IMUNOPARALIZA IN SEPSA

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KOIIM, UKC Ljubljana

IMUNSKI ODGOVOR PRI KRITIČNO BOLNIH

1. Večina raziskav pri **sepsi**, podoben mehanizem pri **drugih etiologijah** (ARDS, srčni zastoj, pankreatitis, travma, opekline, po operaciji…)

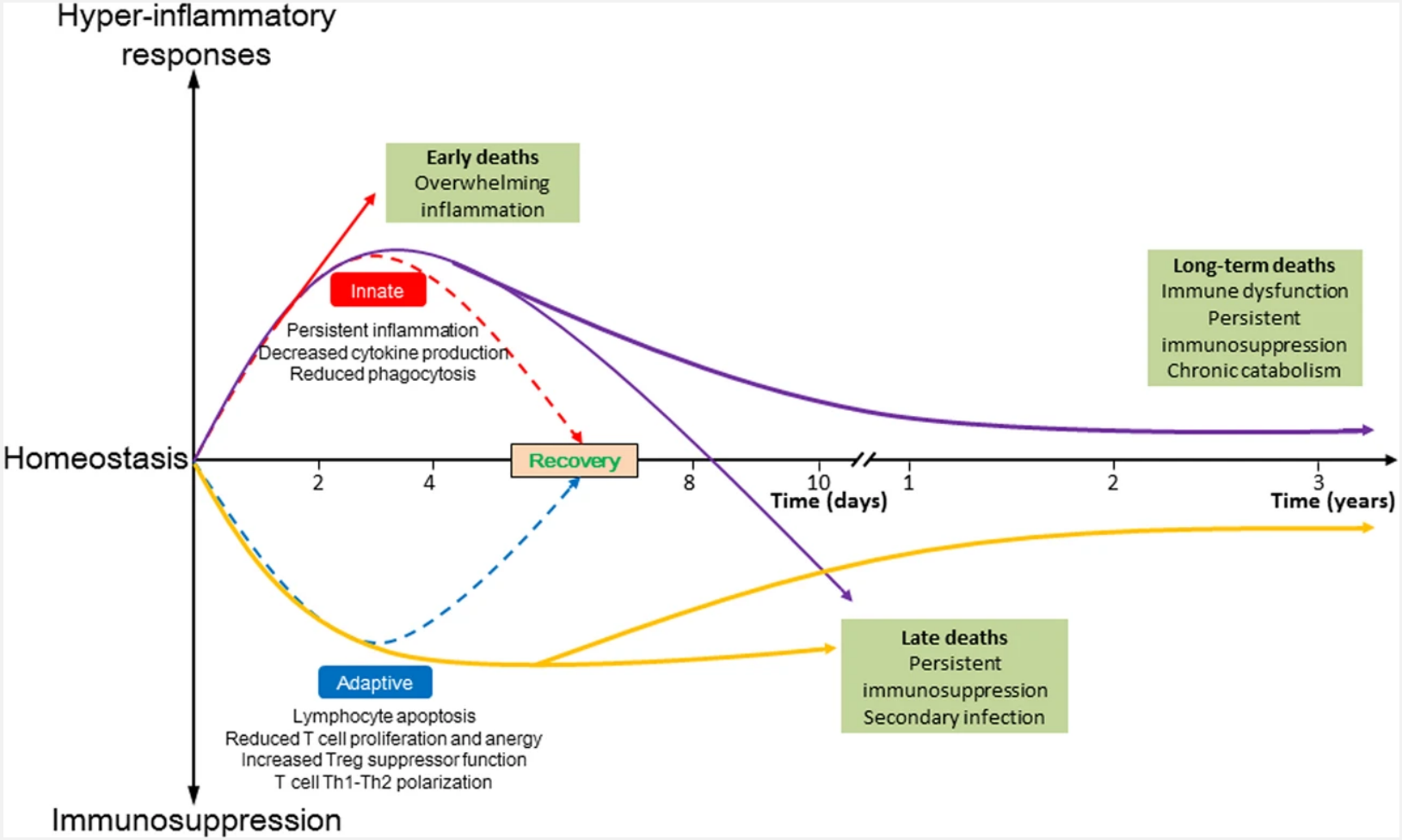
Cell Death Dis 10, 782 (2019)
Cell Death Dis 9, 465 (2023)
Nature 464, 41–42 (2010)

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2. Hipervnetni odgovor in imunoparaliza sta pogosto prisotna **hkrati**

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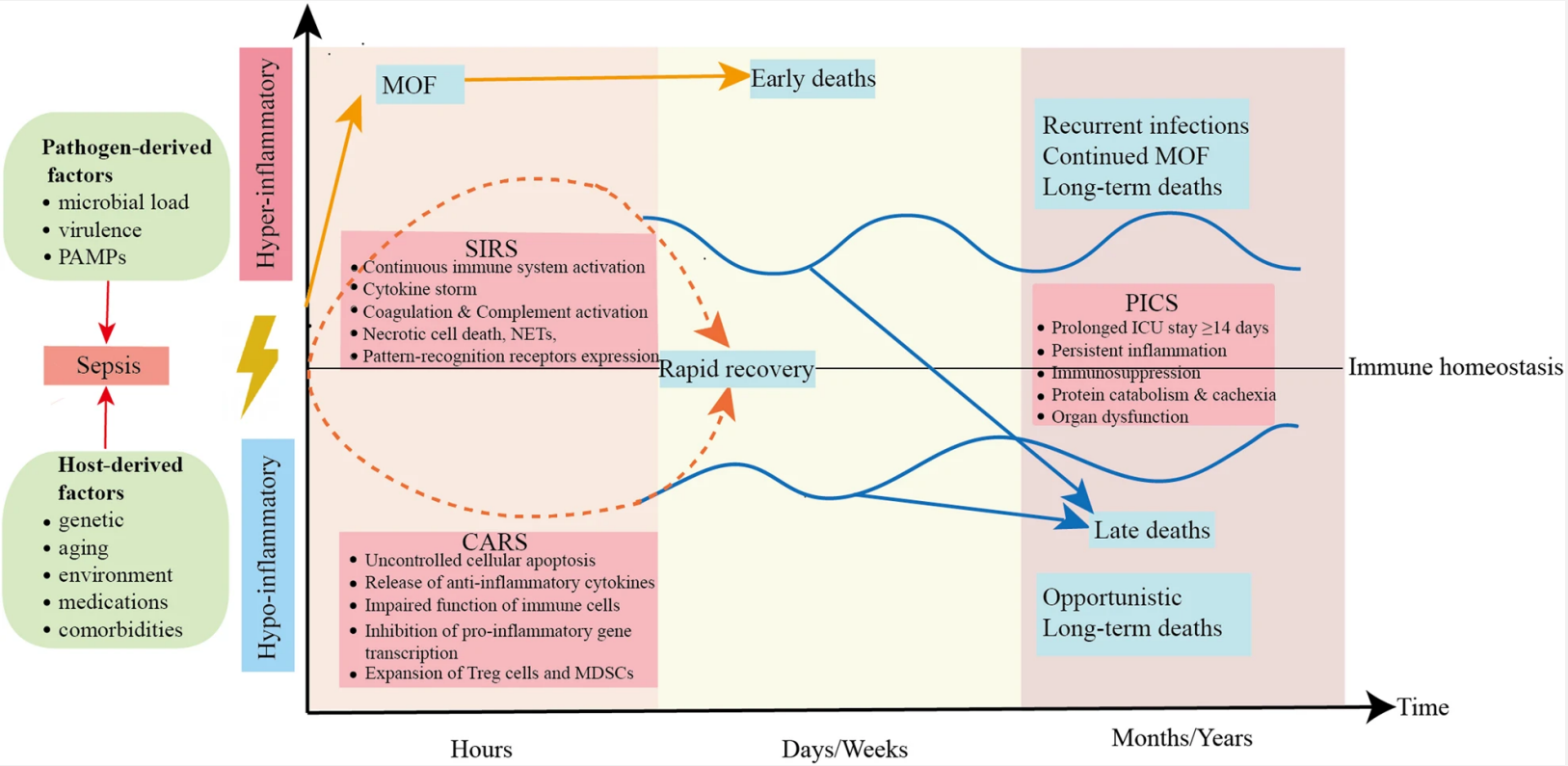
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3. Opisani tudi **drugi fenotipi**
4. **Spremenljiv imunski odgovor** med zdravljenjem v EIT

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4. **Spremenljiv imunski odgovor** med zdravljenjem v EIT
5. Več podatkov za hipervnetni odgovor, vendar se da imunoparalizo prav tako "**izmeriti**"

↑ Feritin
↑ IL-6
trombocitopenija
↑ TAG
↓ fibrinogen
↑ d-dimer

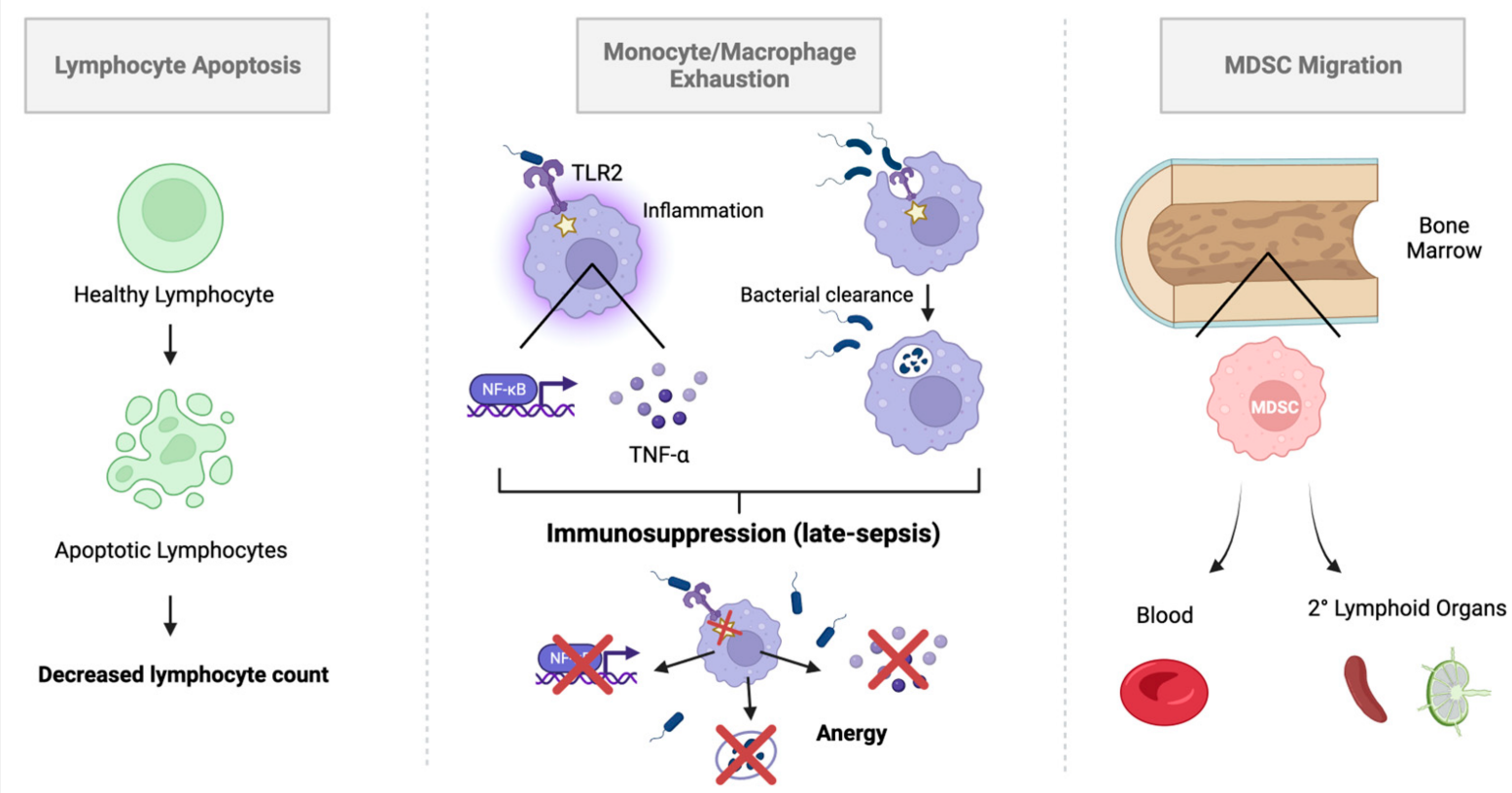
Cell Death Dis 10, 782 (2019)
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KDAJ POMISLIM, DA IMA MOJ BOLNIK IMUNOPARALIZO?



IMUNOPARALIZA PRI KRITIČNO BOLNIH

- Pro- in protivnetni odgovor se aktivirata hitro po nastopu bakteriemije s sepso
- Imunosupresija najbolj izrazita po nekaj dneh



Front Immunol. 2025 Apr 29;16:1577105
Biomedicines 2024, 12, 175

KLINIČNI NAMIGI

- POČASNO OKREVANJE po prvem dogodku
- **SEKUNDARNE OKUŽBE**
- **OPORTUNISTIČNE OKUŽBE**
  - Candida, aspergiloza
  - Nesorazmerno glede na pacientov imunski status



Front Immunol. 2025 Apr 29;16:1577105
Eur Respir Rev. 2025 Feb 19;34(175):240153.

KLINIČNI NAMIGI

- POČASNO OKREVANJE po prvem dogodku
- **SEKUNDARNE OKUŽBE**
- **OPORTUNISTIČNE OKUŽBE**
- **REAKTIVACIJA VIRUSOV**
  - HSV
  - CMV
  - EBV
  - HHV-6



Front Immunol. 2025 Apr 29;16:1577105
Eur Respir Rev. 2025 Feb 19;34(175):240153.

KLINIČNI NAMIGI

- POČASNO OKREVANJE po prvem dogodku
- **SEKUNDARNE OKUŽBE**
- **OPORTUNISTIČNE OKUŽBE**
- **REAKTIVACIJA VIRUSOV**
- SLABO CELJENJE RAN
- KATABOLIZEM



Front Immunol. 2025 Apr 29;16:1577105
Eur Respir Rev. 2025 Feb 19;34(175):240153.

UPORABNI LABORATORIJSKI IZVIDI?



DIAGNOZA

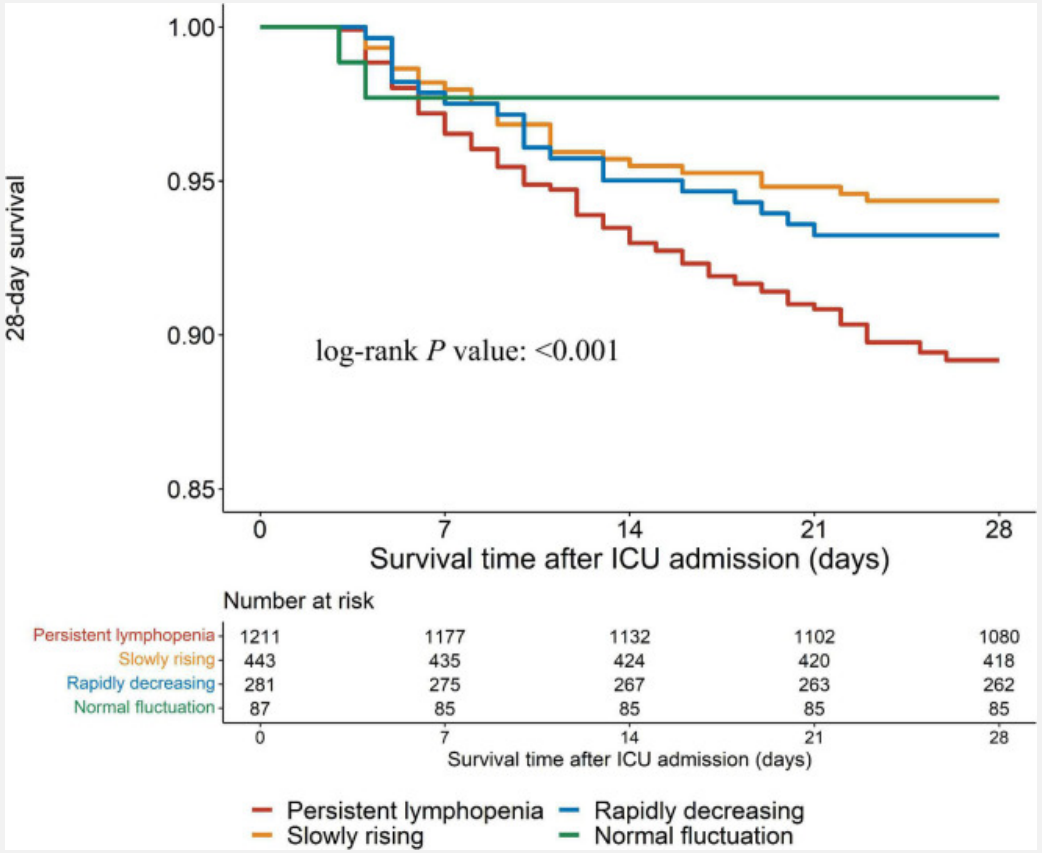
		Biomarker	Role and Correlation with Outcomes Due to Late Sepsis	References
	PD-1/PD-L1	Decreased lymphocyte count	Late-septic patients are reported to have a decreased lymphocyte count compared with non-septic patients. The decrease is thought to be contributed to inappropriate activation of apoptosis pathways. This biomarker is correlated with a higher likelihood of developing secondary infections.	[3,51,89,91,92,96,97]
Immune checkpoint	CTLA-4	Increased MDSC	Late-septic patients have higher levels of MDSCs in the blood and secondary lymphoid organs compared with non-septic patients	[3,98,103,104,106,107,108,109,110,111,112,136,137
			lls are thought to contribute to worse inflammatory nature.	
			non-septic patients. ody will not be able to mount an dary infection. utcomes due to sepsis.	[3,127,128]
			compared with non-septic patients. l pro-resolving mediator (SPM) circuits. on neutrophils is correlated with an	[130,131,132]
			ith non-septic patients. to activate T-cell-mediated adaptive infection. : (SOFA) scores due to sepsis.	[3,70,134,135]

Biomarker	Source or Cell	Clinical Significance	Limitations/Current Validation	References
HLA-DR	Monocytes	Reduced expression linked to immunosuppression and higher risk of secondary infections.	Variability in measurement techniques and lack of standardized clinical thresholds.	[23,24]
PD-1/PD-L1	T lymphocytes (PD-1) and antigen-presenting cells (PD-L1)	Overexpression correlates with T cell exhaustion and sepsis severity.	Requires flow cytometry; expression varies by disease phase.	[6,25]
IL-10	Immune cells (lymphocytes, macrophages)	Elevated levels indicate immunosuppression and worse prognosis.	Non-specific (elevated in other inflammatory conditions).	[26,27]
mtDNA	Mitochondria released during cellular damage	Activates STING pathway in dendritic cells, associated with immunoparalysis.	Technically challenging to quantify; present in other tissue-damage pathologies.	[28,29]
ASC-specks	Monocytes and neutrophils	Indicator of NLRP3 inflammasome activation; low levels predict higher mortality.	Complex detection (flow cytometry); limited clinical validation.	[30]
LDN	Circulating neutrophils	Associated with immune dysfunction, high PD-L1 expression, and infection risk.	Isolation challenges; heterogeneous studies on prognostic value.	[20,31]
Caspase-3/Caspase-9	Lymphocytes and dendritic cells	Activation indicates apoptosis, contributing to lymphopenia and immunosuppression.	Measuring active caspases is technically challenging in clinical settings.	[23,32]
IL-7R	T lymphocytes	Reduced expression linked to T cell dysfunction; potential therapeutic target.	Experimental-phase studies; variability based on patient immune status.	[6,33]

HLA-DR: Human Leukocyte Antigen–DR isotype, PD-1: programmed cell death protein 1, PD-L1: Programmed Death-Ligand 1, IL-10: Interleukin-10, mtDNA: mitochondrial DNA, STING: Stimulator of Interferon Genes, ASC-specks: Apoptosis-Associated Speck-Like Protein Containing a CARD, NLRP3: NOD-, LRR-, and Pyrin Domain-Containing Protein 3, LDN: low-density neutrophils, Caspase-3: cysteine-aspartic protease 3, Caspase-9: cysteine-aspartic protease 9, IL-7R: Interleukin-7 Receptor.

ABSOLUTNO ŠTEVILO LIMFOCITOV

- Retrospektivna, monocentrična
- N=2022, vsi bolniki
- Abs Lym dan 0-5
- Zgodnja vztrajajoča limfopenija in hitro padajoče vrednosti ALC povezani z višjo umrljivostjo



Front Med (Lausanne). 2022 Aug 4;9:953103

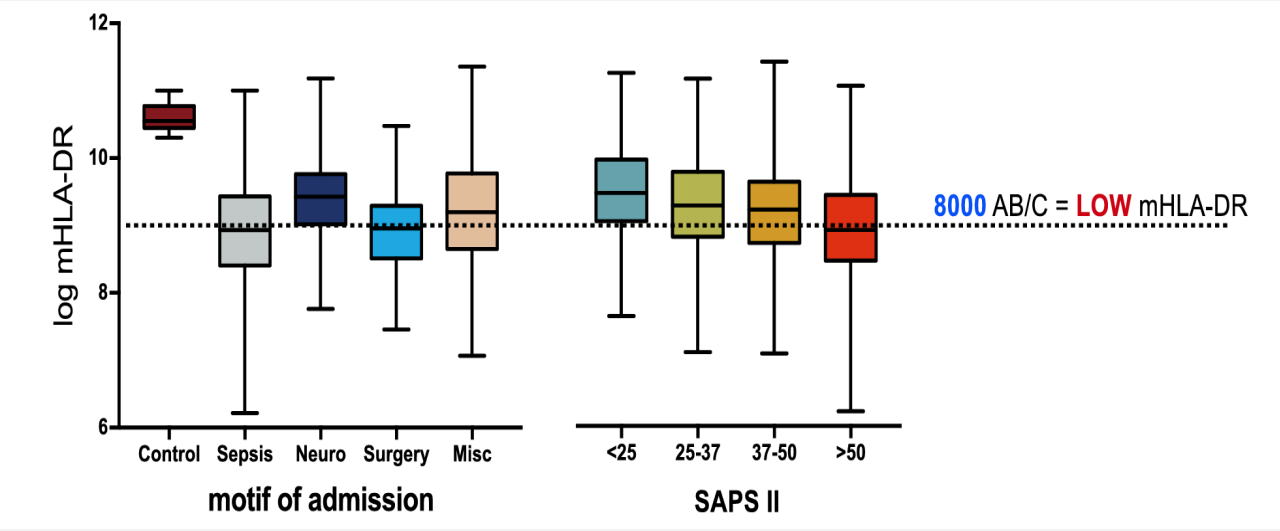
IMUNOGLOBULINI

- Nasprotujoči si podatki
- Meritev bazalnih vrednosti IgA, IgG, IgM
- Več poudarka na kinetiki – **IgM?**

Crit Care 30, 41 (2026).

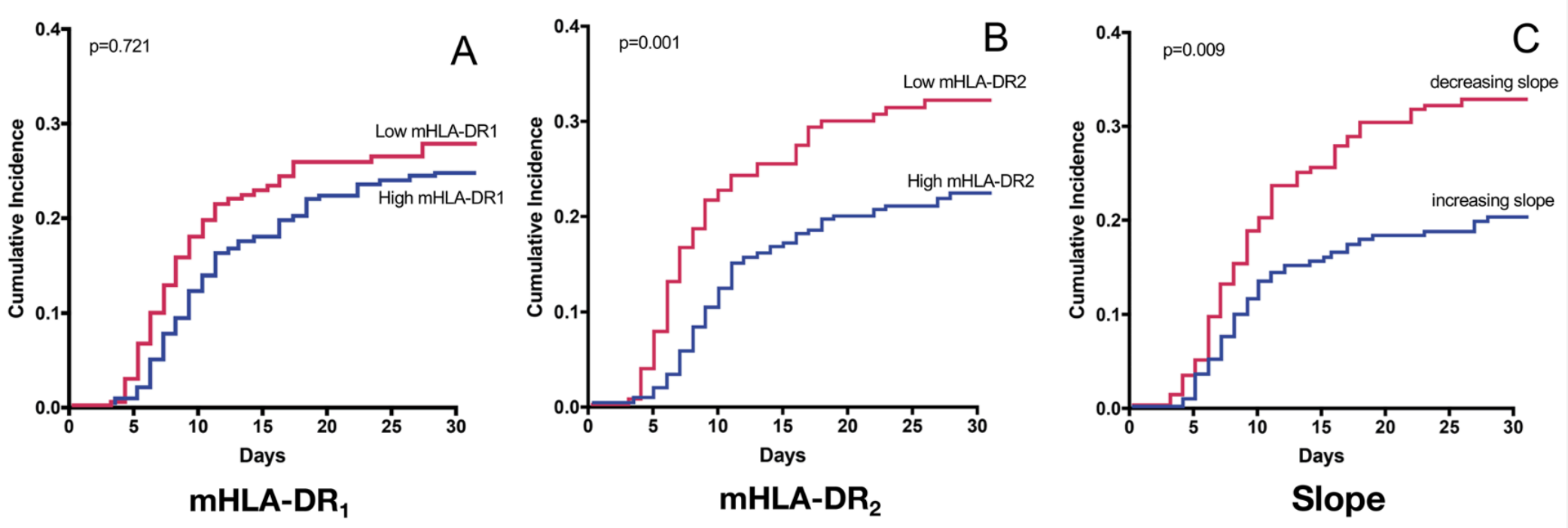
HLA-DR

- Opazovalna, monocentrična
- N=592
- HLA-DR v prvih 3 dneh + dan 5-10
- Primarni izhod: okužbe pridobljene v EIT



Ann Intensive Care. 2022 May 8;12(1):39.

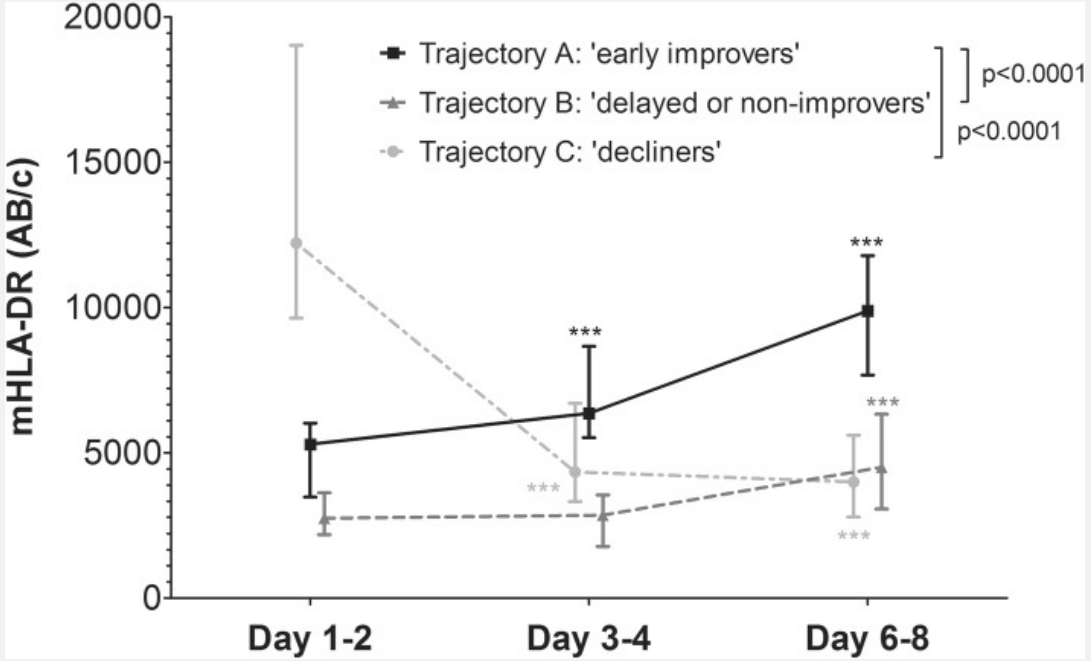
HLA-DR



Ann Intensive Care. 2022 May 8;12(1):39

HLA-DR

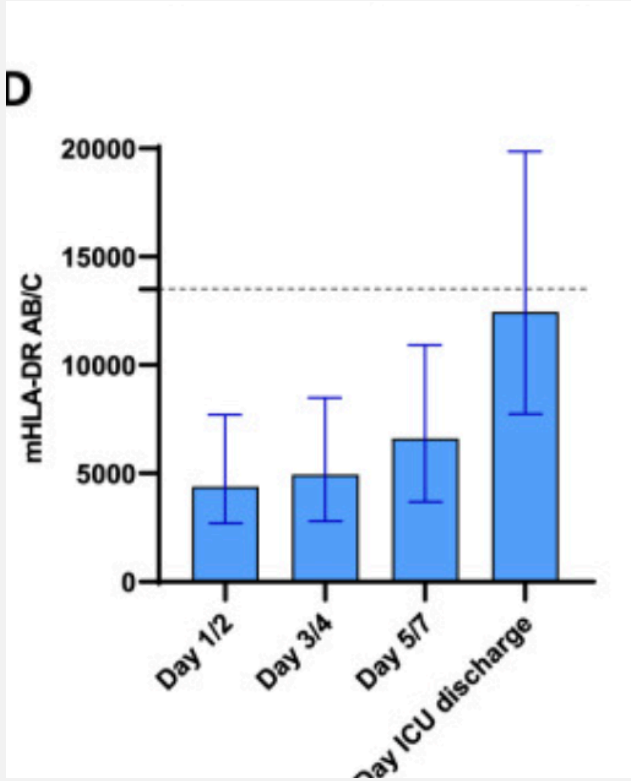
- Opazovalna, monocentrična
- N=241, septični šok
- Kinetika ekspresije receptorjev mHLA-DR
- Primarni izhod: sekundarne okužbe + smrt



Crit Care. 2020 Mar 20;24(1):110

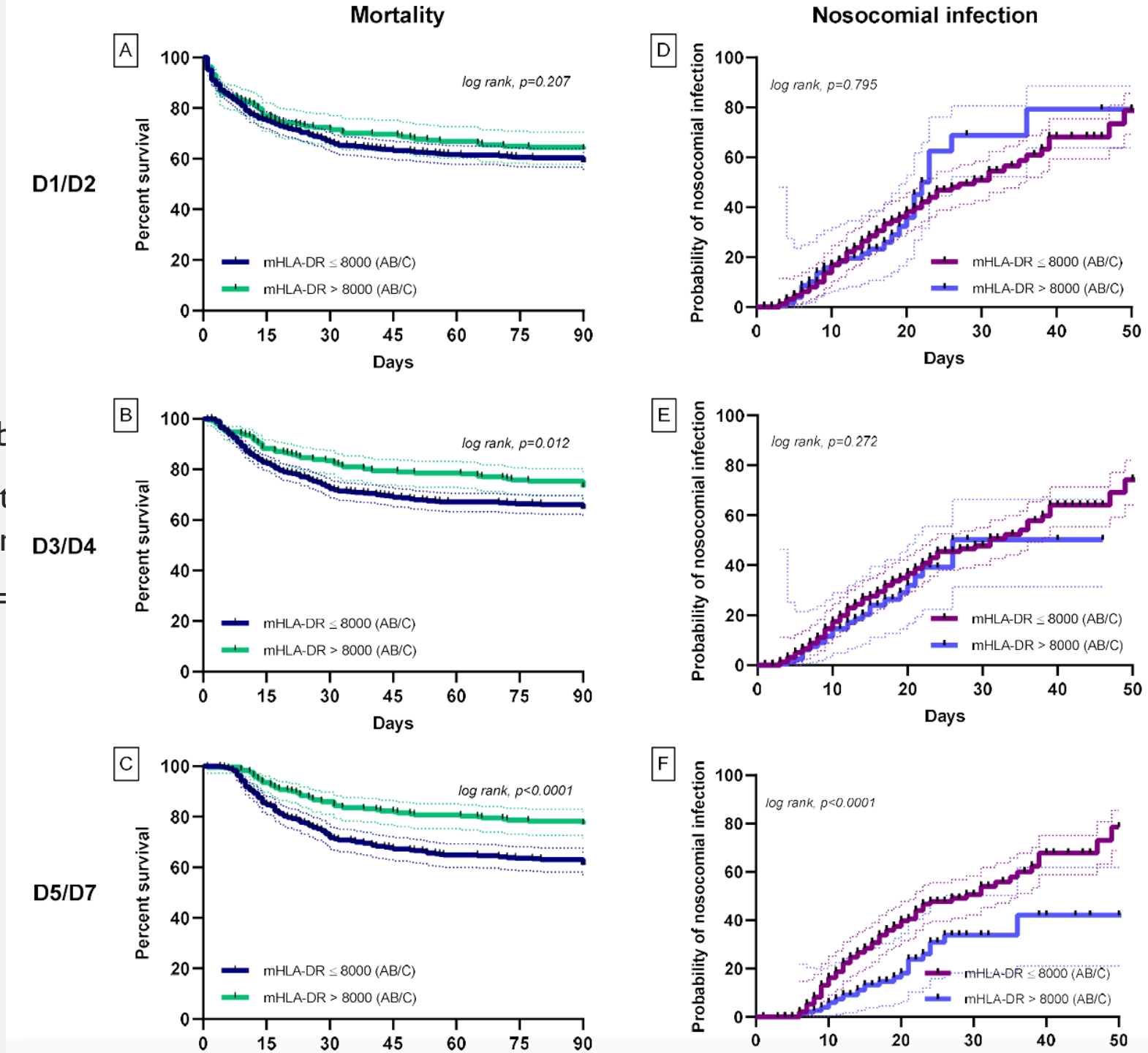
HLA-DR

- Opazovalna, monocentrična, 2005-2024
- Bolniki z diagnozo septičnega šoka ob sprejemu v EIT ali med zdravljenjem v EIT
- N=1023



Intensive Care Med. 2025 Oct;51(10):1820-1832

- Ob
- Pat
  adr
- N=



5 Oct;51(10):1820-1832

DIAGNOZA

Bolniki z visokim tveganjem?

- imunosupresija pred sprejemom
- maligna bolezen
- starejši (>65 let)
- podhranjenost
- sekundarne okužbe

Prepoznava?

- HLA-DR
- abs število limfocitov
- IgA, IgM, IgG vrednosti

Časovnica?

- v prvih 48h, nato spremljanje
- med imunoterapijo

Mil Med Res. 2022 Dec 26;9(1):74

DIAGNOZA

- HLA-DR
  - indikator sposobnosti monocitov za predstavitev antigenov (prirojena imunost)
  - **mHLA-DR** <15.000 AB/C **(<8.000 AB/C)**
- Limfopenija
  - pridobljena imunost
  - **<1.0×10⁹/L**
- Citokini (IL-10)
- Nivo TNFa v monicitih po stimulaciji z LPS
- PD-1, PD-L1

ZDRAVLJENJE?



ZDRAVLJENJE

- INTERFERON-GAMA
- GM-CSF
- IMUNOGLOBULINI (IgM, IgG, IgA)
- TIMOZIN ALFA-1

…

JAMA®

QUESTION Does immunotherapy tailored to the type of immune dysregulation improve outcomes among patients with sepsis?

CONCLUSION Precision immunotherapy targeting macrophage activation-like syndrome and sepsis-induced immunoparalysis improved organ dysfunction.

© AMA

POPULATION



183 Men 93 Women

Adults with sepsis secondary to pneumonia or primary bacteremia

Mean age: 70 years

LOCATIONS



33
Intensive care units in 6 countries

INTERVENTION



Precision immunotherapy
IV anakinra + subcutaneous placebo for patients with macrophage activation-like syndrome, or subcutaneous human recombinant interferon gamma + IV placebo for patients with sepsis-induced immunoparalysis

Control
Placebo administered subcutaneously or intraveneously

PRIMARY OUTCOME

Achievement of at least a 1.4-point decrease in the mean Sequential Organ Failure Assessment (SOFA) score from baseline by day 9

FINDINGS

1.4-point decrease in mean SOFA score

Precision immunotherapy
46 of 131 patients

Control
26 of 145 patients



Precision immunotherapy improved organ dysfunction at day 9:

Difference, **17.2%**

(95% CI, 6.8% to 27.2%; *P* = .002)

Giamarellos-Bourboulis EJ, Kotsaki A, Kotsamidi I, et al; ImmunoSep Study Group. Precision immunotherapy to improve sepsis outcomes: the ImmunoSep randomized clinical trial. *JAMA*. Published online December 8, 2025. doi:10.1001/jama.2025.24175

Giamarellos-Bourboulis. JAMA 2025.

PRIKAZ PRIMERA

- 64 let, kadilec
- hidradenitis, sicer zdrav, aktiven

- 11/2025 subakutni STEMI sprednje stene
- okluzija LAD in PPCI
- LVEF 30 %, kardiogeni šok
- D4: električni vihar, intubacija. Blokada stelatnih ganglijev, antiaritmiki
- D6: Dresslerjev sindrom

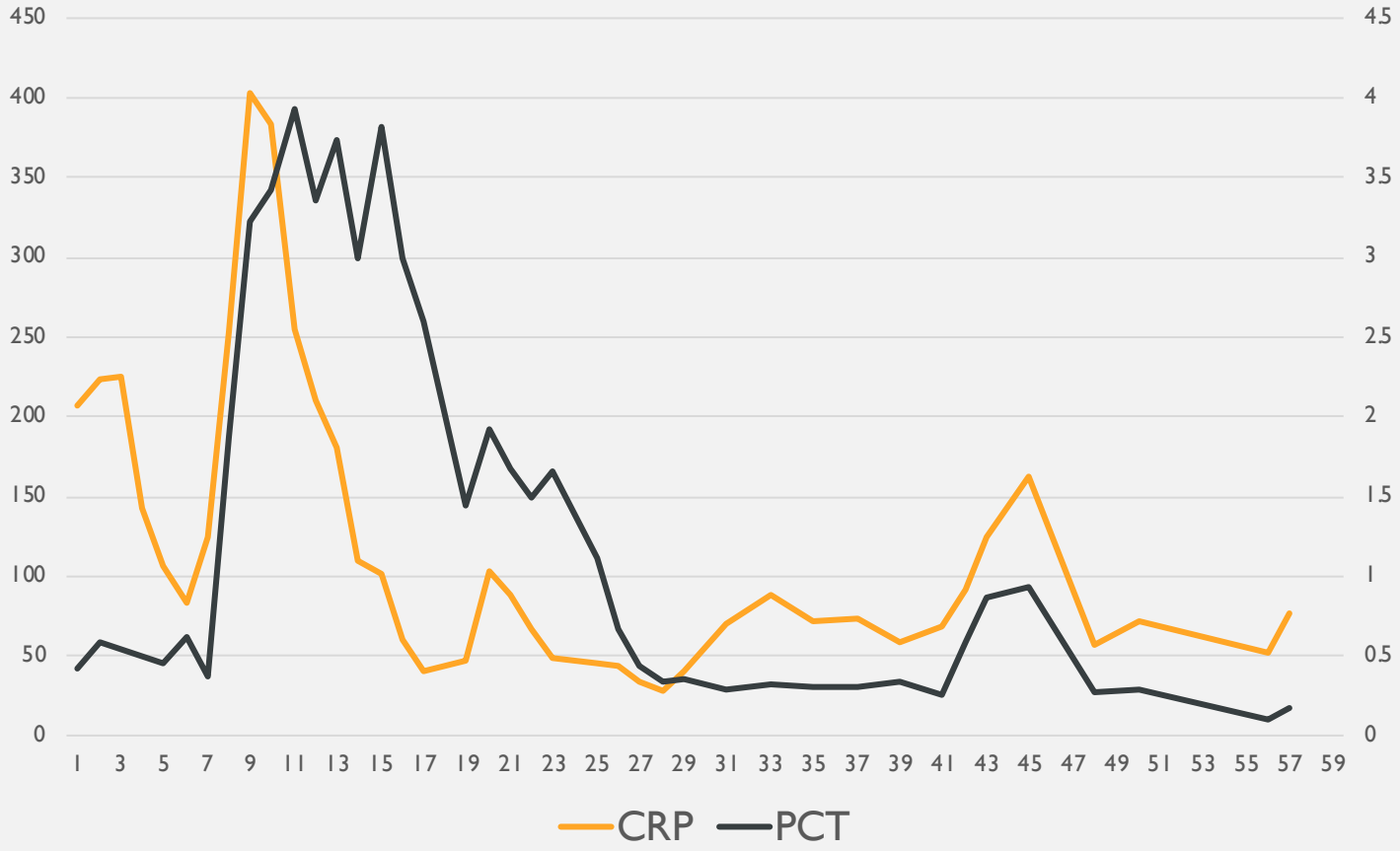
OKUŽBE

- D5: SIRS/sepsa
- D10: K. pneumoniae in C. glabrata traheobronhitis
- D18: K. pneumoniae traheobronhitis
- D22: hud potek CMV kolitisa
- D35: K. pneumoniae in Rothia nasimurium sepsa
- D60: K. pneumoniae sepsa, P. aeruginosa traheobronhitis
- D75: K. pneumoniae sepsa, 2 manjša abscesa jeter
- D93: P. aeruginosa VAP
- D110: C. difficile kolitis

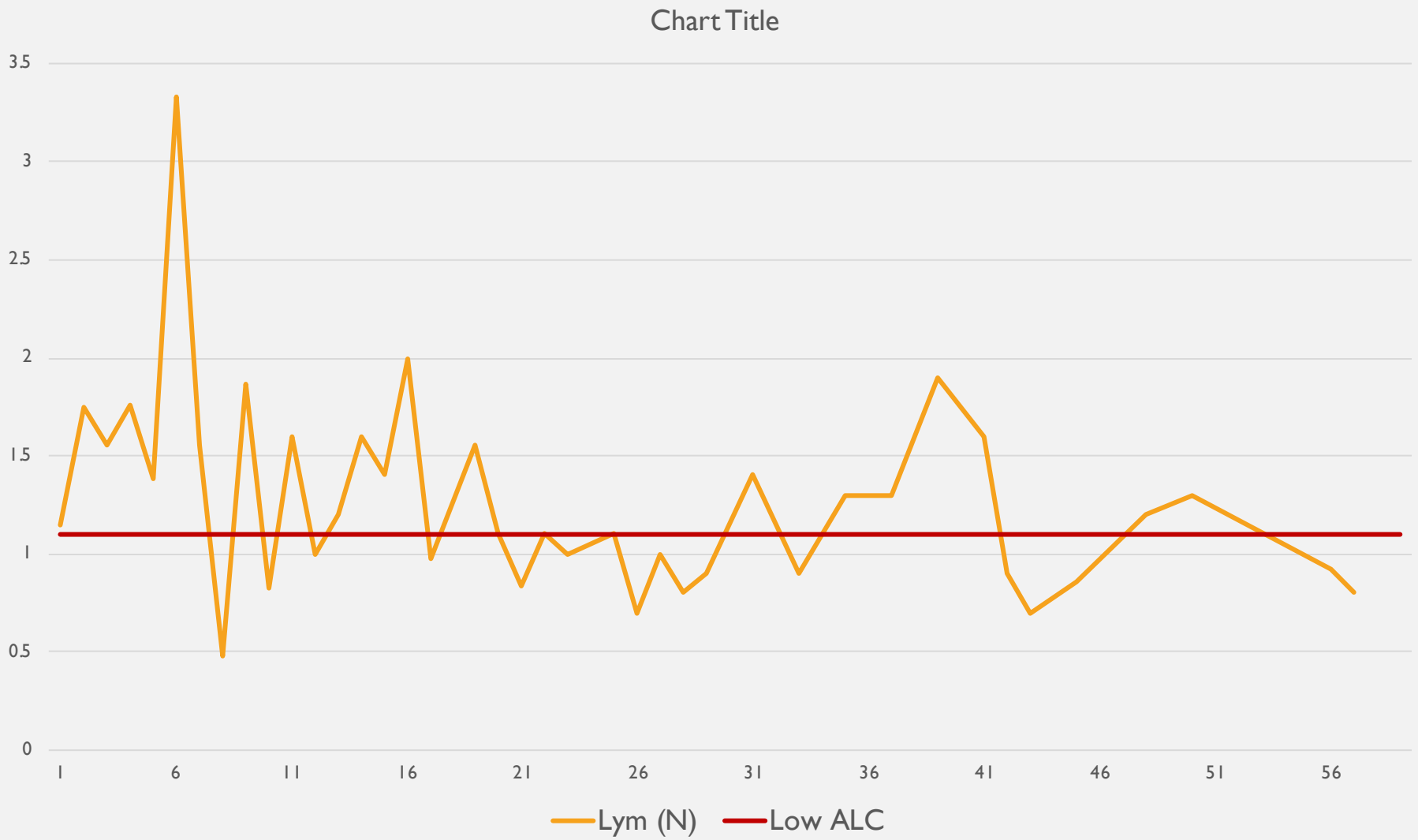
DRUGI ZAPLETI

- F1b ulkus želodca
- Dekubitus sakralno, slabo celjenje
- Dehiscenca rane po traheostomi
- Huda sarkopenija
- Guillain-Barre sindrom
- Sladkorna bolezen

Dan 181 –
odpust iz EIT

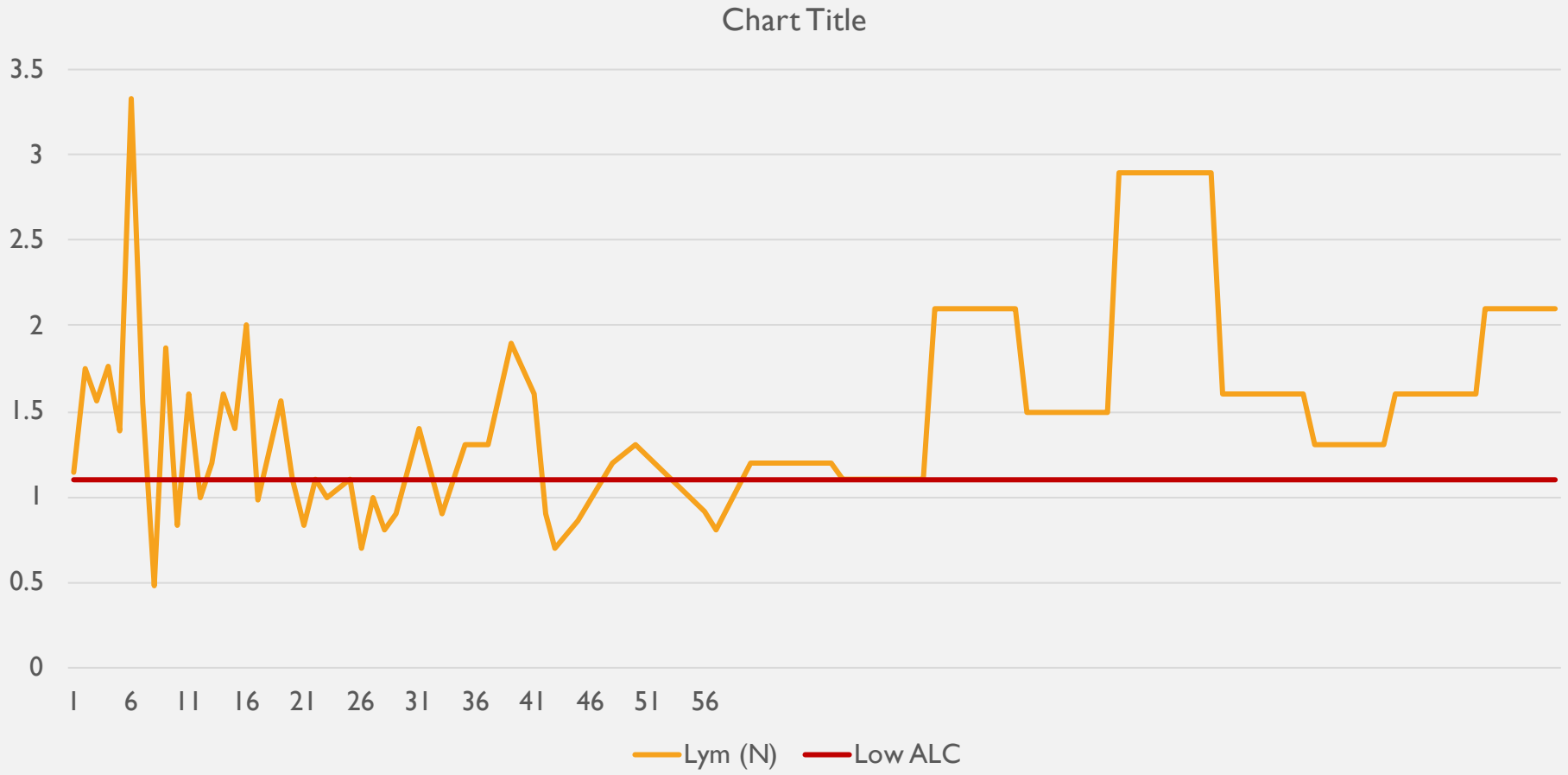


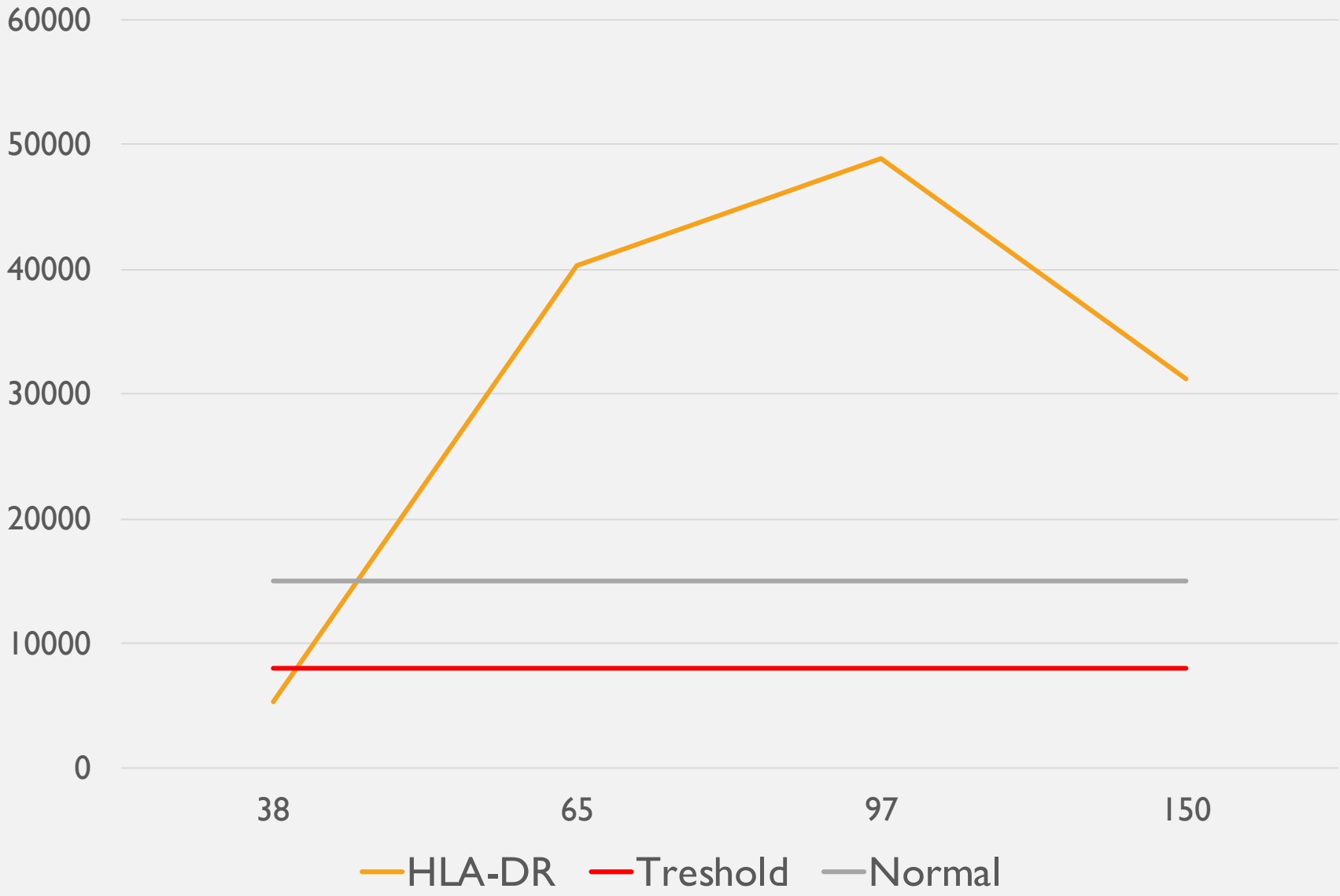
Nizek ferritin,
nizek IL-6



48 % nizke vrednosti

lg v mejah normale


Chart Title
3.5
3
2.5
2
1.5
1
0.5
0
1
6
11
16
21
26
31
36
41
46
51
56
Lym (N)
Low ALC


60000
50000
40000
30000
20000
10000
0
38
65
97
150
HLA-DR
Treshold
Normal

POVZETEK

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