HELLENIC REPUBLIC
National and Kapodistrian University of Athens
EST. 1837

European Sepsis Alliance

ΕΛΛΗΝΙΚΟ ΙΝΣΤΙΤΟΥΤΟ ΜΕΛΕΤΗΣ ΤΗΣ ΣΗΨΗΣ
HELLENIC INSTITUTE FOR THE STUDY OF SEPSIS

PRECISION IMMUNOTHERAPY FOR THE CRITICALLY ILL
Myth or Reality?

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Board Member: Global Sepsis Alliance
President: Hellenic Institute for the Study of Sepsis
President: Hellenic Society of Chemotherapy

HELLENIC SOCIETY OF CHEMOTHERAPY

https://sepsis.gr/

CONFLICT OF INTEREST DISCLOSURE

- Honoraria (paid to the University of Athens) from Abbott Products Operations AG, bioMérieux, Brahms ThermoFisher GmbH Germany, GSK and Sobi
- Consultant for Fab’nTech, and UCB
- Independent educational grants (paid to the University of Athens) from AbbVie USA, Fab’nTech, InflaRx GmbH, Novartis, UCB
- Independent educational grants (paid to the Hellenic Institute for the Study of Sepsis) from Abbott Products Operations AG, bioMérieux France, Johnson & Johnson, MSD, Sobi, ThermoFisher Brahms GmbH
- Funding by the Horizon 2020 ITN European Sepsis Academy (granted to the University of Athens), by the Horizon 2020 ImmunoSep and RISKinCOVID (granted to the Hellenic Institute for the Study of Sepsis) and by the Horizon Health EPIC-CROWN-2 (granted to the Hellenic Institute for the Study of Sepsis)

OUR MAIN CHALLENGE: PATIENT HETEROGENEITY (Karakike E, et al. *J Innate Immun* 2022; 14: 218)

Male, 56 years
AH
Neutrophils: 5056/mm^3
Lymphocytes: 1088/mm^3
CRP: 296 mg/l
Ferritin: 6786 ng/ml
D-dimers: 520 µg/l

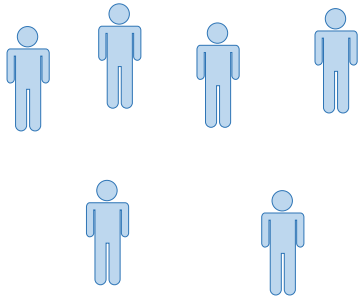
Male, 76 years
No medical history
Neutrophils: 9870/mm^3
Lymphocytes: 1620/mm^3
CRP: 39.8 mg/l
Ferritin: 916 ng/ml
D-dimers: 640 µg/l

Male, 56 years
HF, CHD, COPD
Neutrophils: 11600/mm^3
Lymphocytes: 705/mm^3
CRP: 237 mg/l
Ferritin: 306 ng/ml
D-dimers: 1370 µg/l

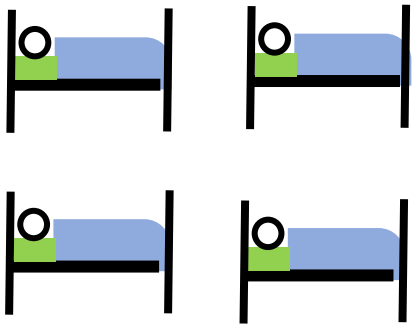
AH: arterial hypertension
CHD: coronary heart disease
COPD: chronic obstructive pulmonary disease
CRP: C-reactive protein
HF: heart failure

THE VISION OF PRECISION IMMUNOTHERAPY

BIOMARKER
(Lab test, phenotype)



Patients admitted to hospital for infection

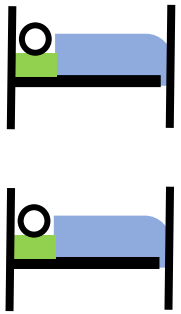


BIOMARKER
(Lab test, phenotype)

RECOGNIZE
- Risk for sepsis progression
- PRECISE mechanism

TARGETED THERAPY

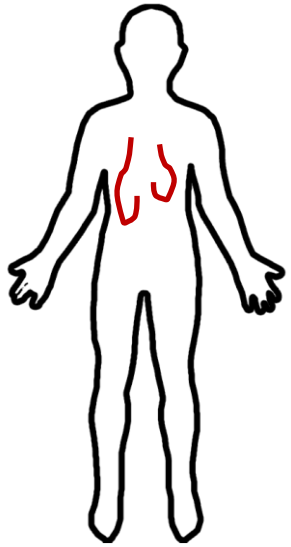
PREVENT
- Organ dysfunction
- Deaths



Patients already hospitalized and develop hospital-acquired infection

suPAR-GUIDED ANAKINRA TREATMENT FOR VALIDATION OF THE RISK AND EARLY MANAGEMENT OF SEVERE RESPIRATORY FAILURE BY COVID-19

THE SAVE STRATEGY



STOP
IL-1α
IL-1β

PREVENT
Unfavorable outcome

Pneumonia

- Hospitalization
- pO_2/FiO_2: 150-400
- Oxygen mask/nasal oxygen/high-flow oxygen
- suPAR ≥6 ng/ml

Anakinra

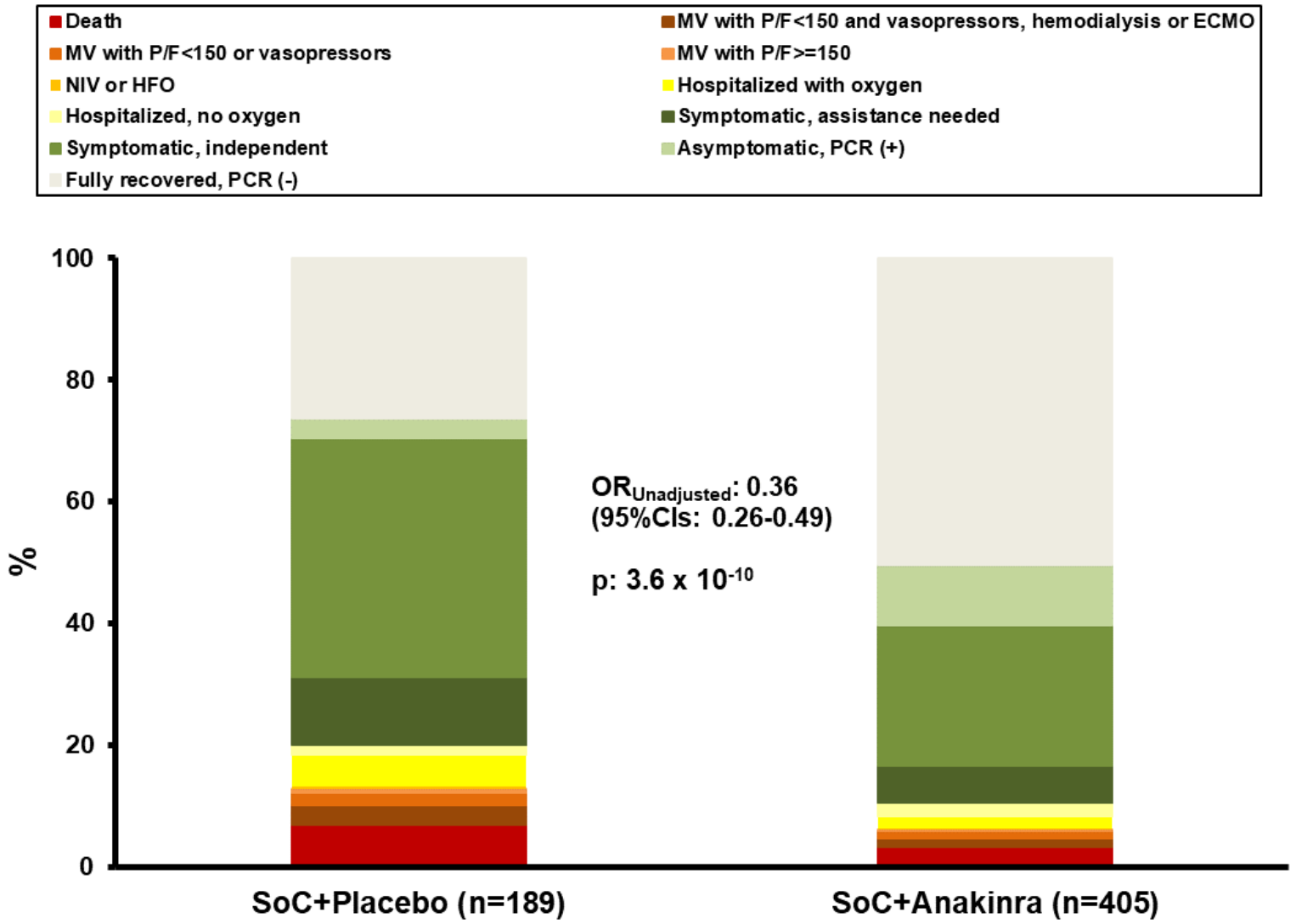
- Recombinant human receptor antagonist
- Blocks the action of IL-1α and IL-1β

suPAR: soluble urokinase Plasminogen Activator Receptor

11-point WHO Clinical Progression ordinal Scale by day 28 (Kyriazopoulou E, et al. *Nat Med* 2021; 27: 1752)

Assumption of ordinal regression analysis
Goodness-of-fit test
(Pearson's chi-square test)
p: 0.172

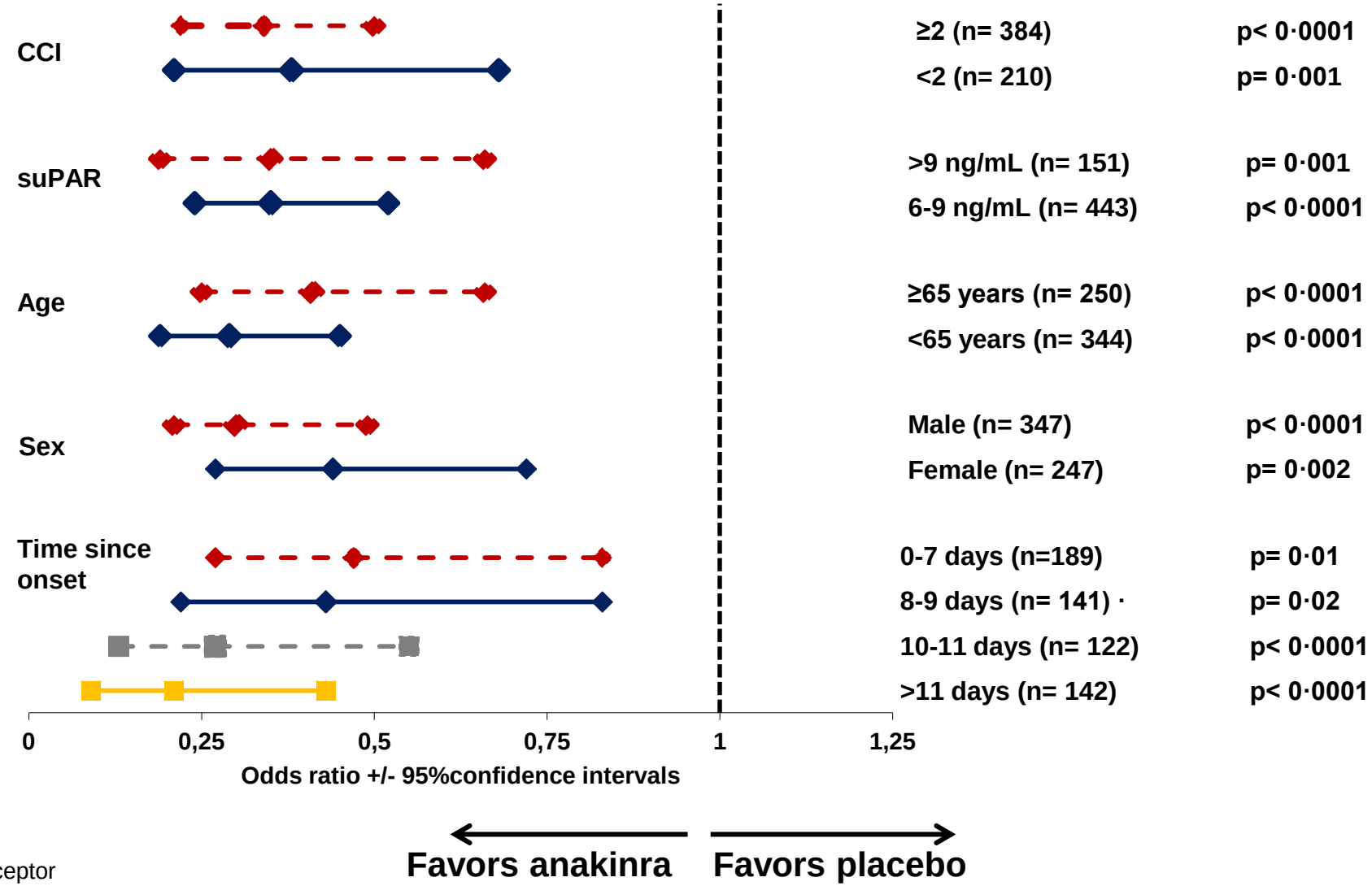
Assumption of proportional odds
(test of parallel lines)
p: 0.131



CIs: confidence intervals
OR: odds ratio
MV: mechanical ventilation
NIV: non-invasive ventilation
PCR: polymerase chain reaction
SoC: standard-of-care

SIMLAR BENEFIT FOR ALL SUBGROUPS

(Akinosoglou K, et al. *eClinicalMedicine* 2023; 56: 101785)



CCI: Charlson's comorbidity index
suPAR: soluble urokinase plasminogen activator receptor

ANAKINRA REGISTRY BY THE INTERNATIONAL REGULATORY AGENTS

FDA U.S. FOOD & DRUG ADMINISTRATION

Kineret may only be used by healthcare providers to treat COVID-19 in hospitalized adults with positive results of direct SARS-CoV-2 viral testing with pneumonia requiring supplemental oxygen (low- or high-flow oxygen) who are at risk for progressing to severe respiratory failure and are likely to have an elevated suPAR.

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EMA recommends approval for use of Kineret in adults with COVID-19 Share

News 16/12/2021

Update: Kineret is now authorised across the EU to treat COVID-19. This follows the granting of an extension of indication by the European Commission on 17 December 2021.

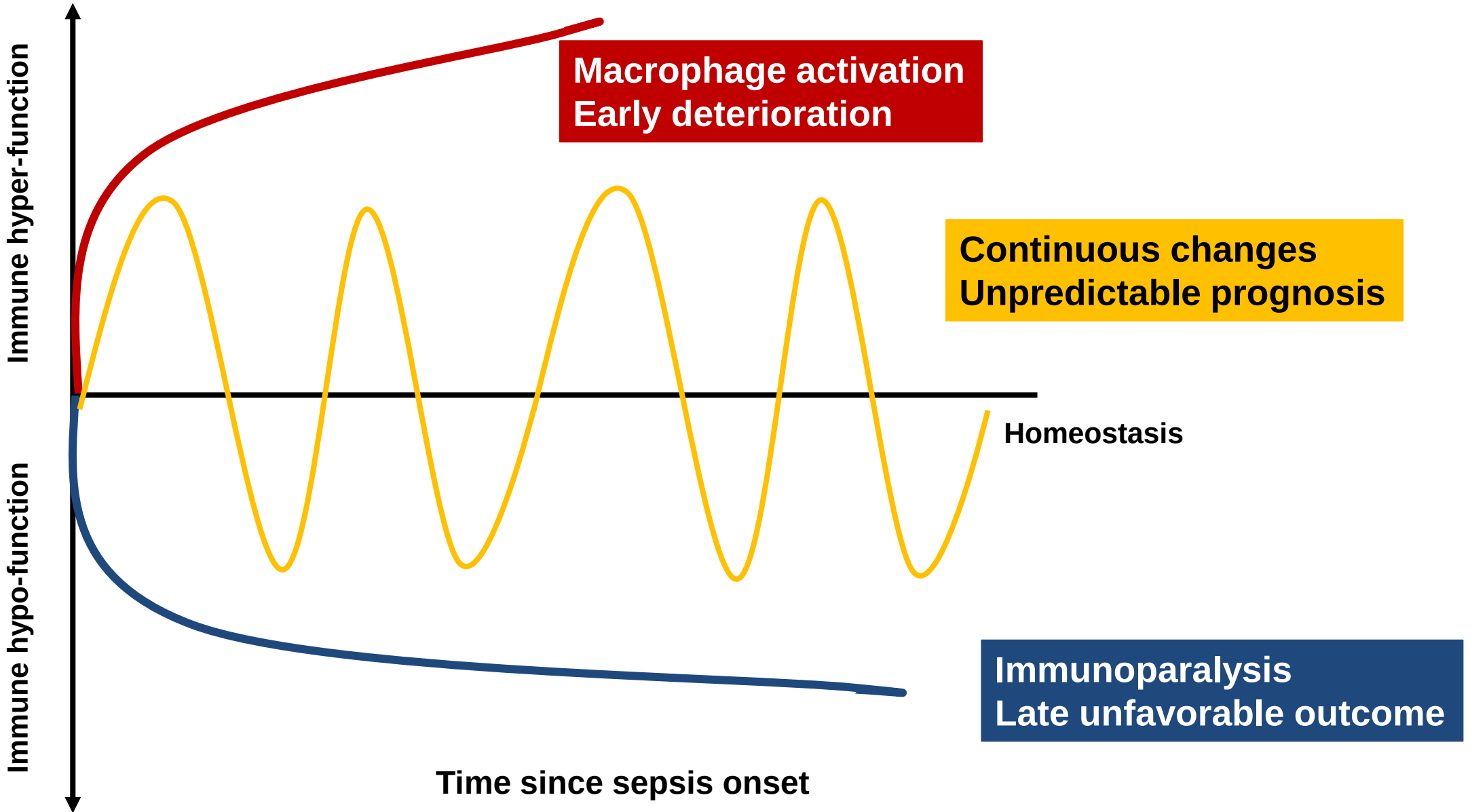
EMA's human medicines committee (CHMP) has recommended extending the indication of Kineret (anakinra) to include treatment of COVID-19 in adult patients with pneumonia requiring supplemental oxygen (low or high flow oxygen) and who are at risk of developing severe respiratory failure, as determined by blood levels of a protein called suPAR (soluble urokinase plasminogen activator receptor) of at least 6 ng per ml.

PRECISION MEDICINE: REQUIREMENTS

(https://www.fda.gov/medical-devices/in-vitro-diagnostics/precision-medicine)

Therapeutics	→	GUIDED by biomarkers
BIOMARKER	→	INFORMATIVE on the degree of implication of a certain pathway
PATHWAY	→	DETRIMENTAL for outcome
AVAILABLE DRUG	→	MODULATES the pathway
START OF TREATMENT	→	IMMEDIATE *IRRESPECTIVE of* clinical signs

ASSUMPTION OR CRITICAL CONSIDERATION?



RATIONALE FOR TREATMENT OF SEPSIS AND MALS WITH ANAKINRA

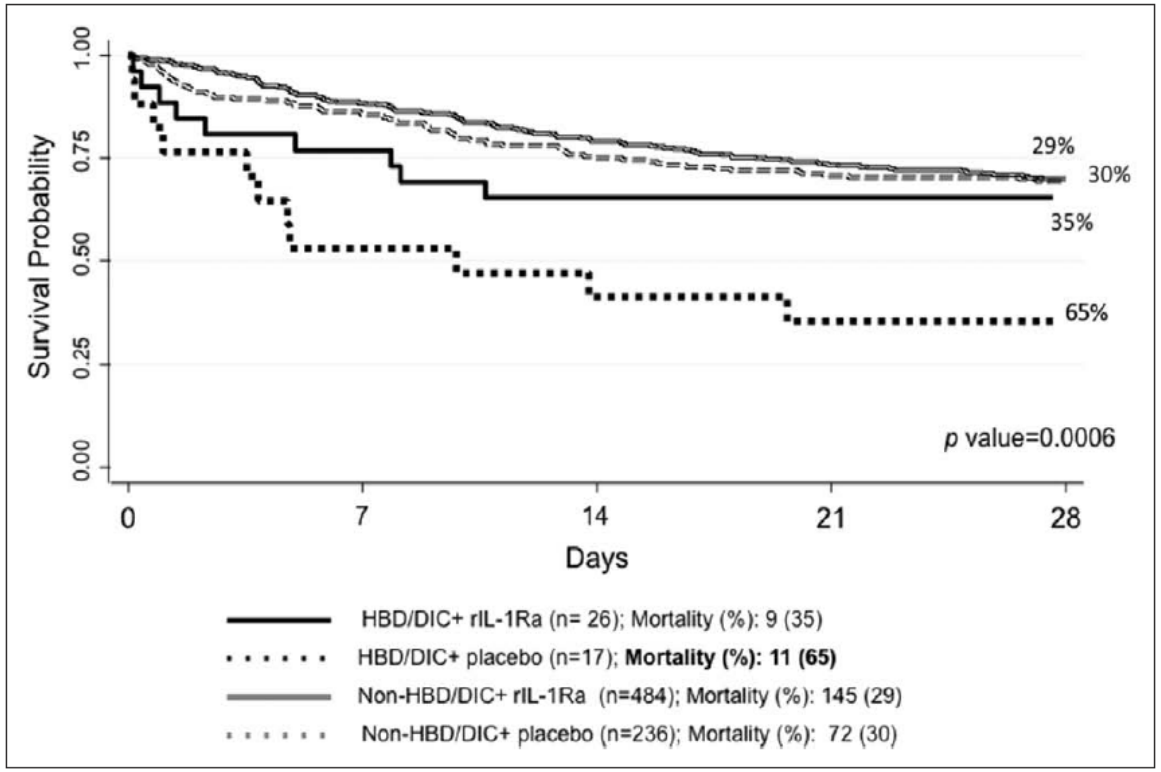
(Shakoory B, et al. *Crit Care Med* 2016; 44: 275)

MALS is defined as co-presence of HBD and DIC

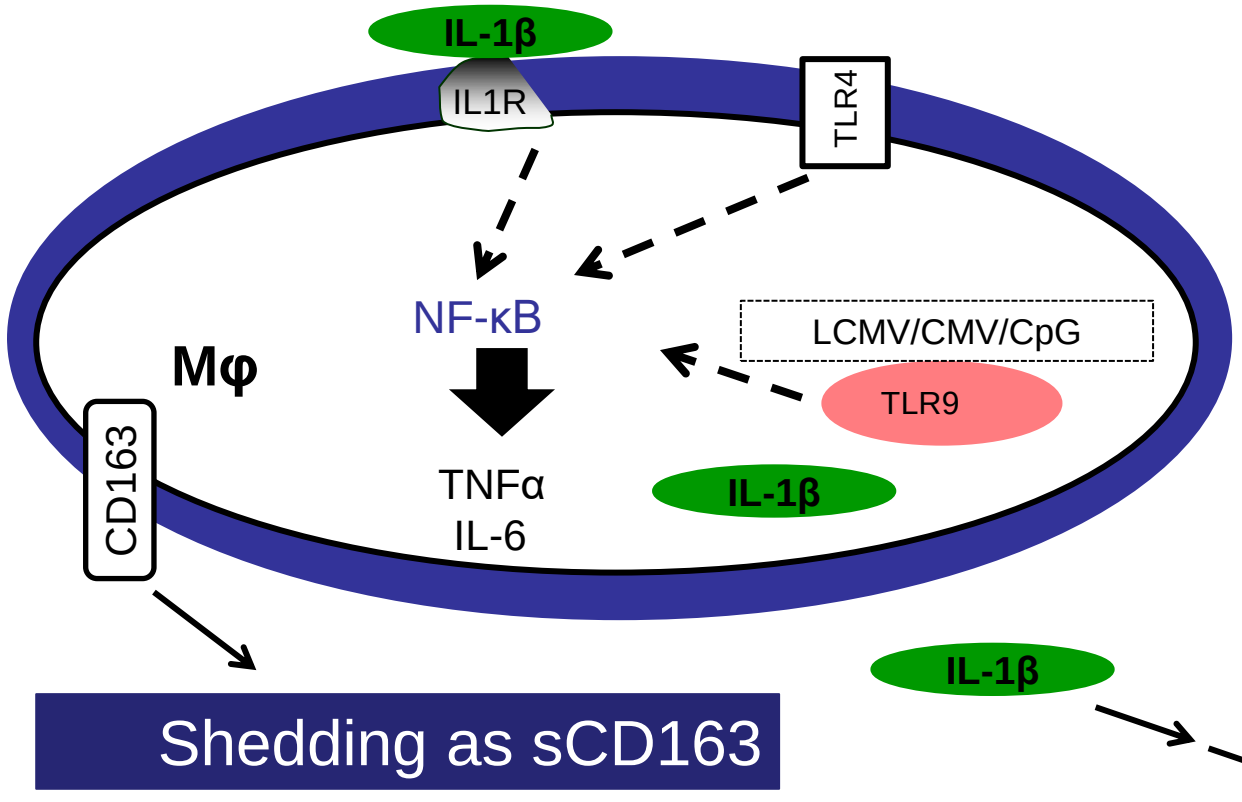
HBD: hepatobiliary dysfunction (bilirubin >1.2mg/dl)

+

DIC (acute coagulopathy): platelets <100,000/mm^3 + INR>1.2



MALS: macrophage-activation like syndrome

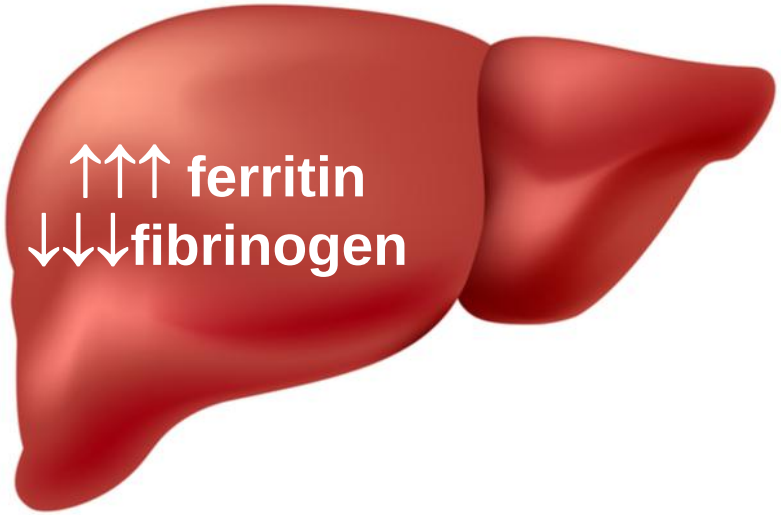


Shedding as sCD163

IL-1β

Macrophage activation-like syndrome in sepsis

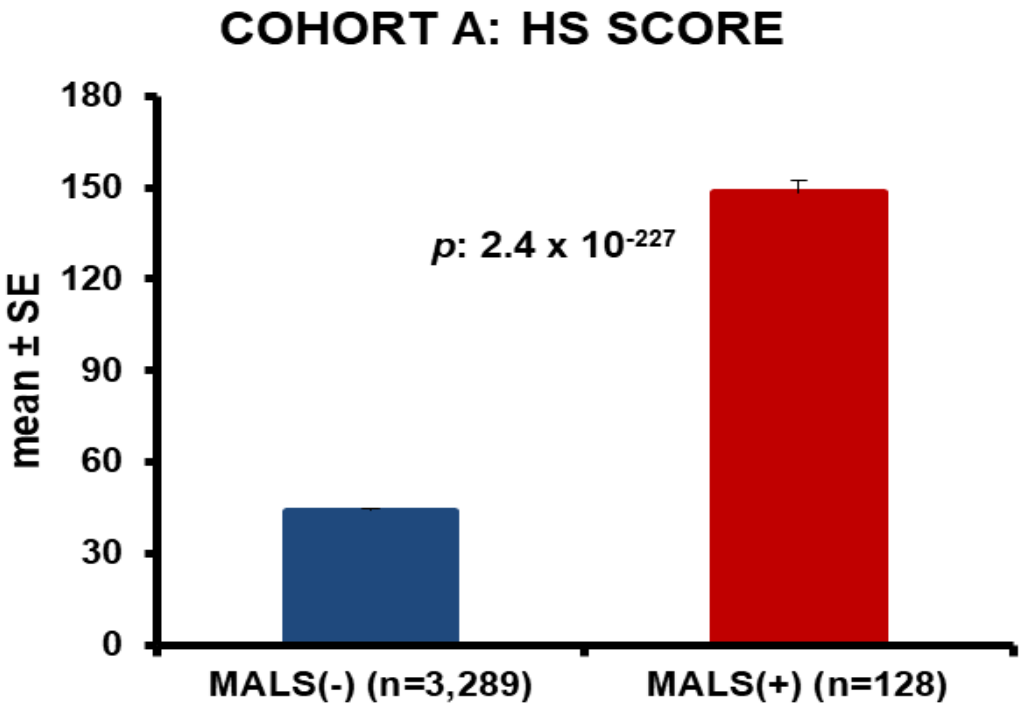
- Different than primary HLH and CAR-T associated CRS
- IL-1 driven and IFNγ driven

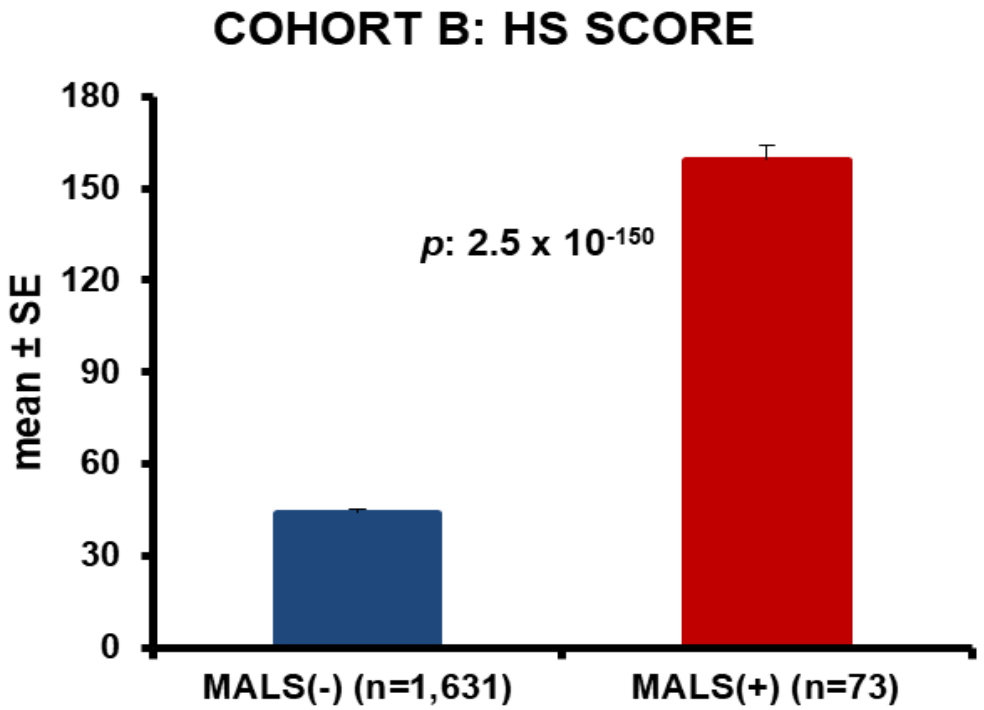


CRS: cytokine release syndrome
HLH: hemomophagocytic lymphohistiocytosis
IFN: interferon
IL: interleukin
IL-1R: IL-1 receptor
LPS: lipopolysaccharide
Mφ: macrophage
PDG: peptidoglycan
TLR: toll-like receptor
TNFα: tumour necrosis factor-alpha

Karakike & Giamarellos-Bourboulis. *Front Immunol* 2019; 10: 55

CHARACTERISTICS OF MACROPHAGE-LIKE ACTIVATION SYNDROME (MALS) IN SEPSIS (Kyriazopoulou E, et al. *BMC Med* 2017; 15: 172)



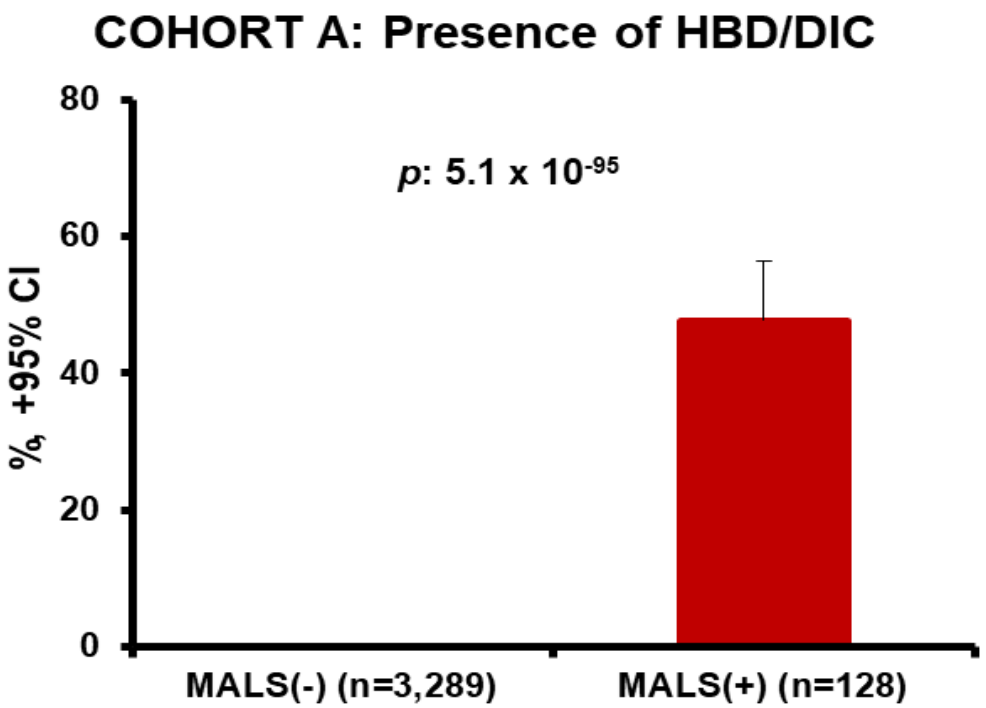


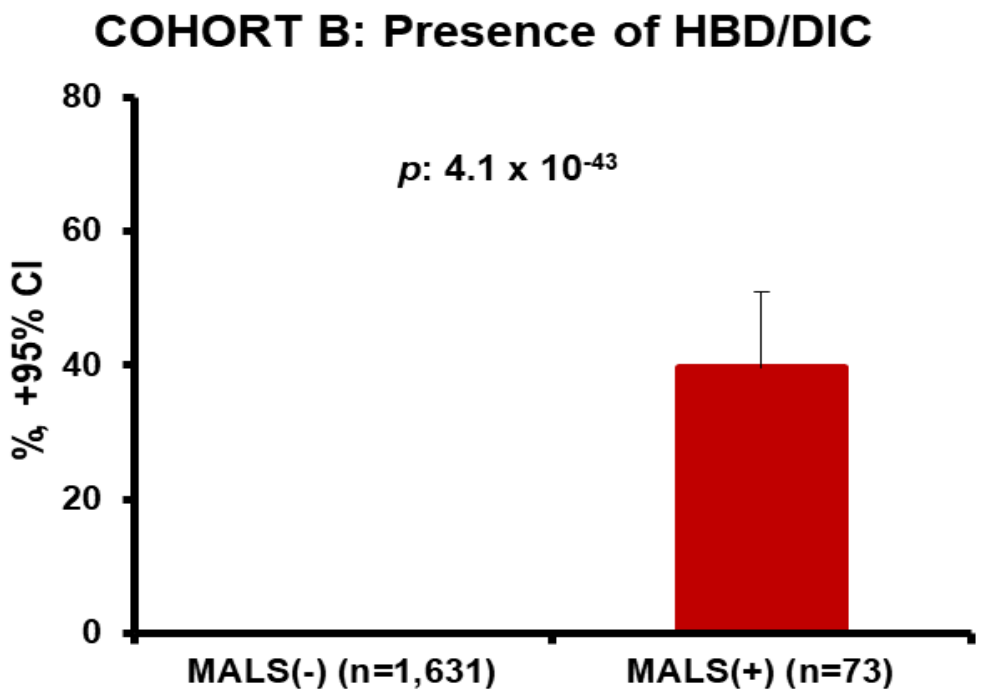
MALS
3.7% Cohort A; 4.3% Cohort B

HS: hemophagocytosis score

MACROPHAGE-LIKE ACTIVATION SYNDROME (MALS) AND COAGULATION

(Kyriazopoulou E, et al. *BMC Med* 2017; 15: 172)





Coagulopathy= alert for MALS

DIC: disseminated intravascular coagulation
HBD: hepatobiliary dysfunction

MALS= INDEPENDENT DRIVER OF 10-DAY MORTALITY ON TOP OF OTHER DYSFUNCTIONS

(Kyriazopoulou E, et al. *BMC Med* 2017; 15: 172)

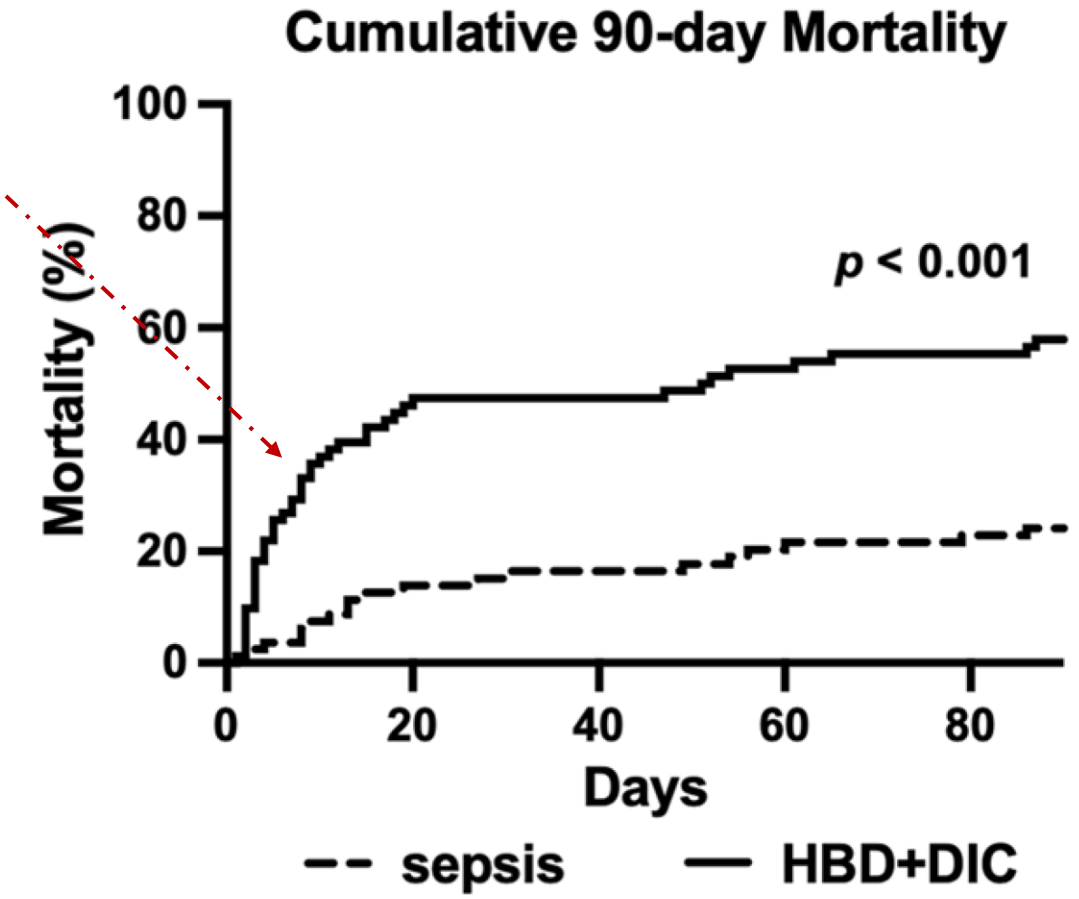
	Cohort A		Cohort B	
	OR	p	OR	p
MALS	**1.86**	**0.003**	**2.81**	**<0.0001**
ARDS	**1.72**	**<0.0001**	**1.81**	**<0.0001**
AKI	**3.12**	**<0.0001**	**3.79**	**<0.0001**
Shock	**3.45**	**<0.0001**	**4.16**	**<0.0001**

AKI: acute kidney injury
ARDS: acute respiratory distress syndrome
MALS: macrophage-activation like syndrome
OR: odds ratio

SIMILAR FINDINGS FROM THE ProCESS STUDY
(Anderko RR, et al. *ICMx* 2022; 10: 6)

- 1,341 patients
- 6.1% with MALS (defined as HBD + DIC used as classifier

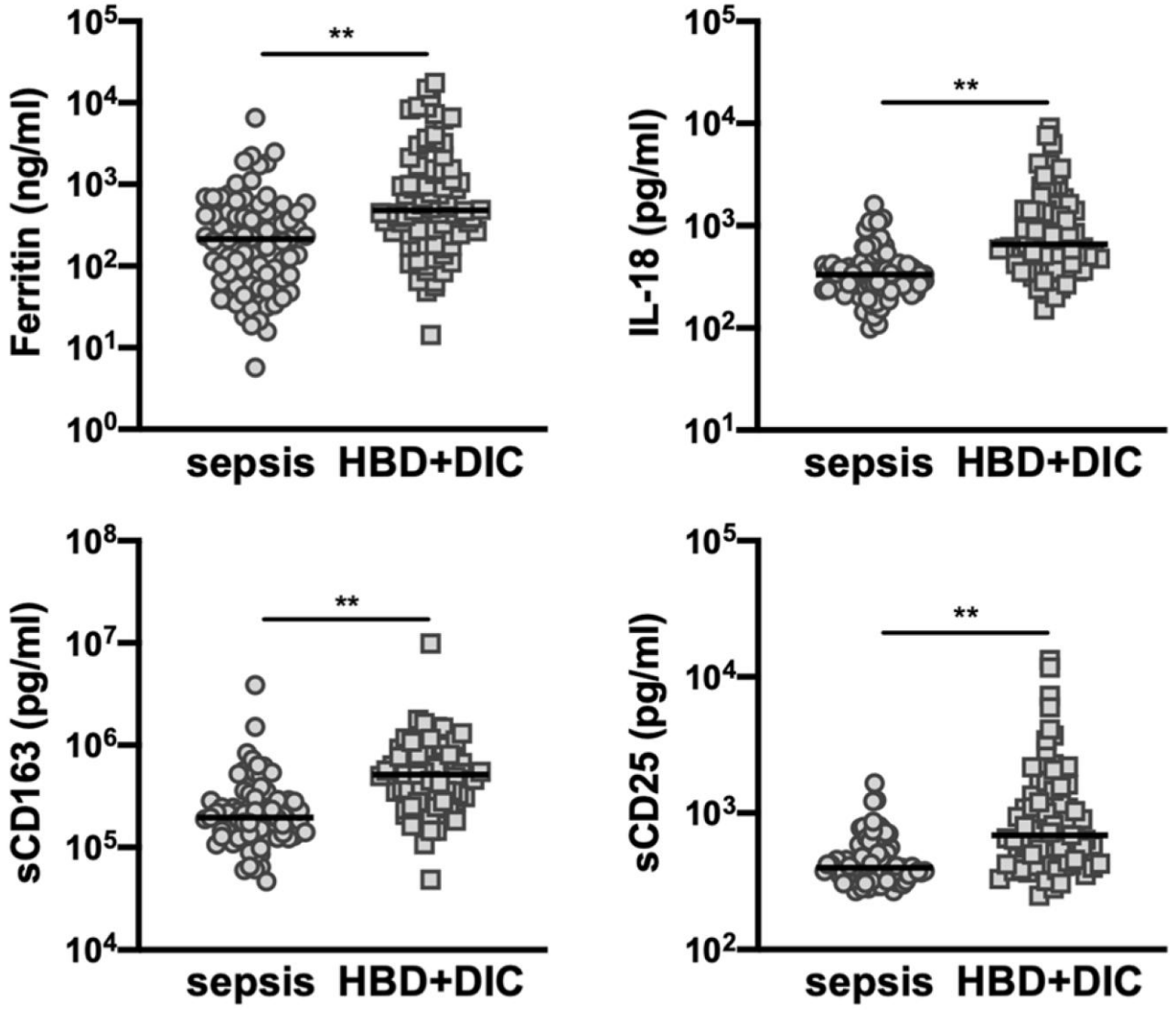
Early death



DIC: disseminated intravascular coagulation
HBD: hepatobiliary dysfunction
MALS: macrophage-activation like syndrome

BIOMARKERS OF MACROPHAGE ACTIVATION

(Anderko RR, et al. *ICMx* 2022; 10: 6)

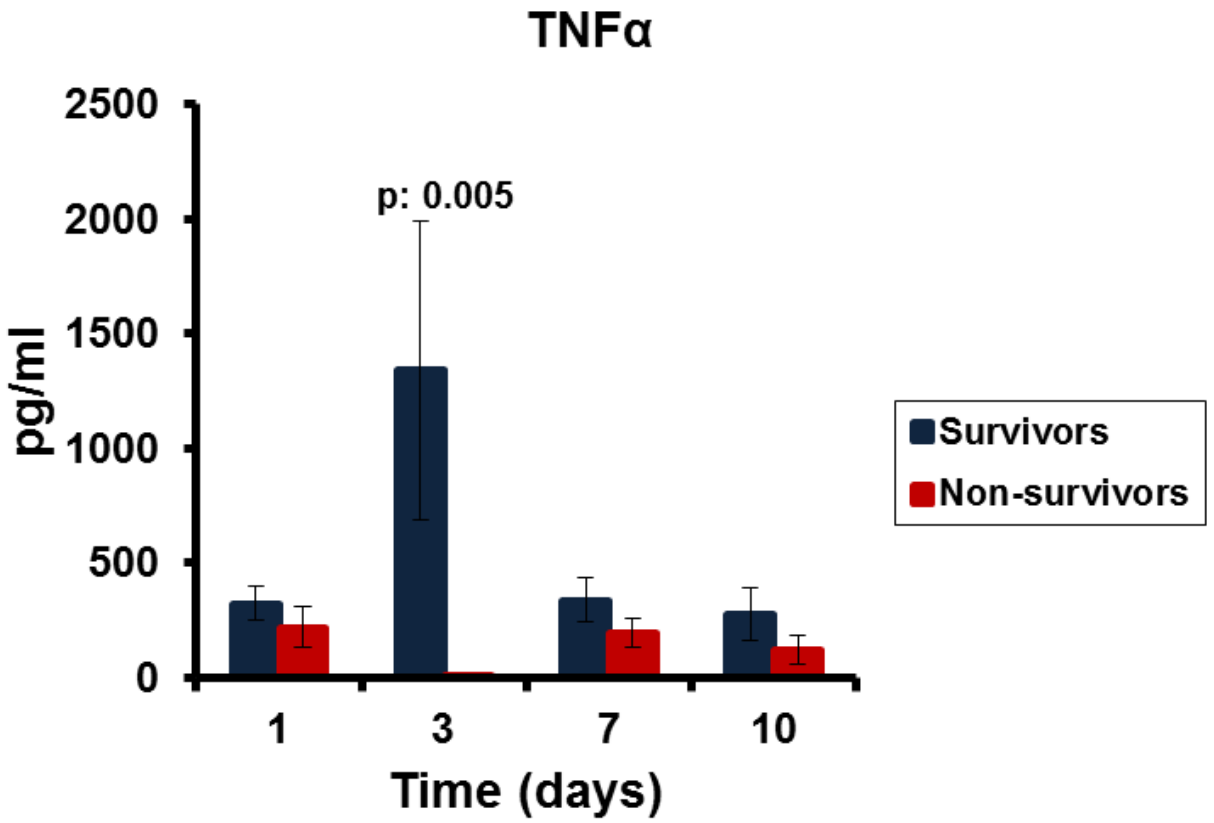


**p<0.01
DIC: disseminated intravascular coagulation
HBD: hepatobiliary dysfunction

IMMUNOPARALYSIS: THE OTHER EDGE
(Antonakos N, et al. *Critical Care* 2017; 24: 48)

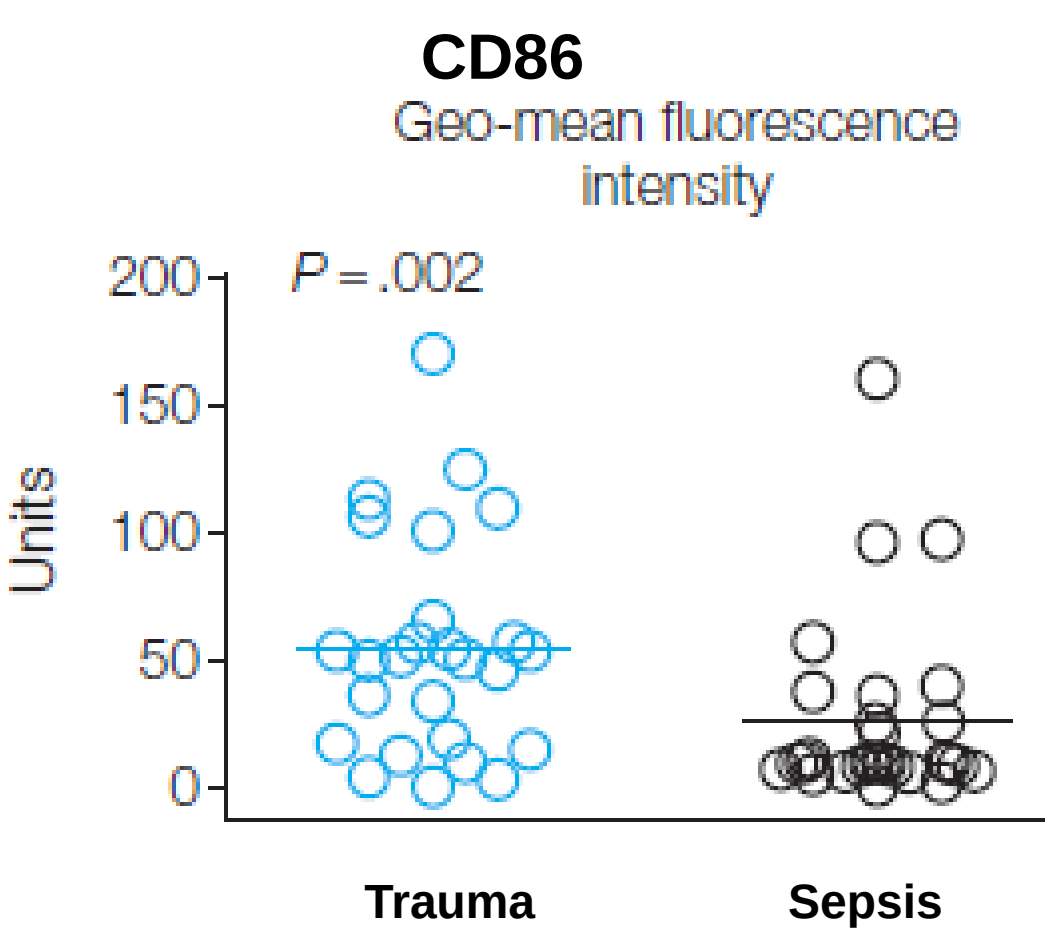
- 95 patients with septic shock
- Ex-vivo cytokine production by peripheral blood mononuclear cells
- Repeat after 3, 7 and 10 days

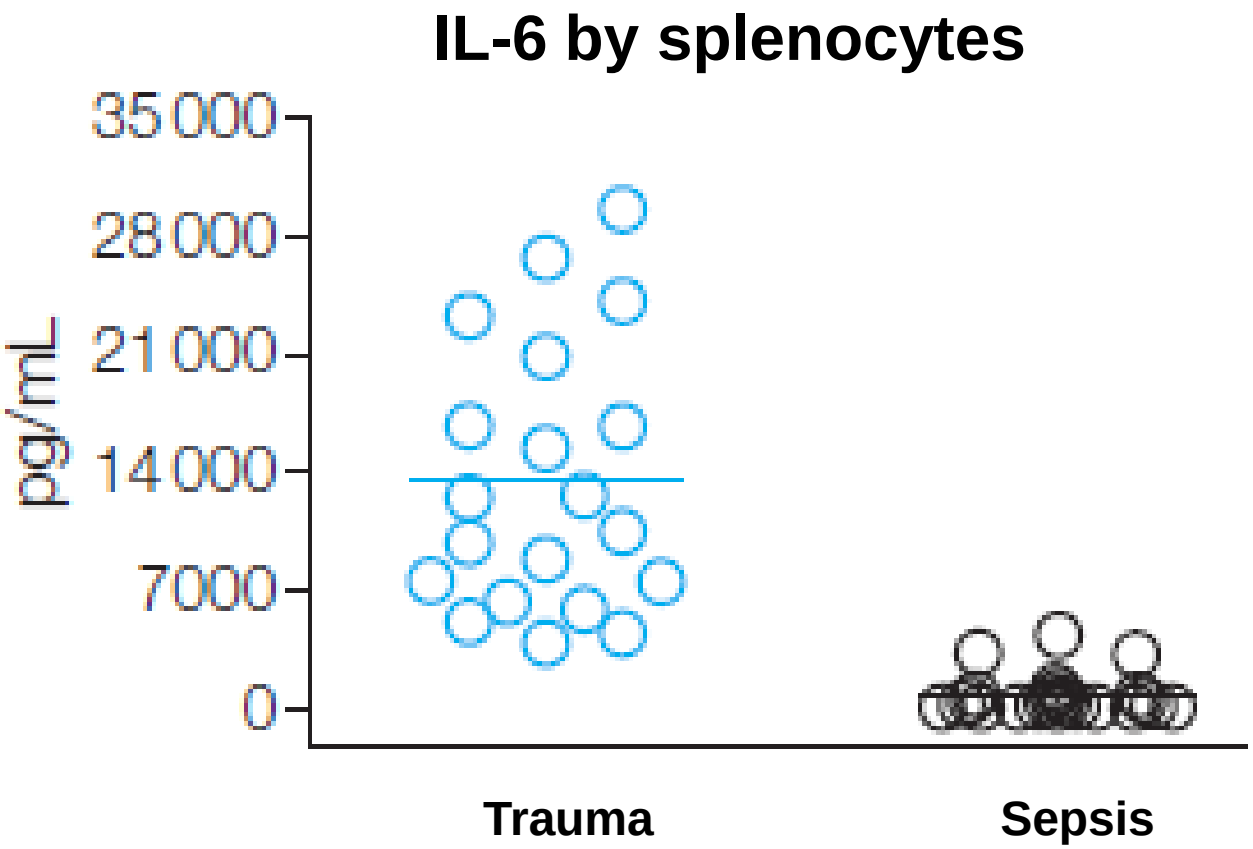
Sepsis-induced immunoparalysis
- Failure to engulf the bacteria
- Risk for secondary infections



IMMUNOPARALYSIS IN EARLY HUMAN CADAVERS

(Boomer JS, et al. *JAMA* 2011; 306: 2594-2605)





A Personalized Randomized trial Of Validation and restoration of Immune Dysfunction in severE infections and Sepsis

PROVIDE (Clinicaltrials.gov NCT03332225)

- Community-acquired pneumonia or hospital-acquired pneumonia or ventilator-associated pneumonia or primary bacteremia
- Classify the immune state of sepsis as MALS, intermediate or immunoparalysis
- Investigate if this classification reflects final outcome
- Assess if anakinra in patients with MALS influences outcome

Macrophage activation-like syndrome (MALS): serum ferritin >4,420ng/ml.

Immunoparalysis combination of : a) serum ferritin ≤4,420ng/ml; and b) <5,000 receptors of HLA-DR on CD14-monocytes

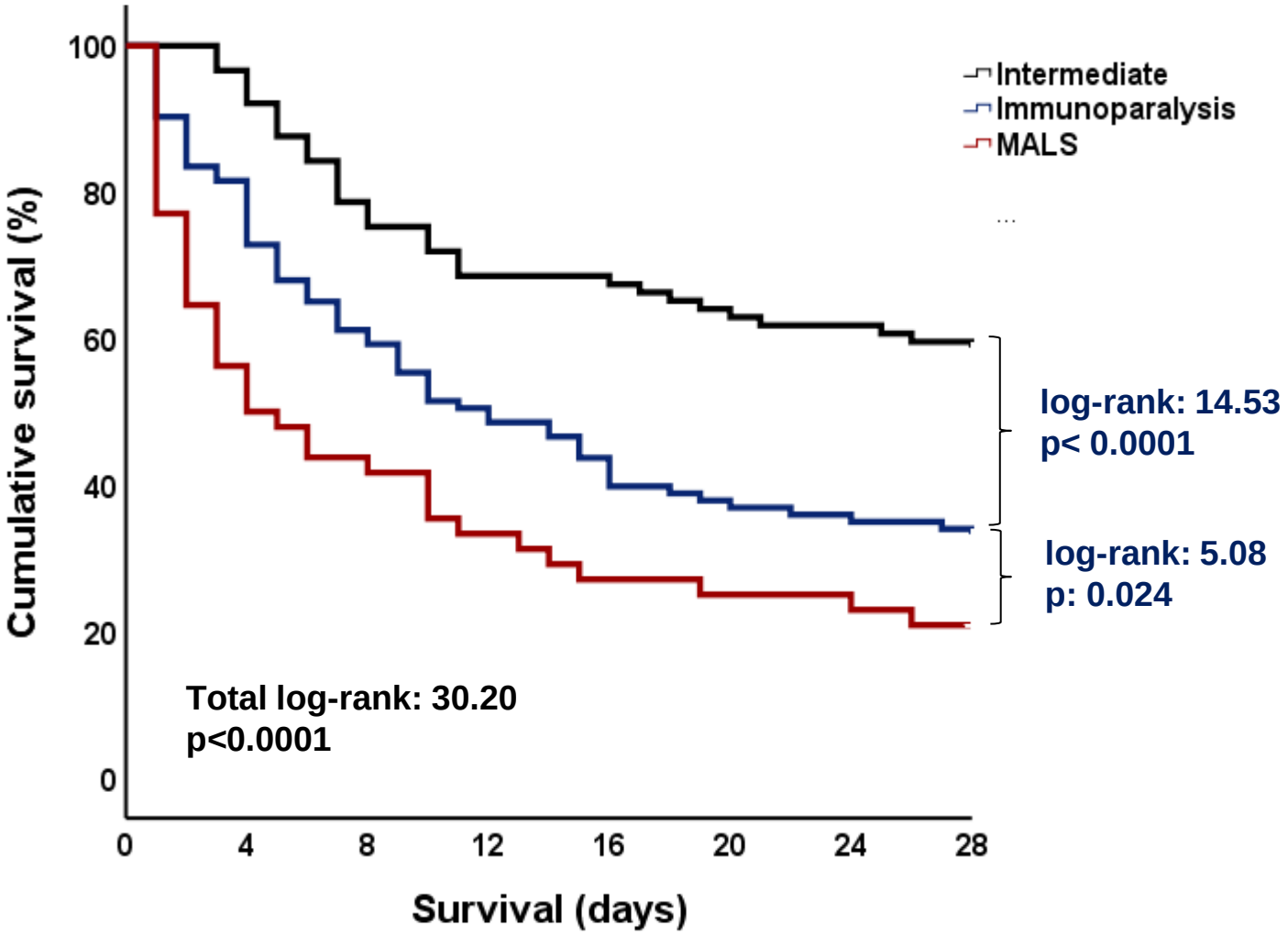
Intervention in MALS

- IV anakinra 200mg q8h for 7 days
- If creatinine clearance < 30 ml/min adjustment to 100mg q8h for 7 days

Leventogiannis K, et al. *Cell Rep Med* 2022; 3: 100817

IMMUNE CLASSIFICATION DRIVES OUTCOME

(Leventogiannis K, et al. *Cell Reports Medicine* 2022; 3: 100817)



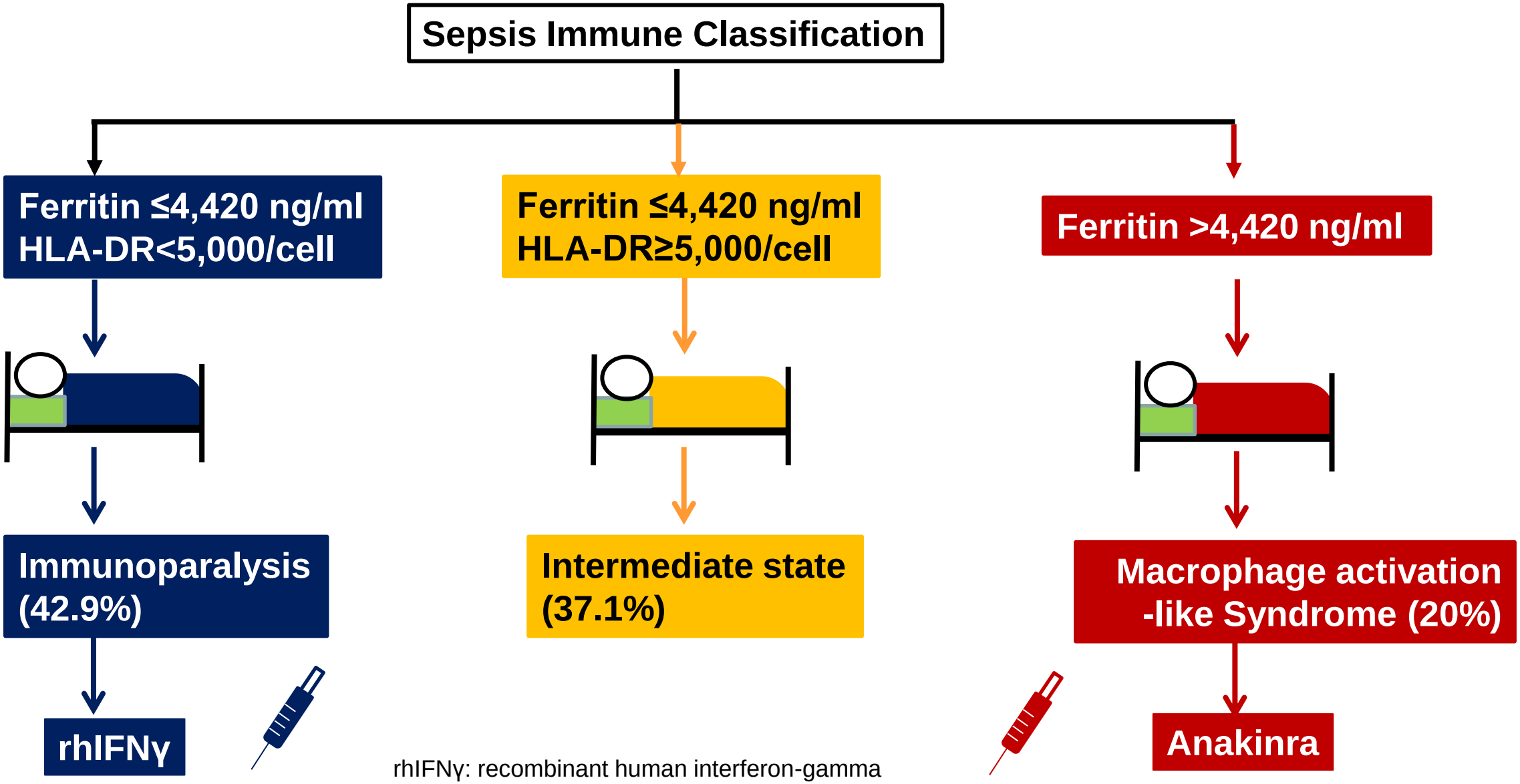
Intermediate (n= 89) 37.1%

Immunoparalysis (n= 103) 42.9%

Macrophage Activation-like Syndrome (MALS, n= 48) 20%

Ferritin >4,420 ng/ml

THE VISION OF ImmunoSep



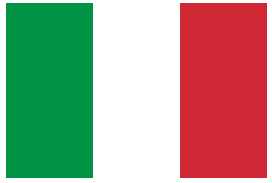
rhIFNγ: recombinant human interferon-gamma

THE ImmunoSep Randomized Clinical Trial

(EudraCT number: 2020-005768-74; Clinicaltrials.gov: NCT04990232)

Jena University Hospital
(M.Bauer)

Hellenic Sepsis Study Group
(E.Giamarellos)



Gemelli University Hospital
(M.Antonelli)

Amsterdam Medical Center
(T.van der Poll)
Radboud Nijmegen
(M.Netea)

Cluj-Napoca
(M.Lupse)

Centre Hospitalier
Universitaire Vaudois
(T.Calandra)

Patient population

- Lung infection or primary bacteremia
- Sepsis-2
- MALS or immunoparalysis
- Within 72 hours

Precision immunotherapy x 15 days + Standard Care

- Double-blind
- Double-dummy
- IV Anakinra for MALS
- sc rhIFNγ for immunoparalysis

Placebo x 15 days + Standard Care

- Double-blind
- Double-dummy
- IV N/S for MALS
- sc N/S for immunoparalysis

IV: intravenous
MALS: macrophage activation-like syndrome
N/S: normal saline
rhIFNγ: recombinant human interferon-gamma
sc: subcutaneous
SC: standard-of-care
SOFA: sequential organ failure assessment

INCLUSION CRITERIA

- Age ≥ 18 years
- Both genders; in case of women, unwillingness to become pregnant during the study period.
- Community-acquired pneumonia OR hospital-acquired pneumonia OR ventilator-associated pneumonia OR primary bloodstream infection
- Sepsis-3 definitions
- Presence of MALS or SII.
- Time from meeting Sepsis-3 definitions until start of study drug < 72 hours.

COVID-19

- Patients *<u>without</u>* secondary VAP/HAP/BSI are enrolled ONLY if classified with MALS
- Patients *<u>with</u>* secondary VAP/HAP/BSI are enrolled as ALL other patients

BSI: bloodstream infection
CAP: community-acquired pneumonia
HAP: hospital-acquired pneumonia
MALS: macrophage activation-like syndrome
SII: sepsis-induced immunoparalysis
VAP: ventilator-associated pneumonia

immunoSEP

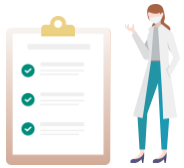
EXCLUSION CRITERIA

- Age < 18 years
- Acute pyelonephritis or intraabdominal infection or meningitis or skin infection
- Any stage IV malignancy
- Absolute neutrophil count < 1000/mm^3
- Any “do not resuscitate” decision.
- Patients with bacteraemia (BSI):
  - *Staphylococcus* growing coagulase-negative staphylococci
  - Skin commensals
  - Catheter-related infections

- Active tuberculosis
- Known infection by the human immunodeficiency virus
- Any primary immunodeficiency
- Oral or intravenous corticosteroids: ≥ 0.4mg/kg/day equivalent prednisone more than 15 days
- Anti-cytokine drugs the last month
- Medical history of systemic lupus erythematosus
- Medical history of multiple sclerosis or other demyelinating disorder
- Pregnancy or lactation

Screening process

24/7



Eligibility of the patient & informed consent → 672 screened
36 not eligible

Blood sample for classification of the immune state of the patient → 3ml into one pyrogen-and anticoagulant free tube
2 ml into one EDTA-coated tube

Transportation to the central lab → 1272 tubes transported to central lab

Ferritin and Quantibrite measured: 3 immunogroups

Classification into sepsis and enrolment: **in less than 72 hours** → 281 patients enrolled

STUDY ENDPOINTS ACCORDING TO THE STATISTICAL ANALYSIS PLAN

Primary endpoint

Change of the mean SOFA score from baseline until day 9

- Patients with ≥1.4 point decrease of mean SOFA score between days 2 to 9 from baseline day 1.
- Last observation carried forward applies (discharge before day 9); when death arrives SOFA 24.

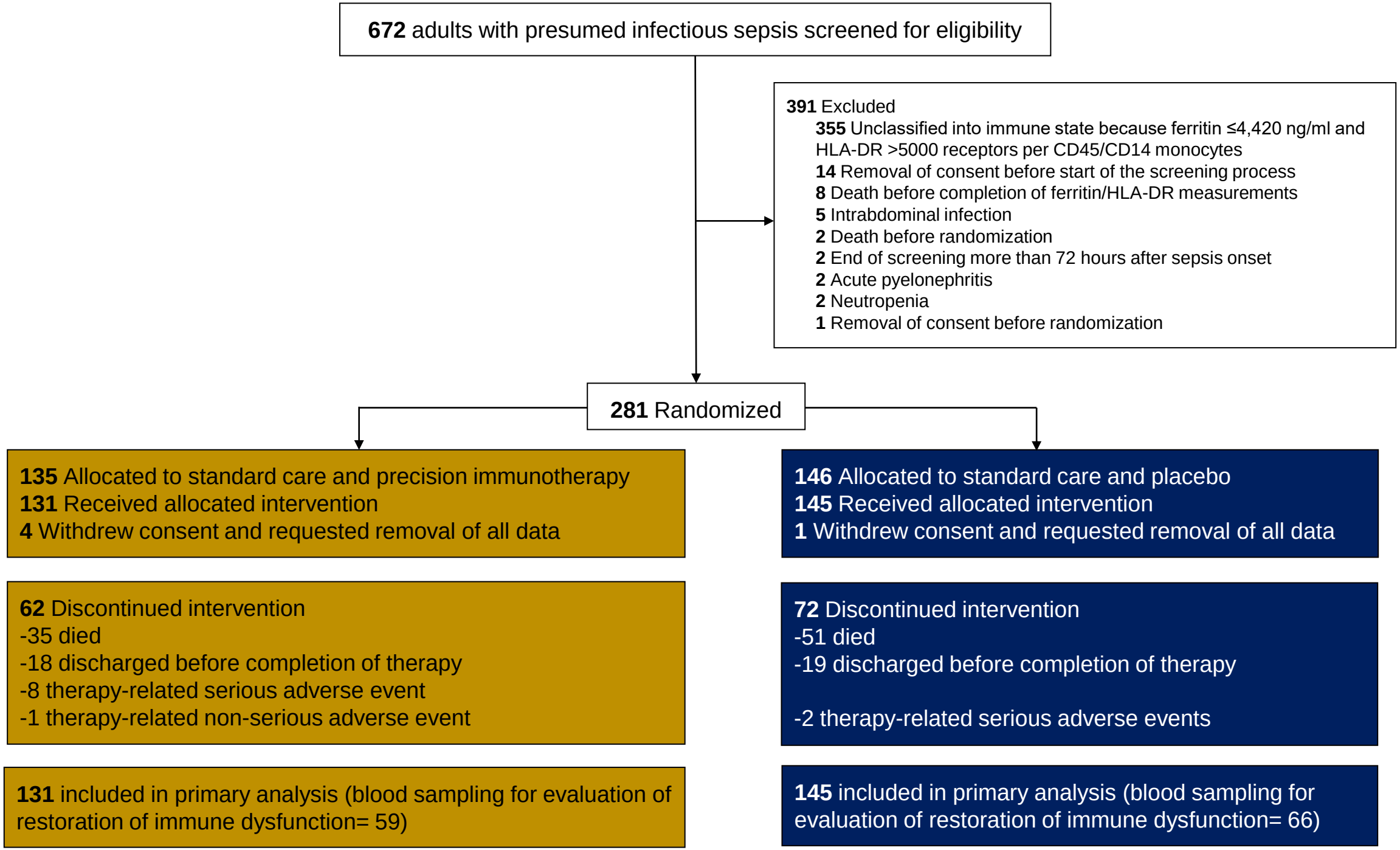
Secondary endpoints

- Change of the mean SOFA score from baseline until day 9 separately for MALS and SSI
- Change of the mean SOFA score from baseline until day 15
- 28-day mortality
- 90-day mortality
- Restoration of immune dysfunction
- Infection disposition on day 15

Post-hoc Subgroup analysis

- Time to restoration of organ dysfunction
- Subgroups of APACHE II, CCI and SOFA surrogating mortality (Change of the mean SOFA score until day 9; 28-day mortality; and 90-day mortality)

APACHE: acute physiology and chronic health evaluation
CCI: Charlson's comorbidity index
MALS: macrophage activation-like syndrome
SII: sepsis-induced immunoparalysis
SOFA: sequential organ failure assessment


672 adults with presumed infectious sepsis screened for eligibility
391 Excluded
355 Unclassified into immune state because ferritin ≤4,420 ng/ml and HLA-DR >5000 receptors per CD45/CD14 monocytes
14 Removal of consent before start of the screening process
8 Death before completion of ferritin/HLA-DR measurements
5 Intrabdominal infection
2 Death before randomization
2 End of screening more than 72 hours after sepsis onset
2 Acute pyelonephritis
2 Neutropenia
1 Removal of consent before randomization
281 Randomized
135 Allocated to standard care and precision immunotherapy
131 Received allocated intervention
4 Withdrew consent and requested removal of all data
146 Allocated to standard care and placebo
145 Received allocated intervention
1 Withdrew consent and requested removal of all data
62 Discontinued intervention
-35 died
-18 discharged before completion of therapy
-8 therapy-related serious adverse event
-1 therapy-related non-serious adverse event
72 Discontinued intervention
-51 died
-19 discharged before completion of therapy
-2 therapy-related serious adverse events
131 included in primary analysis (blood sampling for evaluation of restoration of immune dysfunction= 59)
145 included in primary analysis (blood sampling for evaluation of restoration of immune dysfunction= 66)

THE PATIENT POPULATION

	Standard care + Precision Immunotherapy (N=131)	Standard care + Placebo (N=145)
Male/Female, n (%)	89 (67.9) / 42 (32.1)	94 (64.8) / 51 (35.2)
Age, mean (SD), years	69 (13)	70 (14)
Medical history, n (%)		
Diabetes mellitus	45 (34.4)	48 (33.1)
COVID-19	34 (26.0)	35 (24.1)
Chronic obstructive pulmonary disease	26 (19.8)	39 (26.9)
Coronary heart disease	25 (19.1)	34 (23.4)
Atrial fibrillation	23 (17.6)	36 (24.8)
Chronic heart failure	19 (14.5)	22 (15.2)
Cerebral stroke	18 (13.7)	18 (12.4)
Chronic renal disease	13 (9.9)	16 (11.0)
APACHE II, median (Q1-Q3)	20 (16-25)	19 (14-25)
CCI, median (Q1-Q3)[d]	4 (3-6)	5 (3-6)
SOFA score, median (Q1-Q3)	10 (7-12)	9 (6-11)
Interventions, n (%)		
Mechanical ventilation	116 (88.5)	129 (89.0)
Norepinephrine	110 (84.0)	126 (86.9)
Vasopressin	31 (23.7)	34 (23.4)
CVVH	23 (17.6)	24 (16.6)

APACHE: acute physiology and chronic health evaluation
CCI: Charlson's comorbidity index
CVVH: continuous veno-venal hemofiltration
n: number of patients
Q: quartile
SD: standard deviation
SOFA: sequential organ failure assessment

UNDERLYING INFECTIONS AND TREATMENTS

	Standard care + Precision Immunotherapy (N=131)	Standard care + Placebo (N=145)
Underlying Infection, n (%)		
Ventilator-associated pneumonia	48 (36.6)	54 (37.2)
Hospital-acquired pneumonia	35 (26.7)	32 (22.1)
Community-acquired pneumonia	31 (23.7)	44 (30.3)
Primary bacteremia	16 (12.2)	12 (8.3)
Pneumonia by SARS-CoV-2	1 (0.8)	3 (2.1)
Most common prescribed antibiotics, n (%)		
Piperacillin/tazobactam	27 (20.6)	25 (17.2)
Ceftazidime/avibactam	31 (23.7)	34 (23.4)
Meropenem	47 (35.9)	43 (29.7)
Tigecycline	27 (20.6)	25 (17.2)
Colistin	74 (56.5)	84 (57.9)
Linezolid	39 (29.8)	42 (29.0)
Glycopeptide (Vancomycin or Teicoplanin)	32 (24.4)	29 (20.0)
Daptomycin	37 (28.2)	40 (27.6)
Treatment with at least one active antibiotic against the isolated pathogen, n/N (%)	34/41 (82.9)	33/38 (86.8)

AST: antibiotic susceptibility testing
n: number of patients
N: number of patients with AST available

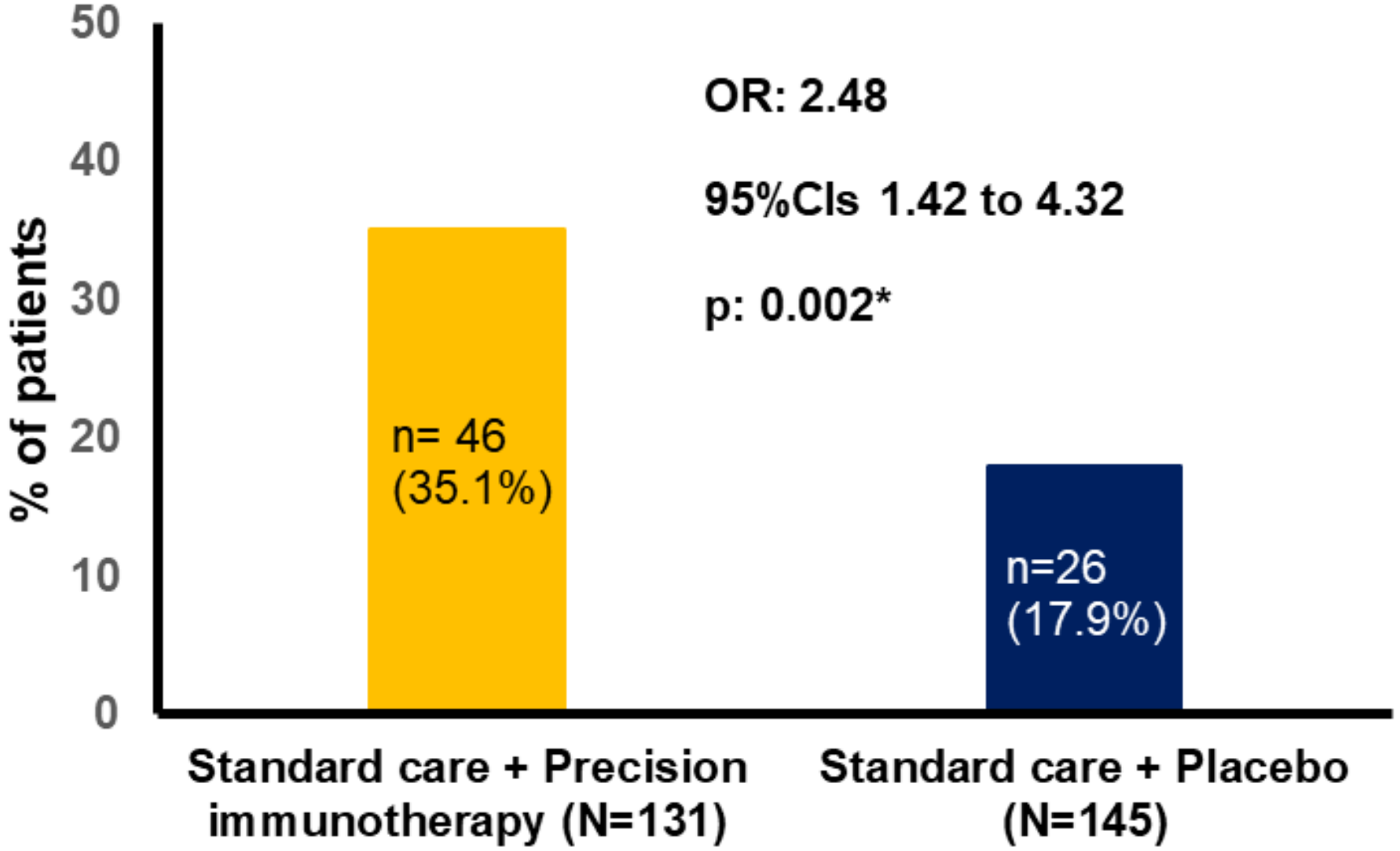
ENDOTYPING AND LABORATORY FINDINGS

	Standard care + Precision Immunotherapy (N=131)	Standard care + Placebo (N=145)
pO_2/FiO_2, median (Q1-Q3), mmHg	161.6 (127.0-247.0)	171.9 (127.8-232.8)
Lactate, median (Q1-Q3), mmol/l	1.7 (1.10-2.40)	1.7 (1.02-3.15)
C-reactive protein, median (Q1-Q3), mg/l	27.0 (13.9-189.6)	33.1 (14.8-138.5)
Procalcitonin, median (Q1-Q3), ng/ml	1.3 (0.5-5.9)	1.3 (0.5-11.5)
Macrophage activation-like syndrome, n (%)	**25 (19.1)**	**23 (15.9)**
Ferritin, median (Q1-Q3), ng/ml	5438 (5000-7009)	6221 (5000-7500)
mHLA-DR, median (Q1-Q3), antibodies per CD45/CD14 monocytes	3576 (2124-6205)	4990 (3068-7811)
Sepsis-induced immunoparalysis, n (%)	**106 (80.9)**	**122 (84.1)**
Ferritin, median (Q1-Q3), ng/ml	633 (353-1149)	703 (340-1488)
mHLA-DR, median (Q1-Q3), antibodies per CD45/CD14 monocytes	3043 (2297-4135)	3078 (1762-4004)

FiO_2: fraction of inspired oxygen
HLA: human leukocyte antigen
n: number of patients
pO_2: particle oxygen pressure
Q: quartile

immunoSEP

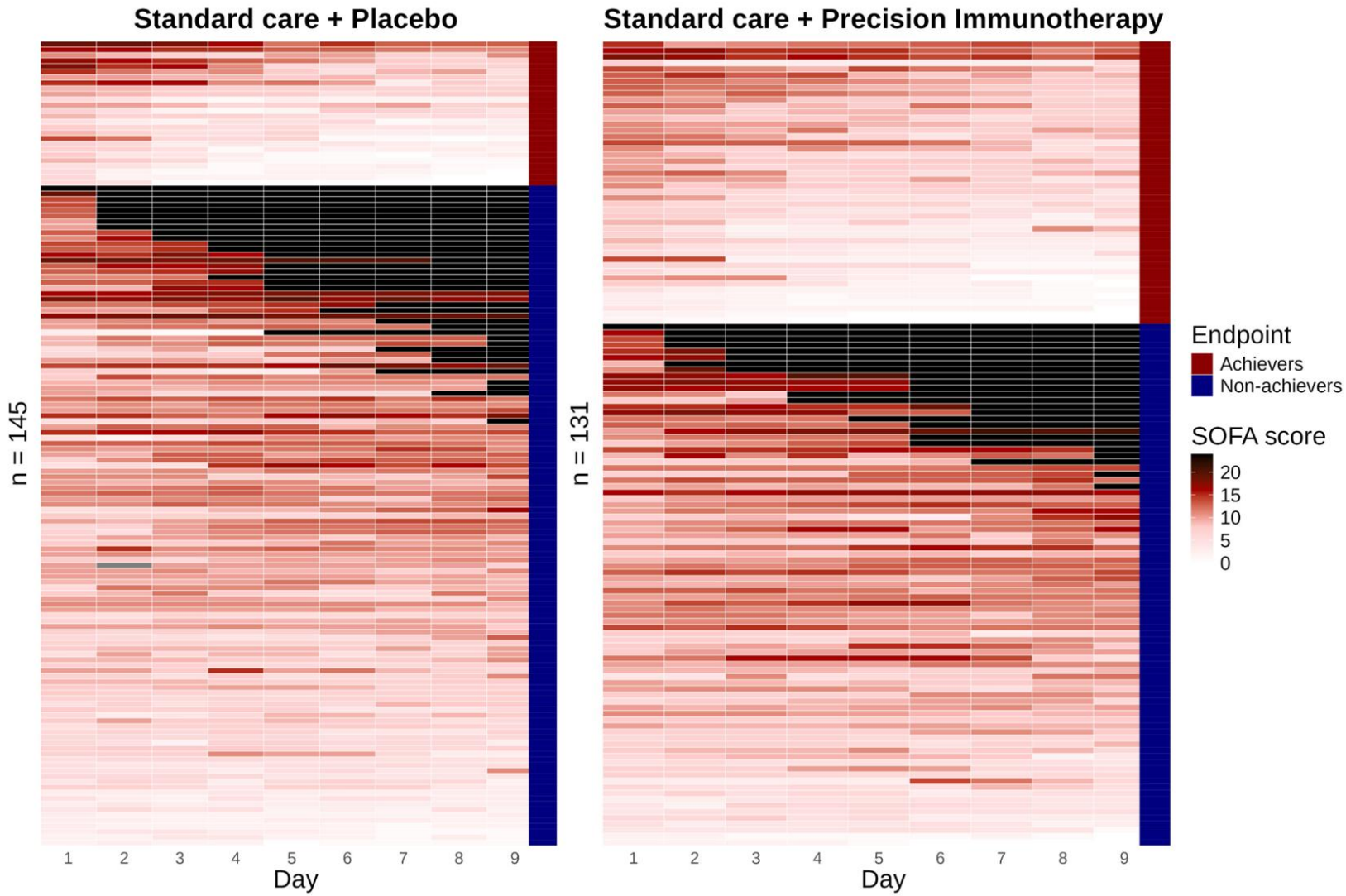
PRIMARY ENDPOINT (IMPROVEMENT OF ORGAN FUNCTION)
≥1.4-point decrease of mean SOFA score until day 9



*by the Fisher's exact test

CI: confidence interval
OR: odds ratio
n: patients meeting the endpoint
N: total number of group patients
SOFA: sequential organ failure assessment

DAILY SOFA SCORES



Achievers: patients attaining the primary endpoint
n: total number of patients per group
SOFA: sequential organ failure assessment

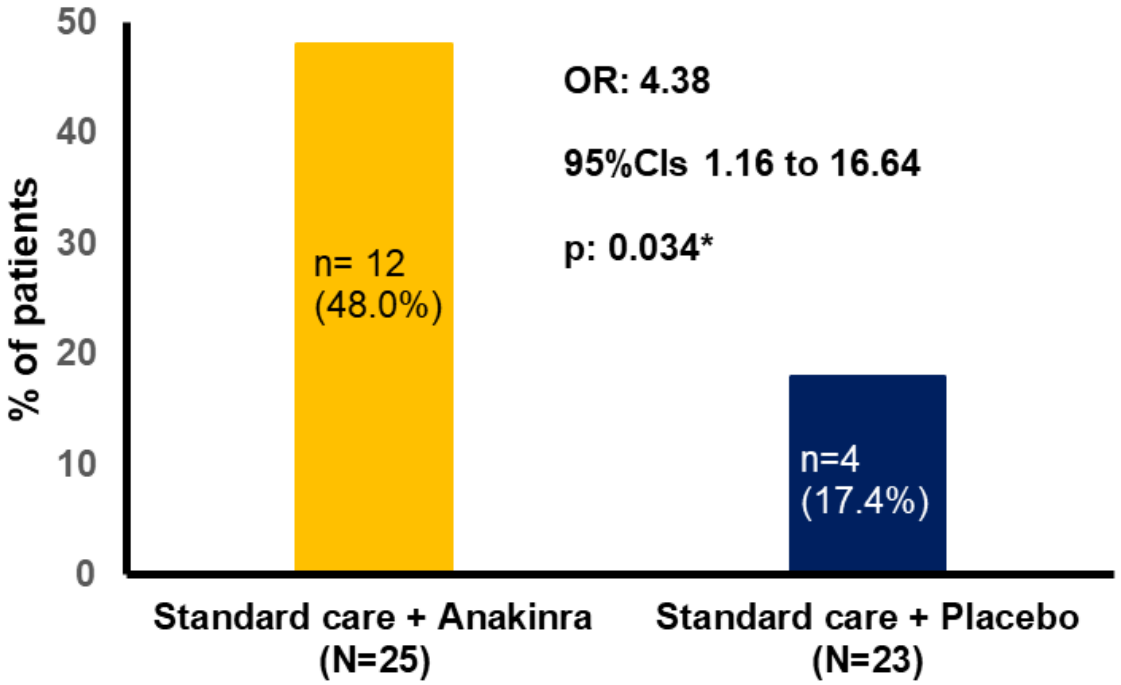
LOGISTIC REGRESSION ANALYSIS OF THE PRIMARY ENDPOINT

	Meeting the endpoint		Univariate analysis		Multivariate analysis	
	No	Yes	OR	P value	OR	P value
APACHE II median (Q1-Q3)	19 (14-25)	20 (16-25)	1.01 (0.97 to 1.05)	0.650	1.00 (0.96 to 1.05)	0.826
CCI median (Q1-Q3)	5 (3-6)	4 (3-6)	0.94 (0.84 to 1.06)	0.338	0.95 (0.84 to 1.07)	0.375
SOFA median (Q1-Q3)	9 (7-11)	9.5 (7-12.8)	1.03 (0.96 to 1.10)	0.433	1.02 (0.95 to 1.09)	0.562
Sites enrolling more than 8%, n (%)	100 (49.0)	32 (44.4)	0.83 (0.48 to 1.42)	0.504	0.80 (0.46 to 1.41)	0.453
Precision immuno-therapy, n/N (%)	85/204 (41.7)	46/72 (63.9)	2.48 (1.42 to 4.31)	0.001	2.49 (1.42 to 4.36)	0.001

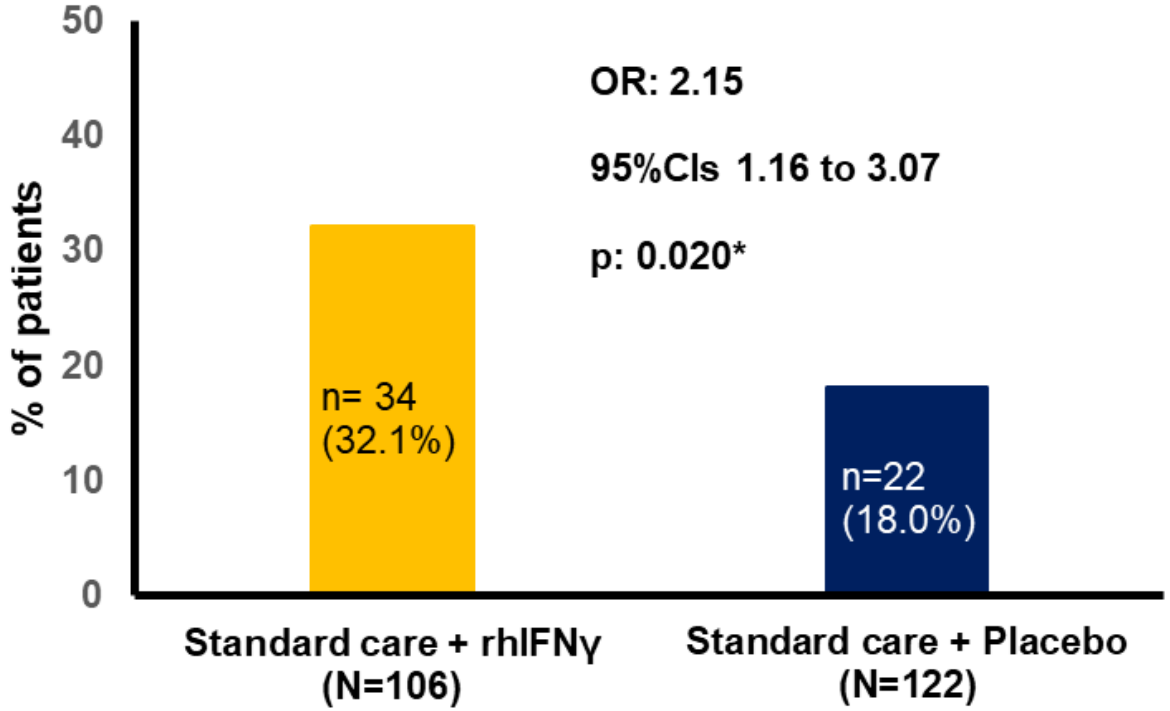
APACHE: acute physiology and chronic health evaluation
CCI: Charlson's comorbidity index
CI: confidence interval
OR: odds ratio
q: quartile
n: number of patients
N: number of patients at the subgroup
SOFA: sequential organ failure assessment

≥1.4-point mean SOFA decrease until Day 9: ATTAINED IN BOTH STATES OF IMMUNE ACTIVATION

MACROPHAGE ACTIVATION-LIKE SYNDROME

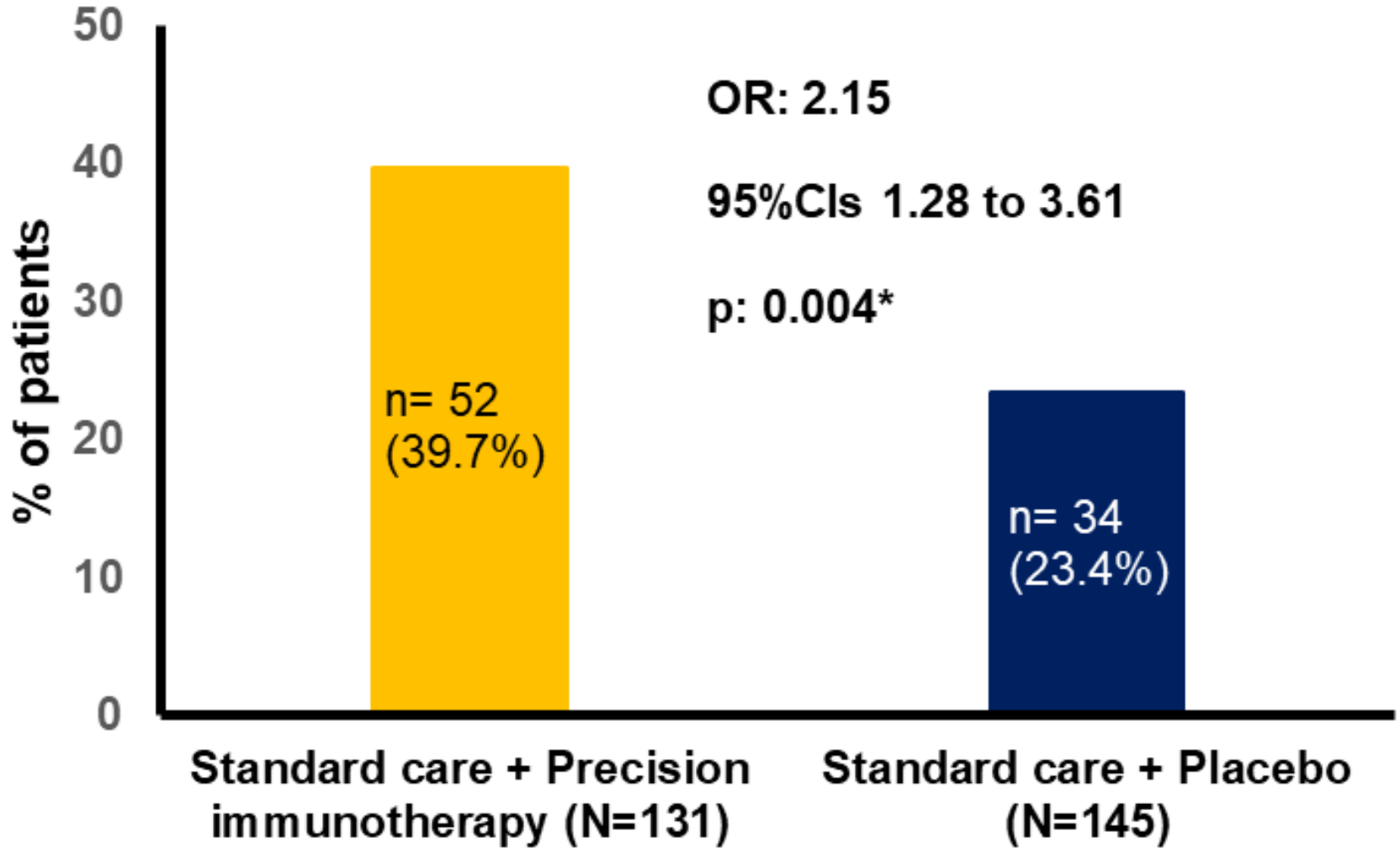


SEPSIS-INDUCED IMMUNOPARALYSIS



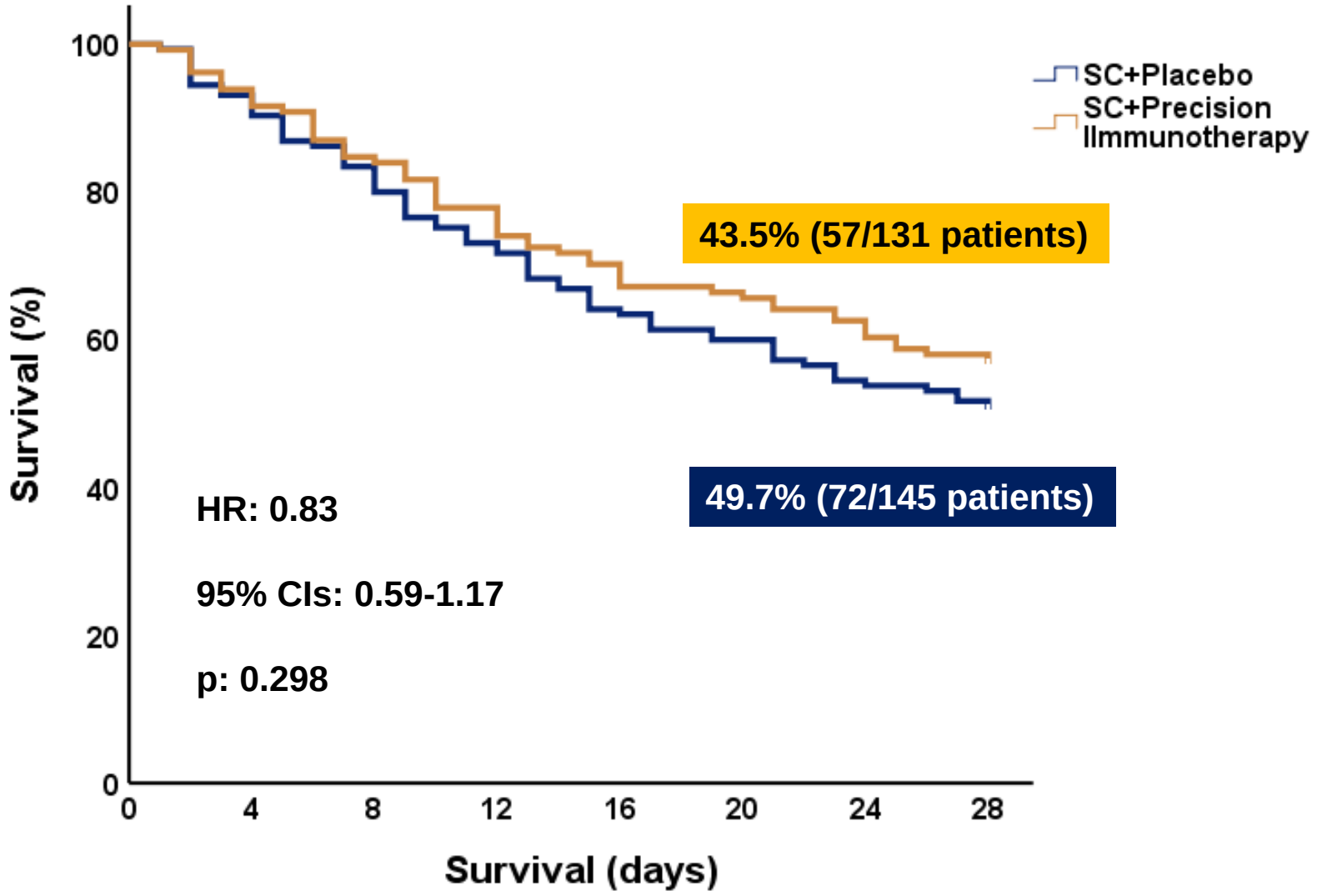
*by the Fisher's exact test
CI: confidence interval
OR: odds ratio
n: patients meeting the endpoint
N: total number of group patients
rhIFNγ: recombinant human interferon-gamma
SOFA: sequential organ failure assessment

≥1.4-point mean SOFA decrease :
ATTAINED UNTIL DAY 15 BY PRECISION IMMUNOTHERAPY



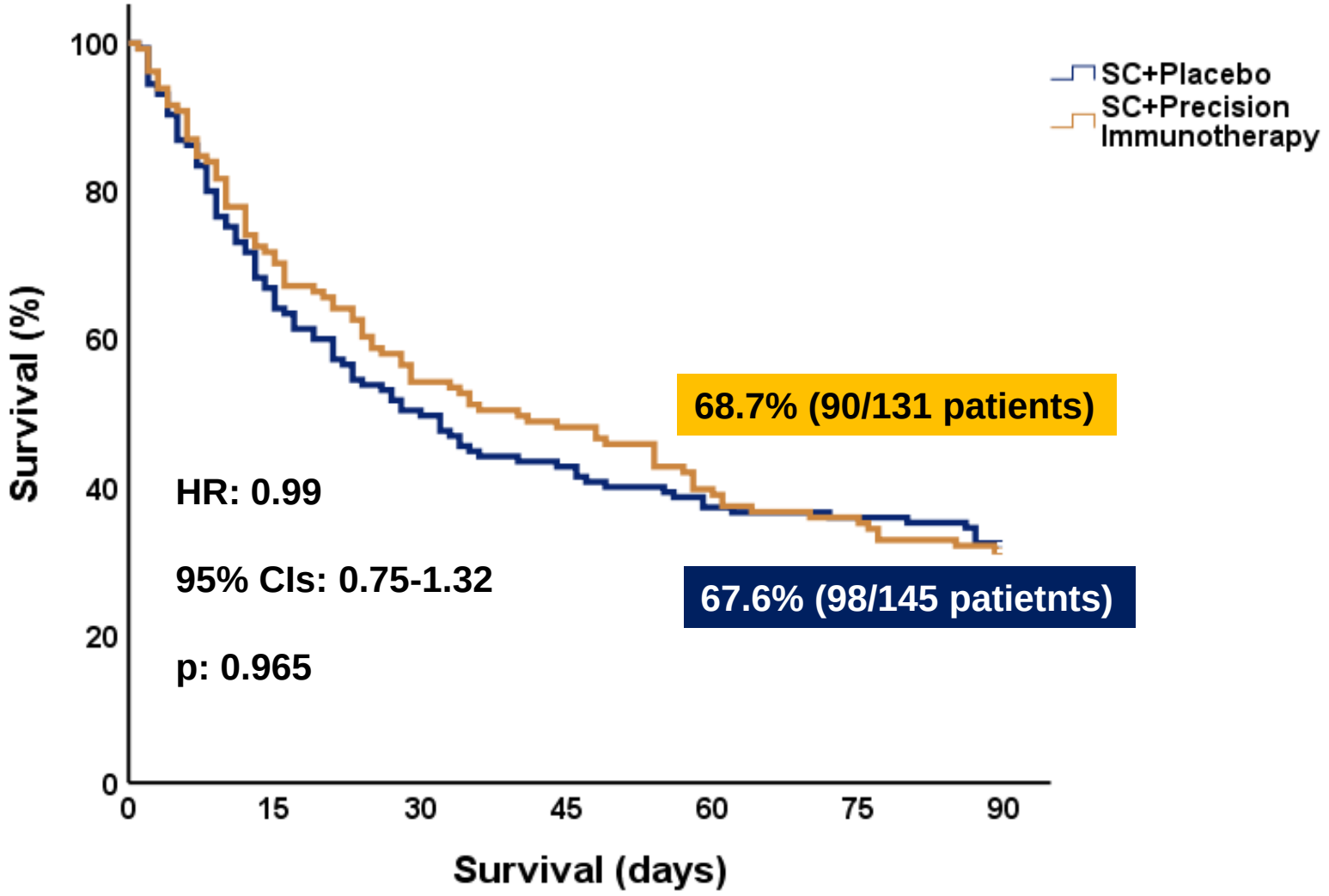
*by the Fisher's exact test
CI: confidence interval
OR: odds ratio
n: patients meeting the endpoint
N: total number of group patients
SOFA: sequential organ failure assessment

NO SIGNIFICANT DECREASE OF 28-DAY MORTALITY WITH PRECISION IMMUNOTHERAPY



CI: confidence interval
HR: hazard ratio
SC: standard care

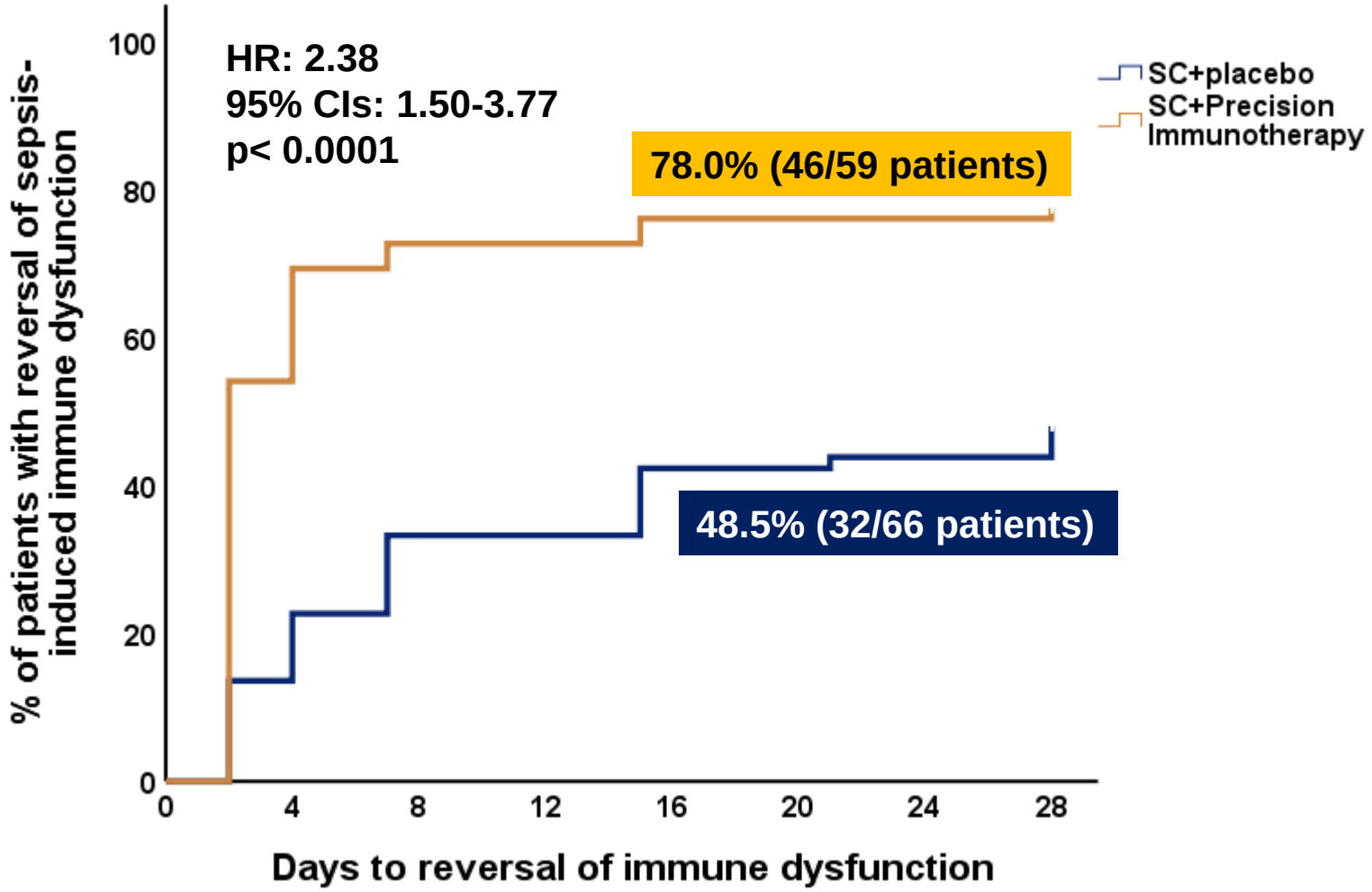
90-DAY MORTALITY UNCHANGEABLE



CI: confidence interval
HR: hazard ratio
SC: standard care

HIGHER AND EARLIER RESTORATION OF IMMUNE DYSFUNCTION BY PRECISION IMMUNOTHERAPY

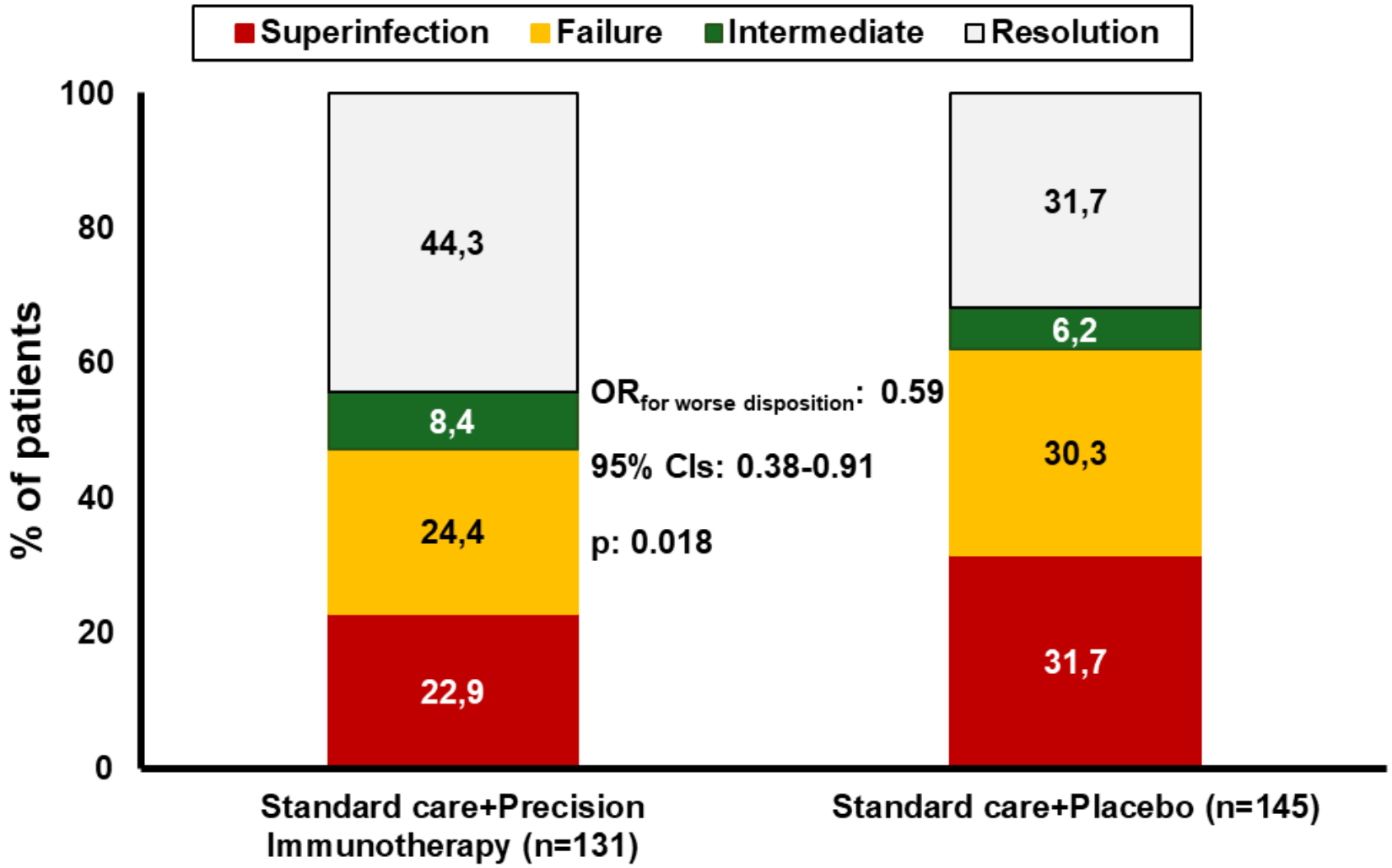
Definition
≥15% decrease of ferritin for patients with MALS remaining decreased over follow-up time blood draws
+
>8,000 HLA-DR receptor per CD45/CD14- monocyte for patients with SII remaining above these values over follow-up time blood draws



CI: confidence interval
HR: hazard ratio
MALS: macrophage activation-like syndrome
SC: standard care
SII: sepsis-induced immunoparalysis

BETTER INFECTION DISPOSITION* ON DAY 15 WITH PRECISION IMMUNOTHERAPY

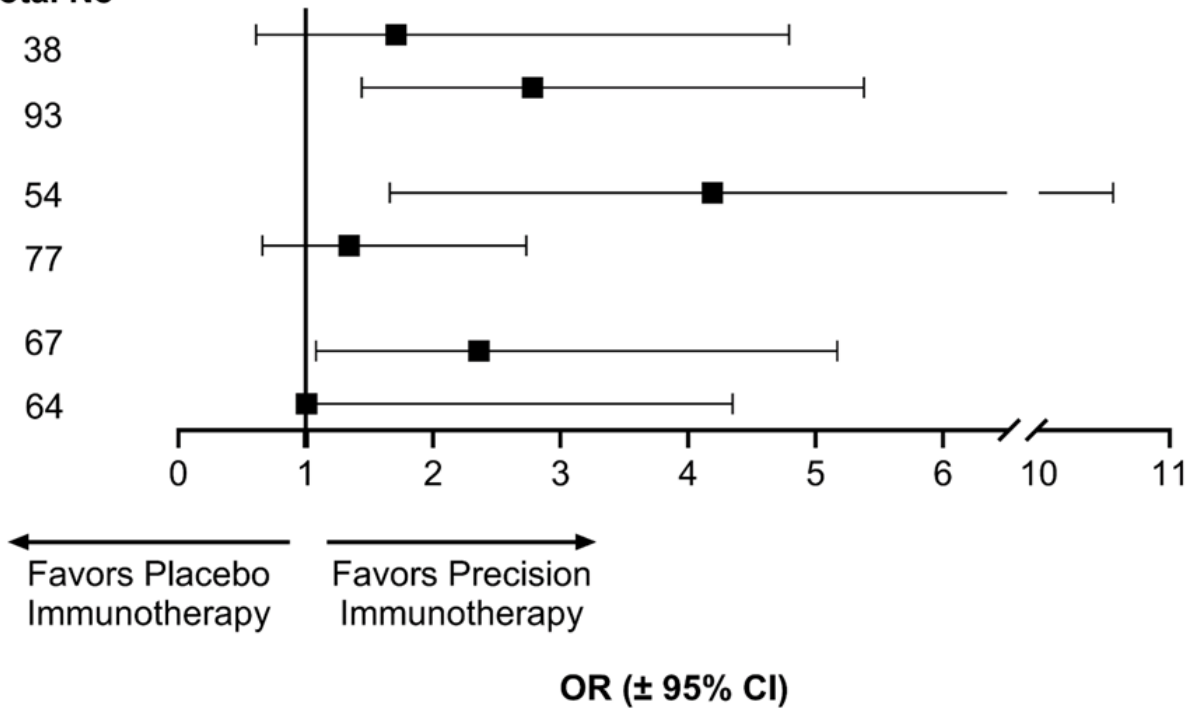
*by predefined criteria



CI: confidence interval
OR: odds ratio

HIGHER ODDS FOR ≥1.4-POINT MEAN SOFA DECREASE UNTIL DAY 9 WHEN CCI≥5 OR SOFA ≥10 (*Post-Hoc*)

	SC + Placebo		SC + Precision Immunotherapy		*P* value
	Events	Total No	Events	Total No	
APACHE II ≥ 25	8	40	12	38	.439
APACHE II < 25	18	105	34	93	.002
CCI ≥ 5	7	76	20	54	.003
CCI < 5	19	69	26	77	.475
SOFA ≥ 10	11	68	25	67	.035
SOFA < 10	15	77	21	64	.083

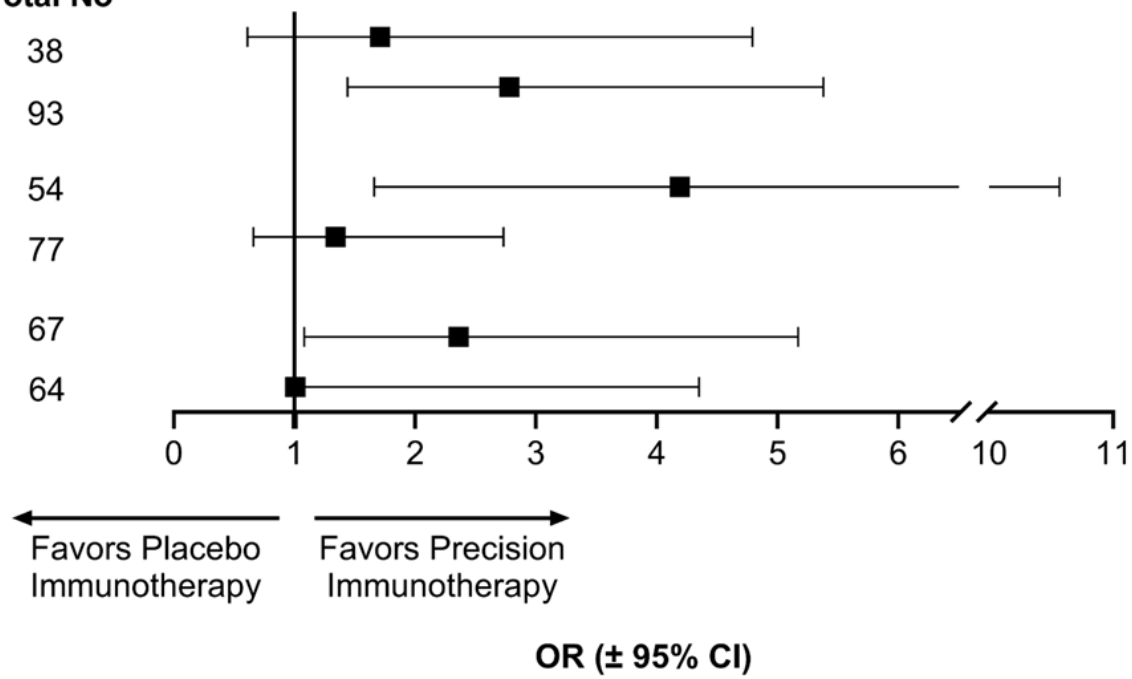


APACHE: acute physiology and chronic health evaluation
CCI: Charlson's comorbidity index
CI: confidence interval
OR: odds ratio
ROC: receiver operator characteristics
SC: standard care
SOFA: sequential organ failure assessment

Cut-offs are defined as the Youden index of the scores after ROC plot for 28-day mortality

HIGHER ODDS FOR 28-SURVIVAL BENEFIT WHEN APACHE II<25 OR CCI ≥5 OR SOFA ≥10 (*Post-Hoc)*

	SoC + Placebo		SoC + Precision Immunotherapy		*P* value
	Events	Total No	Events	Total No	
APACHE II ≥ 25	8	40	12	38	.439
APACHE II < 25	18	105	34	93	.002
CCI ≥ 5	7	76	20	54	.003
CCI < 5	19	69	26	77	.475
SOFA ≥ 10	11	68	25	67	.035
SOFA < 10	15	77	21	64	.083



APACHE: acute physiology and chronic health evaluation
CCI: Charlson's comorbidity index
CI: confidence interval
OR: odds ratio
ROC: receiver operator characteristics
SC: standard care
SOFA: sequential organ failure assessment

Cut-offs are defined as the Youden index of the scores after ROC plot for 28-day mortality

MOST COMMON SERIOUS TREATMENT-EMERGENT ADVERSE EVENTS (Medra 27.0)

	Probably or Possibly related		Probably not related or Unrelated:	
Category, n (%)	**Standard care + Precision Immunotherapy (N=131)**	**Standard care + Placebo (N=145)**	**Standard care + Precision Immunotherapy (N=131)**	**Standard care + Placebo (N=145)**
Any SAE	8 (6.1)	3 (2.1)	108 (82.4)	126 (86.9)
Blood and lymphatic system disorders				
Anaemia	0 (0.0)	0 (0.0)	47 (35.9)	38 (26.2)
Cardiac disorders				
Atrial fibrillation	0 (0.0)	0 (0.0)	19 (14.5)	14 (9.7)
Cardiac arrest	0 (0.0)	1 (0.7)	9 (6.9)	15 (10.3)
Multiple organ dysfunction syndrome	2 (1.5)	0 (0.0)	51 (38.9)	58 (40.0)
Infections and infestations				
Bacteraemia	0 (0.0)	0 (0.0)	36 (27.5)	27 (18.6)
Fungaemia	0 (0.0)	0 (0.0)	17 (13.0)	12 (8.3)
Pneumonia	0 (0.0)	0 (0.0)	35 (26.7)	32 (22.1)
Sepsis	0 (0.0)	0 (0.0)	9 (6.9)	12 (8.3)
Septic shock	0 (0.0)	0 (0.0)	29 (22.1)	17 (11.7)
Renal and urinary disorders				
Acute kidney injury	0 (0.0)	0 (0.0)	21 (16.0)	19 (13.1)
Respiratory, thoracic and mediastinal disorders				
Pleural effusion	0 (0.0)	0 (0.0)	5 (3.8)	3 (2.1)
Pneumothorax	0 (0.0)	0 (0.0)	10 (7.6)	7 (4.8)
Tracheal stenosis	0 (0.0)	0 (0.0)	7 (5.3)	8 (5.5)
Vascular disorders				
Haemorrhage	0 (0.0)	0 (0.0)	6 (4.6)	0 (0.0)

N: number of patients; SAE: serious adverse events

CONCLUSIONS

ImmunoSep meets the primary endpoint (improved organ function until day 9)

Attainment of ≥1.4-point decrease of mean SOFA score is significantly higher in the group of Precision Immunotherapy than in the placebo arm

Secondary endpoints

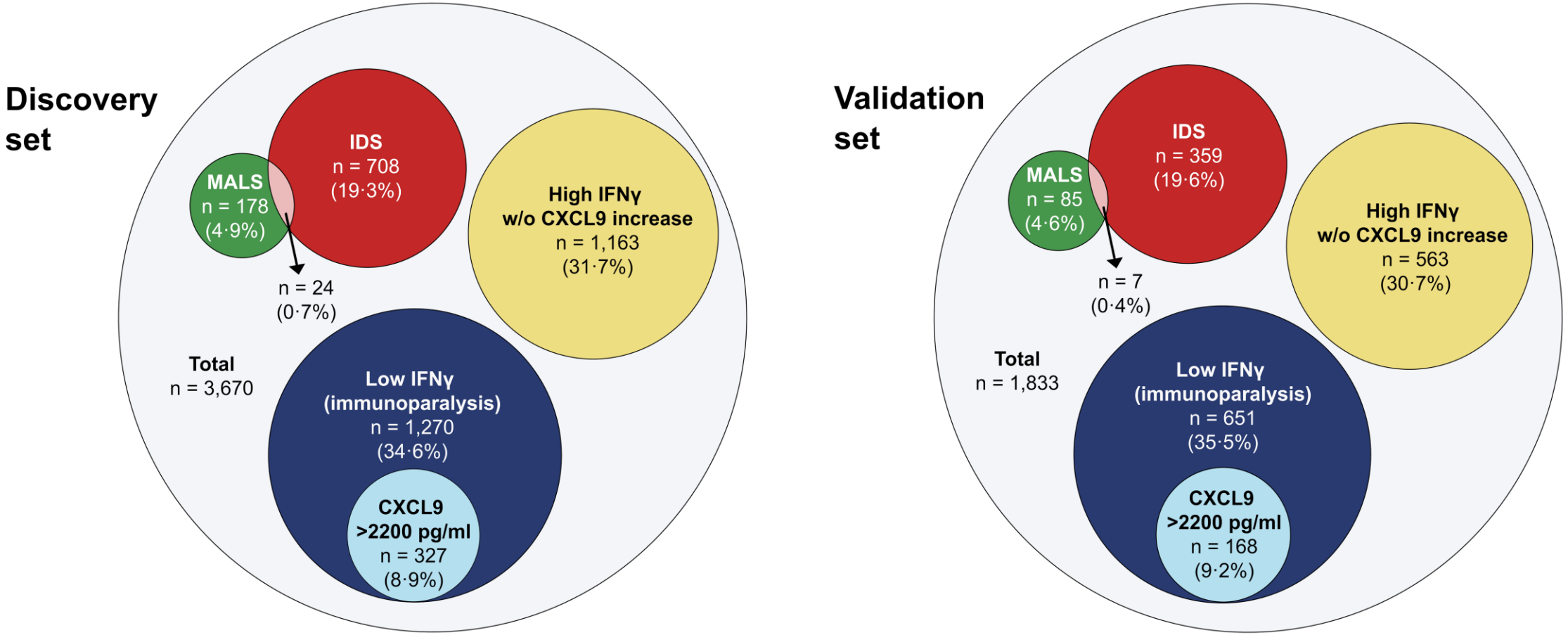
In the Precision immunotherapy arm versus the Placebo therapy

- ↑ attainment of ≥1.4-point decrease of mean SOFA score until day 9 in MALS patients (superiority of Anakinra) and in patients with SII (superiority of rhIFNγ)
- ↑ attainment of ≥1.4-point decrease of mean SOFA score until day 15
- ↓, albeit non-significant, of 28-day mortality
- No difference in 90-day mortality
- ↑ rate of restoration of immune dysfunction (and faster)
- Better infection disposition on day 15

↓: decrease
↑: increase
MALS: macrophage activation-like syndrome
rhIFNγ: recombinant human Interferon-gamma
SII: sepsis-induced iimmunoparalysis
SOFA: sequential organ failure assessment

Endotype classification of 5,503 patients with sepsis split into one discovery set and one validation set

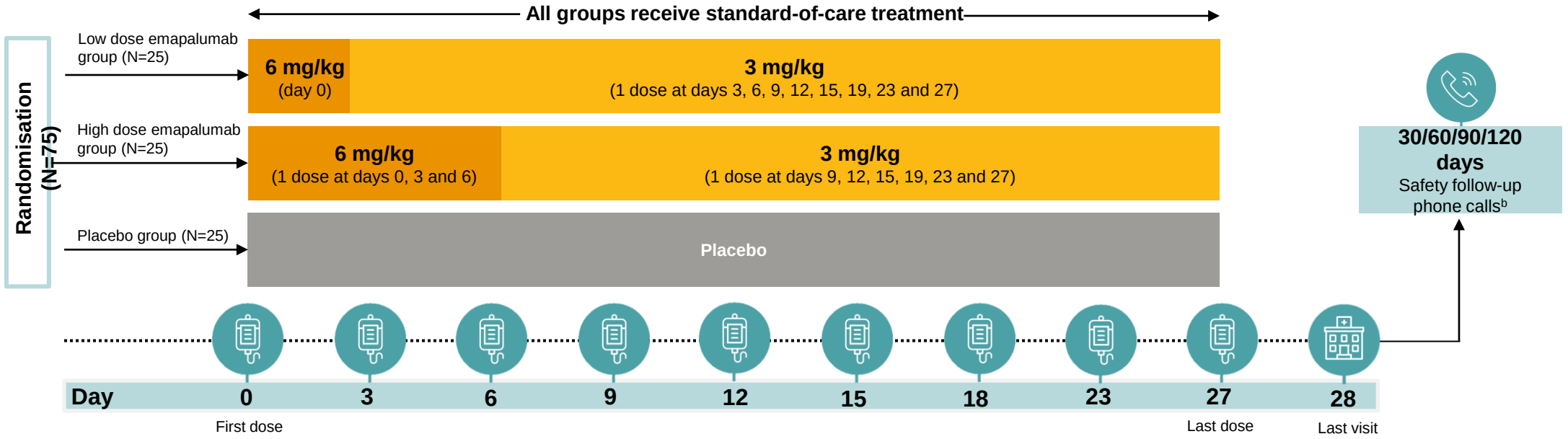
(Giamarellos-Bourboulis EJ, et al. *eBioMedicine* 2024; 109: 105414)



IDS: IFNγ-driven sepsis
IFN: interferon
MALS: macrophage activation-like syndrome
n: number of patients
w/o: without

EMapalumaB treatment foR Anticipated Clinical benefit in sepsis driven by the interferon-gamma Endotype (EMBRACE) (EU CT: 2024-515255-38-00; Clinicaltrials.gov NCT06694701)

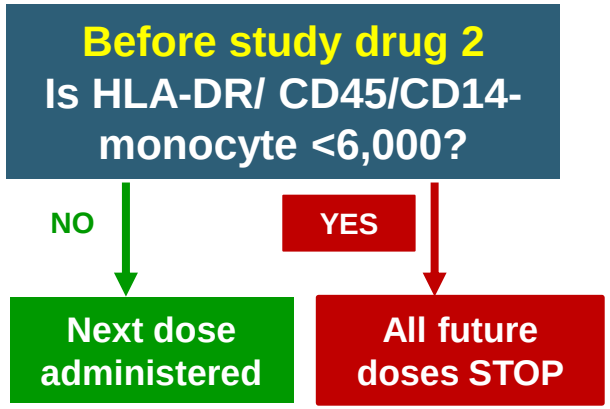
- Three-arm parallel, multicentre, phase 2a, double-blind, randomised controlled trial at **24 study sites in Greece**.
- **Seventy-five patients** randomly assigned into **three groups (1:1:1)** to receive treatment over 28 days.

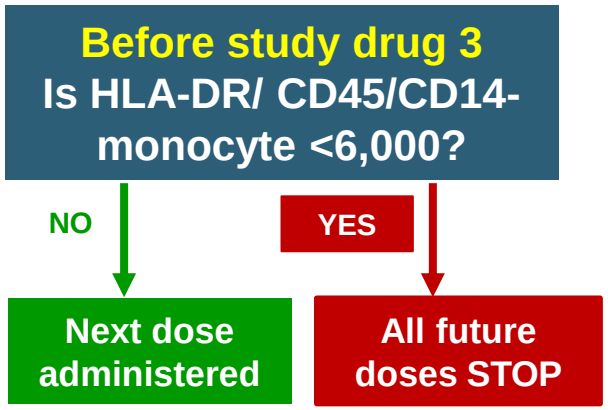


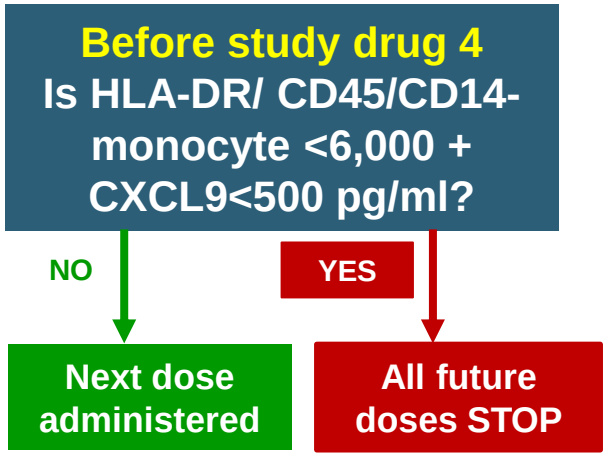
ELIGIBILITY AND MONITORING CRITERIA

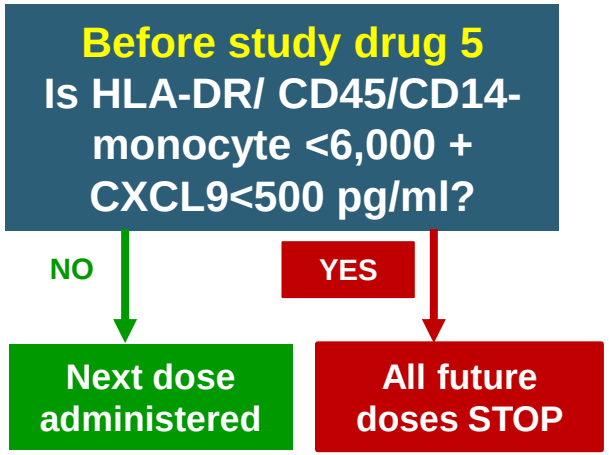
Inclusion criteria

- ≥18 years of age
- Confirmed pneumonia or abdominal infection or acute pyelonephritis or primary bacteremia
- Sepsis defined by the Sepsis-3 criteria
- Serological diagnosis of IDS*









etc…

*IFNγ >lower limit of detection + CXCL9 >2200 pg/ml
+ HLA-DR ≥8000 receptors/CD14-monocyte

The Partners

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BLUE CENTRE