Title: Longitudinal Characterization of Plasma Extracellular Vesicles: From Acute Phase to Late Convalescence of Malaria

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Introduction: *Plasmodium vivax* infection triggers profound immune and metabolic alterations that often persist even after parasite clearance and clinical recovery. In this context, extracellular vesicles (EVs) emerge as key players in pathogen-host communication, although their molecular dynamics over time remain to be fully elucidated. **Objectives:** This study aimed to detail the proteomic composition of plasma EVs at different stages of vivax malaria, investigating how these vesicles reflect the host-parasite interaction from the acute phase to late convalescence. Methods: A longitudinal follow-up was conducted with 12 patients in Manaus-AM, with samples collected on days 0 (acute), 50, and 180 (convalescence). EVs were isolated by ultracentrifugation and analyzed using NTA, TEM, and high-resolution proteomics (LC-MS/MS), integrating the findings with clinical laboratory exams and cytokine profiling. **Results:** We observed a significant increase in EV concentration during the acute phase. Proteomic analysis identified 508 proteins, revealing a continuous functional remodeling of the vesicular cargo. At the onset of infection (D0), there was a strong enrichment of inflammatory pathways and the complement system. This pattern was corroborated by clinical exams and cytokine profiles, evidencing a convergent systemic response. Over the months (D50-D180), the EVs transitioned toward signatures of homeostasis and tissue repair. A crucial finding was the detection of parasite proteins (such as LDH, MSP3α, and MSP3γ) even after treatment, indicating the persistence of molecular signals. Furthermore, recurrence cases showed a marked reactivation of inflammatory pathways. **Conclusion:** Our data demonstrate that plasma EVs act as dynamic sensors of patient health, preserving infection-related information for months. This positions them as promising biomarkers for understanding pathogenesis and the risks of recurrence in malaria.