health Institute, Madrid, Spain
5. University Clinical Hospital of Valladolid, Spain

*Correspondence to irina.rebollo22@uva.es

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BACKGROUND AND AIMS

Postoperative shock, particularly septic shock, is a leading cause of circulatory failure and mortality in the ICU.[1,2] Differentiating septic from non-septic postoperative shock remains a major clinical challenge due to overlapping haemodynamic profiles and the limited sensitivity of conventional clinical scores in detecting early molecular alterations.[3,4] Extracellular vesicle-derived microRNAs (EV-miRNA) have emerged as promising biomarkers reflecting endothelial dysfunction, inflammatory activation, and immunometabolic dysregulation in shock states.[5,6] This study aimed to characterise the EV-miRNome in postoperative shock and evaluate its diagnostic and prognostic utility.

METHODS

The authors conducted a multicentre prospective study including two independent cohorts of adult surgical patients: a discovery cohort (n=164) and a validation cohort (n=84). Patients were classified into postsurgical controls without shock and a shock cohort, including septic and non-septic postoperative shock. Only microbiologically confirmed septic shock cases were included. Plasma EV-miRNAs were isolated within 24 hours of shock diagnosis and profiled using small RNA sequencing. Differential expression analysis was performed using DESeq2 (Bioconductor; Buffalo, New York, USA), followed by Gene Ontology/Kyoto Encyclopedia of Genes and Genomes enrichment, receiver operating characteristic-based prognostic modelling, quantitative PCR validation, and Cox regression for 90-day mortality.

RESULTS

Twenty-six EV-miRNAs were significantly dysregulated in shock patients compared to controls. miR-4488 and miR-3960 showed the strongest association with disease severity, correlating with Sequential Organ Failure Assessment (SOFA) score, haemodynamic impairment, and hepatic dysfunction. Individually, miR-4488 (area under the curve [AUC]: 0.786) and miR-3960 (AUC: 0.775) showed moderate predictive ability for mortality, while their combined model significantly improved prognostic performance (AUC: 0.895), outperforming C-reactive protein, procalcitonin, leukocytes, creatinine, and clinical scoring systems. High expression of both miRNAs was independently associated with increased 90-day mortality in multivariate Cox analysis. Quantitative PCR validation confirmed their overexpression, achieving an AUC of 0.952 in the validation cohort.

DISCUSSION

Postoperative shock represents a heterogeneous clinical syndrome in which early discrimination between septic and non-septic aetiologies remains essential but challenging. Current diagnostic strategies rely on systemic inflammatory markers and physiological parameters that fail to capture underlying molecular heterogeneity, highlighting the need for more sensitive biomarkers.[7] Extracellular vesicles act as mediators of intercellular communication and carry microRNAs reflecting endothelial injury, immune dysregulation, and metabolic reprogramming.[8,9] In this context, EV-miRNAs provide a dynamic and minimally invasive window into disease pathophysiology.[10,11]

The authors' findings identify a distinct EV-miRNA signature associated with postoperative shock. miR-4488 and miR-3960 were consistently linked to organ dysfunction and severity, suggesting their involvement in vascular integrity and systemic inflammatory pathways. Their combined predictive value significantly improved mortality stratification compared with standard biomarkers and clinical scores. These results support the role of EV-miRNAs as active contributors to shock pathophysiology rather than passive markers.

CONCLUSION

In conclusion, postoperative shock exhibits a specific EV-miRNA profile with strong diagnostic and prognostic implications. miR-4488 and miR-3960 emerge as robust biomarkers associated with endothelial dysfunction, immunometabolic activation, and organ failure. Their integration into biomarker panels may improve early risk stratification and mortality prediction in postoperative patients who are critically ill.

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