

Monocyte HLA-DR Dynamics and Host Response in Ageing and Pneumonia-Induced Sepsis

Project brief

Sepsis is a life-threatening syndrome characterized by a dysregulated host response to infection leading to organ failure and remains a major contributor to global mortality. Conventional inflammatory markers provide limited insight into immune function. Monocyte surface HLA-DR, a key molecule involved in antigen presentation, is increasingly recognized as a biomarker of sepsis-associated immunosuppression. Its has been used to stratify patients for immunomodulatory therapies and clinical trials. Understanding the relationship between monocyte HLA-DR dynamics and broader host response features may offer new opportunities for personalized treatment in sepsis.

Methodology

This study was conducted as part of the MENDSEP project (NCT06287684), a prospective, single-centre observational study enrolling 36 adult patients with pneumonia-associated sepsis between September 2023 and April 2025. Sepsis was defined in accordance with Sepsis 3.0 criteria, having sequential organ failure assessment (SOFA) scores greater than 2.0. Age-, sex-, and comorbidity-matched control participants (n=38) were recruited from the community or Saint Vincent de Paul long-term care facility.

Ethical conduct of the study followed the principles outlined in the Declaration of Helsinki and approved by the Mater Dei Hospital Data Protection and Health Ethics Committee (Approval No. HEC08/23) and University of Malta Research Ethics Committee (Approval No. FHS-2023-00473). Saint Vincent de Paul Hospital Data Protection and University of Malta Research Ethics Committees approved the study (Approval No. FHS-2023-00475). Written informed consent was obtained from all participants or their legal representatives before enrolment.

Whole blood (K₃EDTA) was used for flow cytometry and plasma protein profiling targeting soluble mediators of the host response.

Results & Conclusions

Monocyte HLA-DR Declines With Age and Sepsis, Reinforcing Its Role as a Biomarker of Sepsis-Associated Immunosuppression

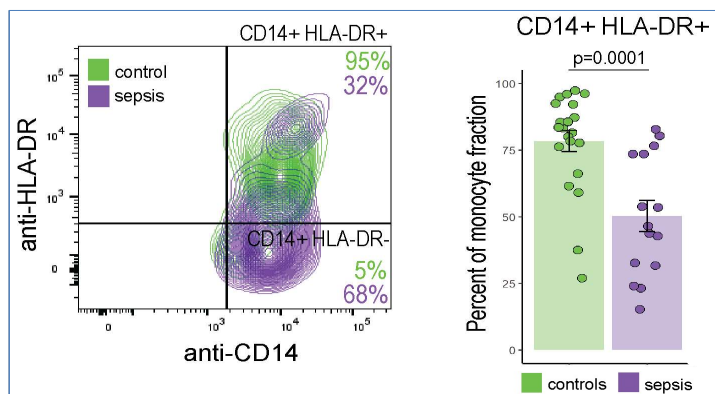


Figure 1: Representative flow cytometry contour plot illustrating the shift in monocyte HLA-DR expression in a sepsis patient compared to a control participant. Percentages reflect events within the monocyte gate. Bar plot depicting the proportion of CD14⁺HLA-DR⁺ cells within the monocyte gate. P-value derived from the Wilcoxon rank sum test.

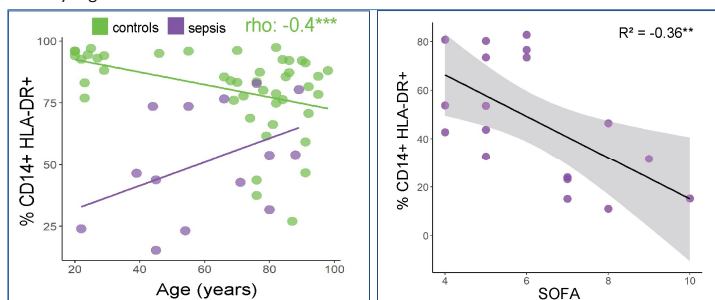


Figure 2: Scatter plot (left panel) showing monocyte HLA-DR expression across age in sepsis and control subjects. Rho, Spearman's correlation coefficient. ***p<0.001. Scatter plot (right panel) illustrating the inverse correlation between clinical severity (SOFA) and the percentage of CD14⁺HLA-DR⁺ cells within the monocyte fraction. Spearman's correlation; p < 0.01.

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Parameter	Sepsis Patients	Control subjects	P-value
n	36	38	-
Demographics			
Age, mean years (SD)	63.7 (17.6)	68.2 (26.7)	0.40 ^a
Sex, males (%)	23 (63.9)	20 (52.6)	0.36 ^b
Nursing home resident, n (%)	5 (13.9)	25 (65.8)	<0.001 ^b
BMI, median (Q1, Q3)	27.1 (24.8, 32.4)	26.7 (24, 30.1)	0.42 ^c
Comorbidities, n (%)			
Hypertension	16 (44.4)	18 (47.4)	0.82 ^b
Diabetes	12 (33.3)	10 (26.3)	0.61 ^b
Cardiovascular Disease	12 (33.3)	14 (36.8)	0.81 ^b
COPD	6 (16.7)	6 (15.8)	1 ^b
Malignancy	4 (11.1)	5 (13.2)	1 ^b
CCI, median (Q1-Q3)	1.0 (0, 2)	-	-
Clinical Severity, median (Q1-Q3)			
SOFA score	5 (4.8, 7.3)	-	-
APACHE II	21.0 (19, 24)	-	-
Shock, n (%)	20 (55.6)	-	-
Outcome, n (%)			
28-day mortality	11 (30.6)	-	-

a Mann-Whitney test p-value, b Fisher exact test p-value, c Wilcoxon rank sum test p-value

Reduced Monocyte HLA-DR Expression Correlates With Elevated ANG-2:ANG-1 Ratio Indicative of Endothelial Barrier Dysfunction

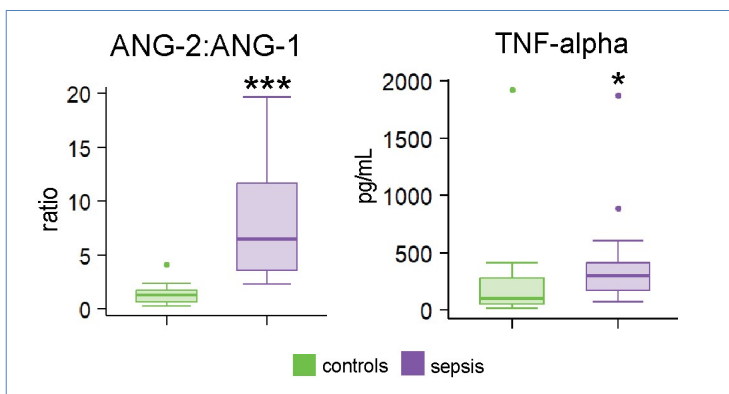


Figure 3: Boxplots depicting concentrations of markers of vascular barrier disruption (ANG-2:ANG-1) as well as early immune activation (TNF-alpha) in plasma of sepsis secondary to pneumonia (n=14) and control participants (n=10). Wilcoxon rank sum test p-value *** <0.001, ** <0.01.

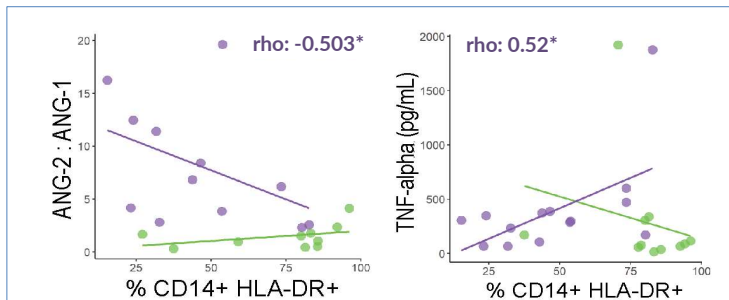


Figure 4: Scatter plot and line-of-best-fit illustrating the relation between soluble mediators of inflammation, vascular barrier disruption and CD14⁺HLA-DR⁺. Spearman's correlation p-value * <0.05.

Conclusions:

Monocyte HLA-DR expression decreases with age and during sepsis. Its correlation with the ANG-2:ANG-1 ratio supports its potential as a biomarker of both immunosuppression and endothelial dysfunction.