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Prospective validation of sepsis endotype classification: results from the EMBRACE trial

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Introduction

- A recent retrospective analysis of 5,503 sepsis patients coming from Germany, Greece and Italy, classified sepsis patients in four endotypes: macrophage activation-like syndrome (MALS); interferon-gamma (IFNγ)-driven sepsis (IDS); Adaptive endotype and sepsis-induced immunoparalysis (SII) [1].
- EMBRACE (NCT06694701) is an ongoing, multicentre, phase 2a, double-blind, randomised controlled trial investigating whether treatment with emapalumab, an anti-IFNγ antibody that binds free and receptor-bound IFNγ, improves outcomes for patients with IDS.
- Prospective validation of these retrospectively identified endotypes is necessary to confirm their existence and prevalence in sepsis population.

Methods

- Between March and November 2025, recruitment for the EMBRACE trial took place in 24 study sites in Greece. 404 patients who met Sepsis-3 criteria were screened for eligibility and underwent blood sampling at the screening stage; 75 patients with IDS were enrolled in the study.
- Blood samples were analyzed by flow cytometry for human leukocyte antigen-DR (HLA-DR) receptors expressed on CD45/CD14-monocytes, and by ELISA for ferritin, IFNγ and CXCL9. Patients were classified into endotypes as follows: MALS as ferritin >4,420 ng/mL [2]; IDS as ≥8,000 HLA-DR receptors with detectable IFNγ (i.e. >0.78 pg/mL) and CXCL9 >2,200 pg/mL; adaptive as ≥8,000 HLA-DR receptors with detectable IFN-γ and CXCL9 ≤2,200 pg/mL; and SII as <8,000 HLA-DR receptors.
- Distribution of sepsis patients into the four predefined sepsis endotypes was compared with their previously described prevalence [1].

Abbreviations: IDS, IFNγ-driven sepsis; IFN, interferon; IL, interleukin; MALS, macrophage activation-like syndrome; n, number of patients; Q, quartile; SD, standard deviation; SII, sepsis-induced immunoparalysis.

Results

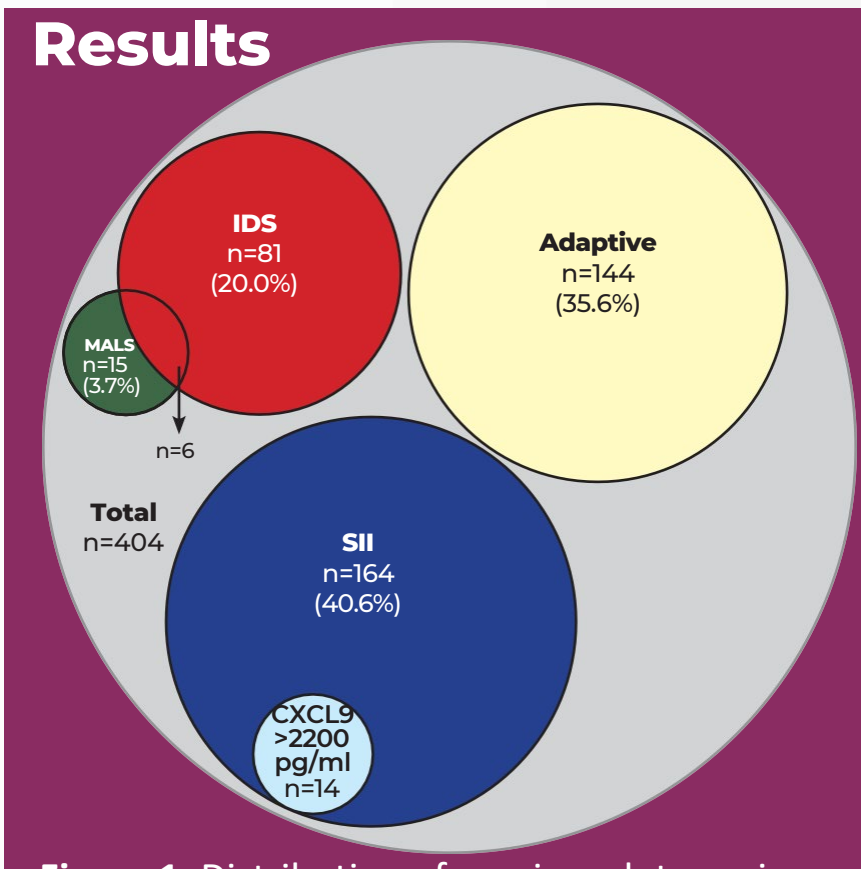

Figure 1. Distribution of sepsis endotypes in patients screened for the EMBRACE trial.

Key findings

- **Prospective confirmation** of previously described prevalence of sepsis endotypes.
- Limited **overlap between hyperinflammatory endotypes; MALS and IDS** with potential therapeutic implications [2].
- Feasibility of **real-time endotype classification** within 6–12 hours of blood sample collection, supporting the potential for timely and targeted therapeutic interventions.
- Considerable differences in SOFA scores, indicating **varying degrees of severity** across endotypes.

Table 1. Characteristics of sepsis endotypes

	MALS (n=15)	IDS (n=81)	SII (n=164)	Adaptive (n=144)
Male/Female, n (%)	4 (26.7)/11 (73.3)	44 (54.3)/37 (45.7)	95 (57.9)/69 (42.1)	94 (65.3)/50 (34.7)
Age, mean (SD), years	71.5 (10.8)	74.7 (12.1)	75.1 (11.1)	70.5 (15.4)
Underlying infection, n (%)				
Lung infection	8 (53.3)	52 (64.2)	99 (60.4)	95 (66.0)
Primary bloodstream infection	2 (13.3)	13 (16.1)	16 (9.8)	16 (11.1)
Acute pyelonephritis	1 (6.7)	6 (7.4)	11 (6.7)	19 (13.2)
Intrabdominal infection	4 (26.7)	10 (12.3)	38 (23.2)	14 (9.7)
Charlon's comorbidity index, median (Q1-Q3)	5 (4-6)	6 (4-7)	5 (4-7)	4 (2-6)
SOFA score, median (Q1-Q3)	12 (11-18)	10 (7-13)	9 (6-12)	7 (5-10)
Biomarkers, median (Q1-Q3)				
C-reactive protein, mg/L	89.0 (52.2-202.0)	106.8 (61.7-208.8)	168.0 (97.1-250.0)	159.7 (91.1-230.2)
Intrelukin-6, pg/mL	159.6 (72.9-1350.5)	127.7 (45.0-641.4)	99.4 (48.8-287.0)	70.4 (28.8-171.1)
Ferritin, ng/mL	6995.0 (5497.0-22800.0)	481.4 (184.2-1122.0)	530.7 (201.9-1055.8)	431.5 (184.6-1018.0)
mHLA-DR, Abs per monocyte	3348 (2194-6437)	11479 (8832-17541)	4131 (2878-5377)	11315 (9193-17344)
CXCL9, pg/mL	1175.0 (725.0-2260.0)	2504.0 (2251.0-3378.5)	847.5 (538.0-1478.0)	862.0 (555.0-1182.8)
IFNγ, pg/mL	4.0 (2.6-11.5)	4.3 (2.2-10.5)	3.1 (1.6-5.5)	4.9 (2.5-12.3)

Conclusion

The described frequency of sepsis endotypes [1] was prospectively validated using the screening data from the EMBRACE trial.

References: 1. Giamarellos-Bourboulis EJ et al. eBioMedicine 2024; 109:105414
2. Giamarellos-Bourboulis EJ et al. JAMA 2025; e2524175.

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