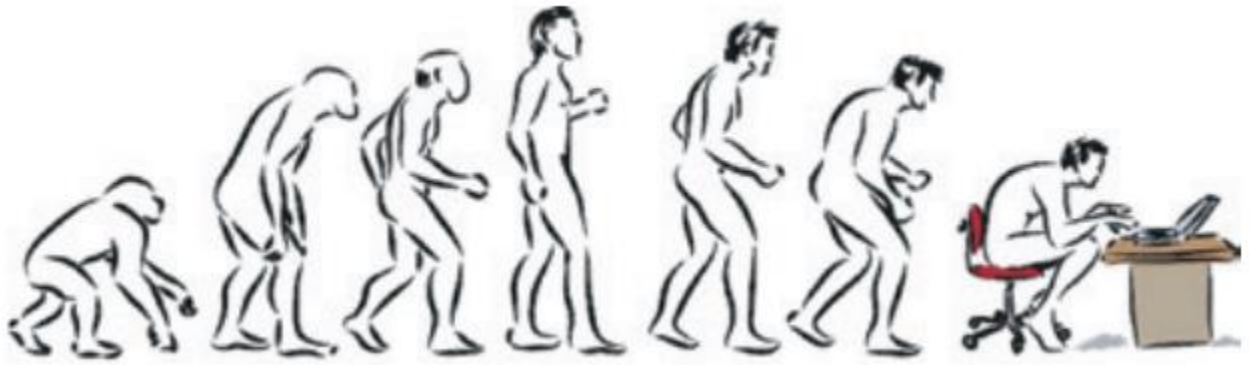


Biomarkerji in sepsa – je kaj novega?

Matej Mavrič, dr. med.

Klinika za infekcijske bolezni in vročinska stanja

Enota intenzivne terapije

Prepoznava sepse samo na podlagi klinične slike je težavna.

Ključna je čim prejšnja diagnoza in uvedba ustrezne antibiotične terapije.

Biomarkers of sepsis: time for a reappraisal

Charalampos Pierrakos[1], Dimitrios Velissaris[2], Max Bisdorff[3], John C. Marshall[4] and Jean-Louis Vincent[3*]

Table 1 Sepsis biomarkers, except for C-reactive protein (CRP) and procalcitonin (PCT), that have been evaluated for their diagnostic value in clinical studies with more than 300 subjects

Biomarker [ref]	No. of patients	Sepsis definition	Study population	Reference group	Sensitivity/ specificity (%)	AUC
Interleukin (IL)-27 [10]	702	Positive blood cultures	Pediatric ICU patients with infection	Non-infected critical care patients	84/63	0.75
Inter-alpha inhibitor proteins [11]	573	Positive blood cultures	Neonates with sepsis	Neonates with risk factors for sepsis	89/99	0.9
Group II phospholipase A2 [12]	525	ACCP 1992	ED patients with sepsis	ED patients with suspected infection (with and without SIRS)	NR (logistic regression analysis)	NR
Bactericidal/ permeability increasing protein [12]	525	ACCP 1992	ED with sepsis	ED patients with suspected infection (with and without SIRS)	NR (logistic regression analysis)	NR
CD64 [13]	468	International Sepsis Definitions Conference 2001	Non-selected ICU population with sepsis	ICU patients admitted without sepsis	89/87	0.94
Selenoprotein P [14]	378	ACCP 1992	Non-selected population with sepsis or septic shock	Healthy individuals	NR (no test)	NR
Lipopolysaccharide-binding protein [15]	327	ACCP 1992	Surgical patients without sepsis at admission	Surgical patients with SIRS without sepsis	60/62	0.66
Syndecan-1 [16]	512	International Sepsis Definitions Conference 2001	Trauma patients (4 h after admission) without sepsis	Trauma patients without sepsis	NR (logistic regression analysis)	NR
Presepsin [17]	440	Sepsis-3	ICU patients with sepsis	ICU patients without sepsis	89/59	0.76
IL-6 [18]	306	SIRS and organ dysfunction, systolic blood pressure < 90 mmHg, or lactate ≥ 4 mmol/L plus infection	ED patients with suspected sepsis	ED patients with SIRS and organ dysfunction, systolic blood pressure < 90 mmHg, or lactate ≥ 4 mmol/L without infection	NR	0.86

8737 objav, 258 različnih biomarkerjev
-> večina preučevanih v manj kot 5 različnih študijah (31% vseh le v eni študiji)
-> poleg CRP in PCT le 26 biomarkerjev, ki so bili preučevani v raziskavah z več kot 300 bolniki

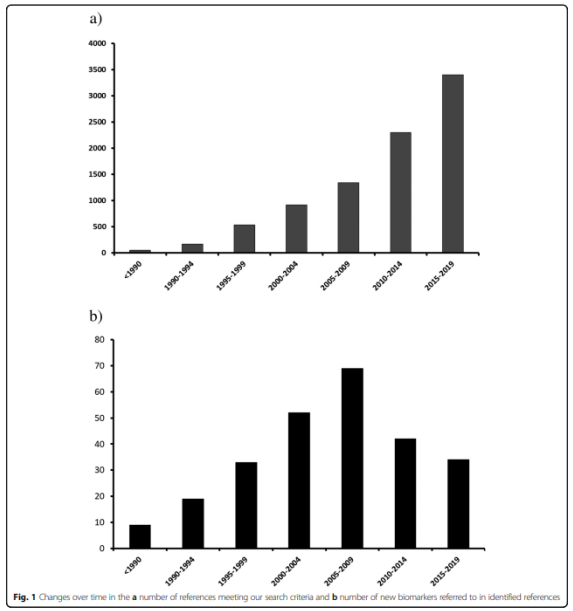


Fig. 1 Changes over time in the **a** number of references meeting our search criteria and **b** number of new biomarkers referred to in identified references

Zaključek: večina novih biomarkerjev ni bila obširno preučevana, **<u>njihova klinična vrednost je vprašljiva</u>**

Pierrakos C et al. Critical Care. 2020

Circulating biomarkers may be unable to detect infection at the early phase of sepsis in ICU patients: the CAPTAIN prospective multicenter cohort study

Marianna Parlato[1], François Philippart[2,3], Alexandra Rouquette[4,5], Virginie Moucadel[6], Virginie Puchois[1], Sophie Blein[6], Jean-Pierre Bedos[7], Jean-Luc Diehl[8,9], Olfa Hamzaoui[10], Djillali Annane[11,12], Didier Journois[5,13], Myriam Ben Boutieb[4], Laurent Estève[6], Catherine Fitting[1], Jean-Marc Treluyer[5,14], Alexandre Pachot[6], Minou Adib-Conquy[1], Jean-Marc Cavaillon[1], Benoît Misset[2,15,16*] and The Captain Study Group

Prospektivna, opazovalna, multicentrična raziskava, 279 bolnikov v EIT, ki so izpolnjevali SIRS kriterije
-> 188 bolnikov s sepso vs. 91 s SIRS brez okužbe
-> 8 biomarkerjev doseglo ROC-AUC nad 0,6

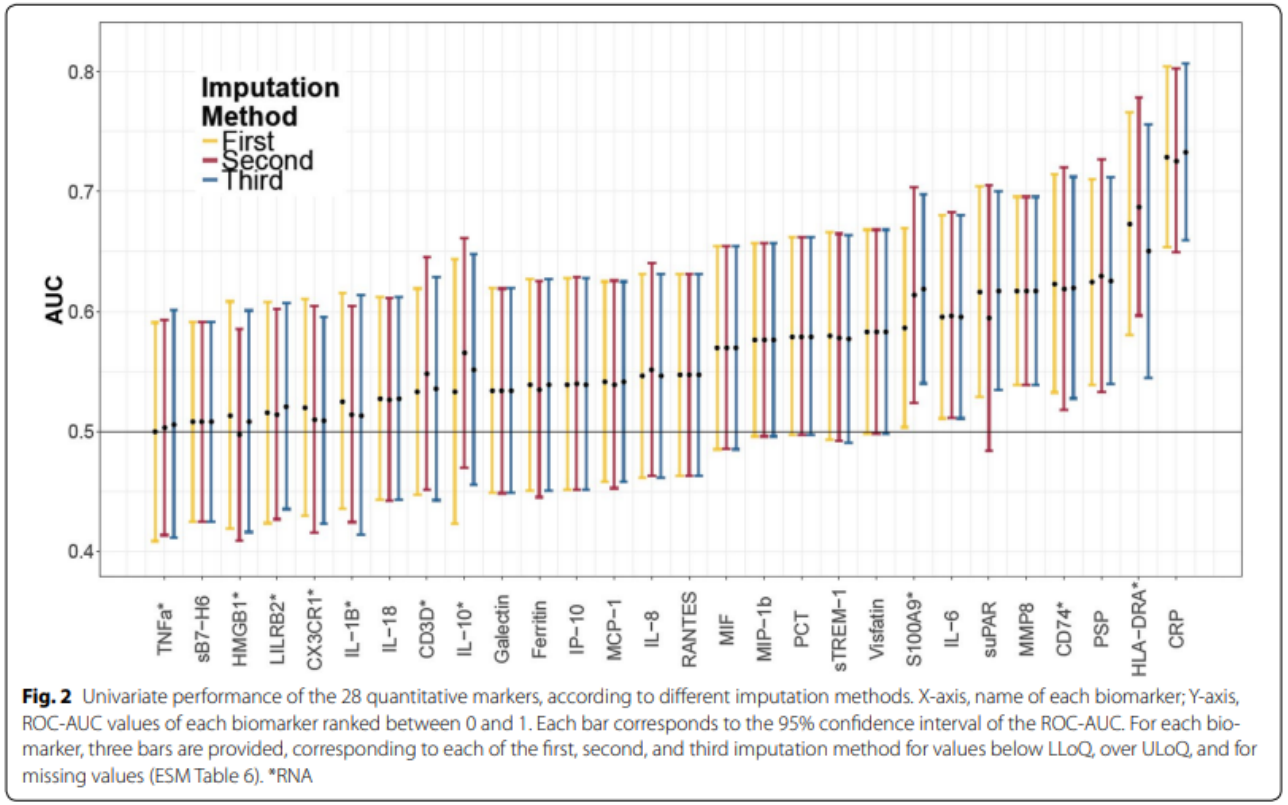


Fig. 2 Univariate performance of the 28 quantitative markers, according to different imputation methods. X-axis, name of each biomarker; Y-axis, ROC-AUC values of each biomarker ranked between 0 and 1. Each bar corresponds to the 95% confidence interval of the ROC-AUC. For each biomarker, three bars are provided, corresponding to each of the first, second, and third imputation method for values below LLoQ, over ULoQ, and for missing values (ESM Table 6). *RNA

Zaključek: cirkulirajoči biomarkerji imajo **slabo napovedno vrednost** za ločevanje sepse od SIRS brez okužbe

Parlato M et al. Intensive Care Med. 2018

Biomarkers in sepsis-looking for the Holy Grail or chasing a mirage!

Neelmani Ahuja, Anjali Mishra, Ruchi Gupta, Sumit Ray

Cong *et al* [20], 2021	Meta-Analysis	Adult 20 studies	CD 64	0.94 (0.91-0.96)	Sens: 0.88 (0.81-0.92); Spec: 0.88 (0.83-0.91); LR+: 7.2; LR-: 0.14; DOR-51 (25-101)	Neutrophil CD64 test has a high sensitivity and specificity in adult sepsis patients, and was superior to the traditional biomarkers PCT and IL6
			PCT	0.87 (0.83-0.89)	Sens: 0.82 (0.78-0.85); Spec-: 0.78 (0.74-0.82); LR+: 3.7; LR-: 0.23; DOR-16 (11-23)	
			IL6	0.77 (0.73-0.80)	Sens: 0.72 (0.65-0.78); Spec: 0.70 (0.62-0.76); LR+: 2.4; LR-: 0.40; DOR-6 (4-9)	
Yeh *et al* [19], 2019	Metaanalysis. 14 studies	Adult, pooled data: Total: 2471; Control: 1167; Sepsis: 1304	Neutrophilic CD 64	0.89 (0.87–0.92)	Sens: 0.87 (0.80-0.92); spec 0.89 (0.82-0.93)	Neutrophil CD64 levels are an excellent biomarker with moderate accuracy outperforming both CRP and PCT determinations
			PCT	0.84 (0.79–0.89)	Sens: 0.76 (0.61-0.86); spec 0.79 (0.70-0.86)	
			CRP	0.84 (0.80–0.88)	Sens: 0.83 (0.78-0.86); spec 0.71 (0.56-0.85)	
Kondo *et al*[14], 2019	Meta-Analysis; 19 studies	Adult. Tot: 3012	Presepsin	0.87	Sens: 0.84 (95% 0.80-0.88); Spec: 0.73 (0.61-0.82)	Diagnostic accuracy of procalcitonin and presepsin in detecting infection was similar
			PCT	0.84	Sens: 0.80 (0.75-0.84); spec 0.75 (0.67-0.81)	
Lai *et al* [7], 2020	Meta-Analysis; 25 studies	GNBSI	CRP	0.85 (0.81–0.87)	Sens: 0.75 (0.56–0.87); Spec: 0.80 (0.68–0.88)	PCT was helpful in recognizing GNBSI, but the test results should be interpreted carefully with knowledge of patients' medical condition and should not serve as the only criterion for GNBSI
			PCT	0.87 (0.84–0.90)	Sens: 0.80 (0.60–0.91); Spec: 0.82 (0.72–0.89)	
			IL6	0.83 (0.80-0.86)	Sens: 0.76 (0.58–0.88); Spec: 0.79 (0.71-0.85)	

Ahuja N et al. World J Crit Care Med. 2023

Nadaljevanje…

Table 3 Biomarkers for diagnosis of sepsis-current understanding in diagnosis of sepsis

Biomarker	Diagnosis of sepsis	Differentiating sepsis and SIRS	Guiding antibiotic initiation	Organism identification
Procalcitonin	Better than CRP; cannot be used independently; diagnosis based on clinical context	Better than CRP; cannot be used independently; diagnosis based on clinical context	Delays antibiotic administration; No short term mortality benefit	Higher in Gram negative bacteremia than Gram positive. Higher in bacteremia than in candidemia. No defined cutoffs. Treatment to be based on clinical judgement
Presepsin	Possible role	Possible role	No significant data	No significant data
nCD64	Possible role; when combined with CRP, higher diagnostic accuracy and high negative predictive value	No significant data	No significant data	Increased in bacterial and viral infection more than fungal
suPAR	Possible role	Performed poorly	No significant data	No significant data
IL6	Inferior to PCT, CRP	Inferior to PCT, CRP	No significant data	No significant data

Ali nam biomarkerji lahko pomagajo pri vodenju antibiotične terapije?

Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: a patient-level meta-analysis of randomized trials

Yannick Wirz[1†], Marc A. Meier[1†], Lila Bouadma[3], Charles E. Luyt[4], Michel Wolff[3], Jean Chastre[4], Florenc Stefan Schroeder[6], Vandack Nobre[7], Djillali Annane[8], Konrad Reinhart[9], Pierre Damas[10], Maarten Nijste Arezoo Shajiei[11], Dylan W. deLange[12], Rodrigo O. Deliberato[13], Carolina F. Oliveira[14], Yahya Shehabi[15] Jos A. H. van Oers[17], Albertus Beishuizen[18], Armand R. J. Girbes[19], Evelien de Jong[19], Beat Mueller[1,2] and Philipp Schuetz[1,2*]

Wirz et al. Critical Care. 2018

Procalcitonin-guided antibiotic therapy in intensive care unit patients: a systematic review and meta-analysis

Hui-Bin Huang[1,2], Jin-Min Peng[1], Li Weng[1], Chun-Yao Wang[1], Wei Jiang[1] and Bin Du[1*]

Huang et al. Ann. Intensive Care. 2017

Procalcitonin-guided antibiotic therapy may shorten length of treatment and may improve survival—a systematic review and meta-analysis

Márton Papp[1,2], Nikolett Kiss[1,3,4], Máté Baka[1], Domonkos Trásy[1], László Zubek[1,4], Péter Fehérvári[1,6], Andrea Harnos[1,6], Caner Turan[1,4], Péter Hegyi[1,7,8] and Zsolt Molnár[1,4,5*]

Papp M et al. Critical Care. 2023

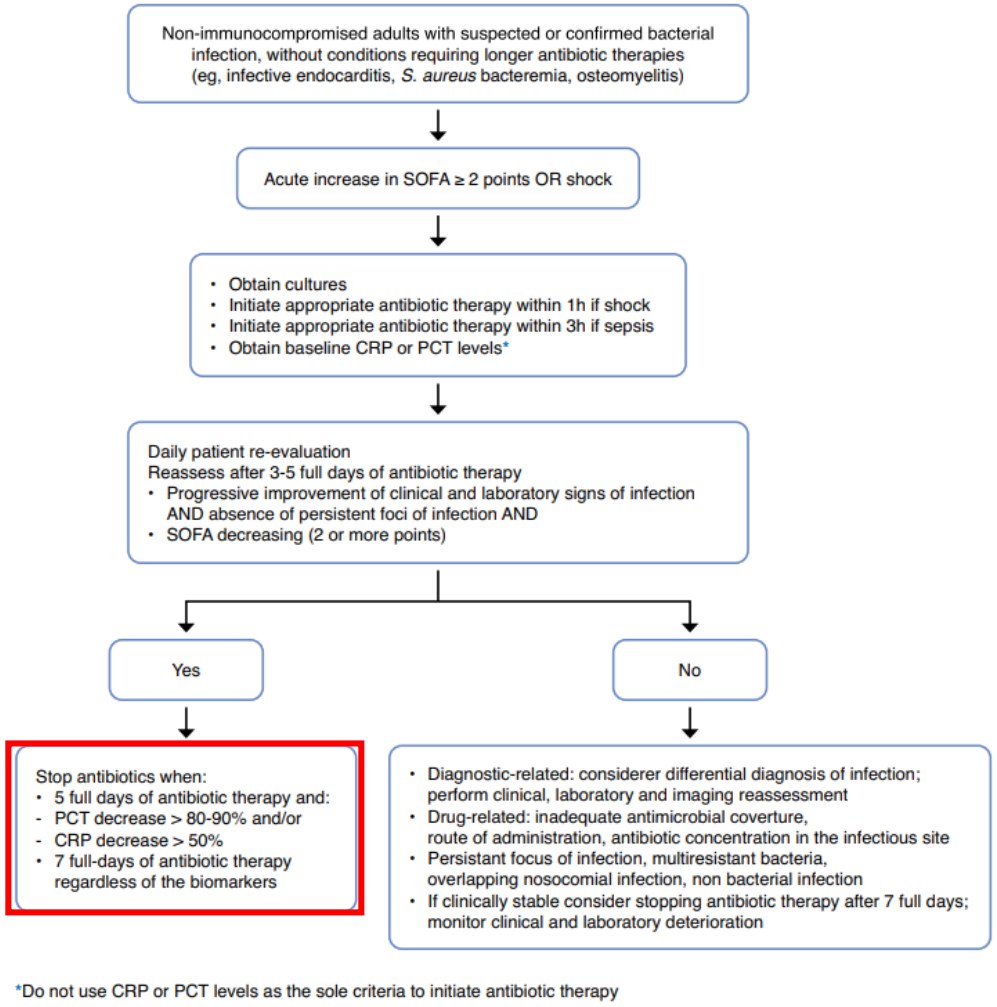
nižja smrtnost,
manjša izpostavljenost antibiotikom

Omejitve:
- Heterogenost v protokolih
- SOC ni standardizirana
- Večinoma izključeni bolniki z imunsko oslabelostjo
- (Pre)majhne populacije bolnikov
- Ne-kompliantnost zdravnikov

hand and, on the other hand, a possible impact on outcomes cannot be excluded according to the 15 studies reporting PCT protocol adherence, which ranged between 44 and 97%. Furthermore, AB appropriateness

but not all RCTs, showed significant variability, ranging from 0 to 59%. In most case of non-compliance, physicians were reluctant to stop antibiotics, even with a very low PCT level (Additional file 4: Table S4), possibly due

Kritika zgodnjih raziskav –> „predolgo“ zdravljenje v SOC skupini, morda sprememba pristopa, t. i. „**double trigger strategy**“ – antibiotik ukinemo po ustreznem upadu CRP/PCT ali po zaključenih 5-7 dneh zdravljenja



Póvoa P et al. Intensive Care Med. 2023

Kaj pa smernice?

Biomarkers to Start Antibiotics

Recommendation
16. For adults with suspected sepsis or septic shock, we **suggest against** using procalcitonin plus clinical evaluation to decide when to start antimicrobials, as compared to clinical evaluation alone. *Weak recommendation, very low quality of evidence.*

Biomarkers to Discontinue Antibiotics

Recommendation
31. For adults with an initial diagnosis of sepsis or septic shock and adequate source control where optimal duration of therapy is unclear, we **suggest** using procalcitonin AND clinical evaluation to decide when to discontinue antimicrobials over clinical evaluation alone. *Weak recommendation, low quality of evidence.*

SSG 2021

Kaj pa kakšen bolj dostopen, enostaven in cenovno ugoden biomarker?

Review

The Value of a Complete Blood Count (CBC) for Sepsis Diagnosis and Prognosis

Luisa Agnello [1], Rosaria Vincenza Giglio [1], Giulia Bivona [1], Concetta Scazzone [1], Caterina Maria Gambino [1,2], Alessandro Iacona [2], Anna Maria Ciaccio [3], Bruna Lo Sasso [1,2] and Marcello Ciaccio [1,2,*]

Table 1. Clinical usefulness of CBC parameters for sepsis.

	Parameter	Alteration	Clinical Usefulness
Basic	WBC	↑	Diagnosis
	Neutrophils	↑	Prognosis
	Lymphocytes	↓	Prognosis
	Monocytes	↑↓	Controversial
	Eosinophil	↓	Diagnosis
	Basophil	↓	Prognosis
	RBC	↓	None
	Hemoglobin	↓	Guide RBC transfusion
	Hematocrit	↓	Target for RBC transfusion
	MCV	-	-
	MCH	-	-
	MCHC	-	-
	RDW	↑	Prognosis
	Platelets	↓	Diagnosis and prognosis
CPD	MDW	↑	Diagnosis
	MNV	↑	Diagnosis
	MMV	↑	Diagnosis
	NE-SFL	↑	Diagnosis and prognosis
	MO-X	↑	Diagnosis and prognosis
	IPF	↑	Diagnosis and prognosis
	DNI	↑	Prognosis and monitoring therapy

WBC, white blood cells; RBC, red blood cells; MCV, mean cell volume; MCH, mean corpuscular hemoglobin, MCHC, mean cell hemoglobin concentration, RDW, red distribution width; MDW, monocyte distribution width; MNV, mean neutrophil volume; MMV, mean monocyte volume; NE-SFL, neutrophil fluorescence intensity; MO-X, monocyte internal structure; IPF, immature platelet function; DNI, delta neutrophil index.

Agnello et al. Diagnostics (Basel). 2023

Luisa Agnello, Matteo Vidali, Bruna Lo Sasso, Rosaria Vincenza Giglio, Caterina Maria Gambino, Concetta Scazzone, Anna Maria Ciaccio, Giulia Bivona and Marcello Ciaccio*

Monocyte distribution width (MDW) as a screening tool for early detecting sepsis: a systematic review and meta-analysis

Table 1: Characteristics of the studies included in the meta-analysis.

Study	Study design	Clinical setting	Sepsis criteria	Study population		Anticoag	MDW cut-off value	AUC
				Total	Sepsis			
Crouser et al., 2017 [18]	Prospective	ED	Sepsis-2	1,320	98	K_2	20.5	0.790
Guo et al., 2019 [19]	Retrospective	ICU	Sepsis-3	249	54	NA	19.2	0.767
Polilli et al., 2020 [20]	Prospective	Inf. Dis. Unit	Sepsis-3	260	105	K_3	21.9	0.870
Agnello et al., 2021 [21]	Retrospective	ED	Sepsis-2	2,215	88	K_3	23.5	0.964
Agnello et al., 2021 [22]	Retrospective	ICU	Sepsis-3	82	23	K_3	23.9	0.937
Hausfater et al., 2021 [15]	Prospective	ED	Sepsis-2	1,517	260	K_3	21.5	0.810
Hausfater et al., 2021 [15]	Prospective	ED	Sepsis-3	1,517	144	K_3	21.5	0.820
Hou et al., 2021 [23]	Retrospective	ED	Sepsis-2	1,480	296	NA	22.1	0.625
Piva et al. 2021 [24]	Prospective	ICU	Sepsis-3	506	112	K_2	24.6	0.785
Woo et al., 2021 [25]	Prospective	ED	Sepsis-3	549	188	K_2	19.8	0.710

Agnello et al. Clin Chem Lab Med. 2022

Monocyte distribution width (MDW) performance as an early sepsis indicator in the emergency department: comparison with CRP and procalcitonin in a multicenter international European prospective study

Pierre Hausfater[1,2,3*], Neus Robert Boter[4,5], Cristian Morales Indiano[5,7], Marta Cancella de Abreu[1,2], Adria Mendoza Marin[4,5], Julie Pernet[1], Dolores Quesada[5,8], Iris Castro[9], Diana Careaga[9], Michel Arock[6], Liliana Tejidor[9] and Laetitia Velly[1,2]

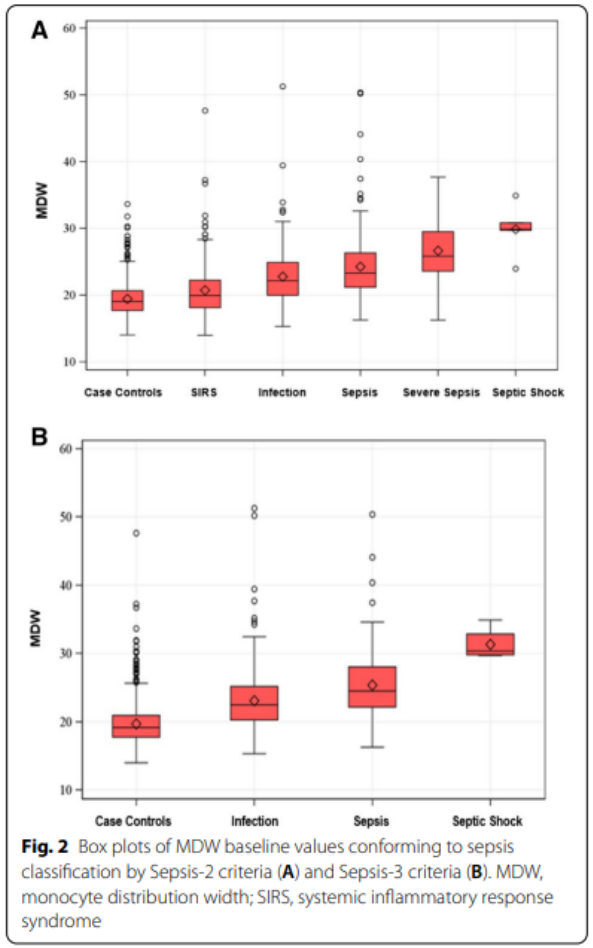


Fig. 2 Box plots of MDW baseline values conforming to sepsis classification by Sepsis-2 criteria (**A**) and Sepsis-3 criteria (**B**). MDW, monocyte distribution width; SIRS, systemic inflammatory response syndrome

Hausfater et al. Crit Care. 2021

Prospektivna multicentrična raziskava v urgentnih ambulantah 1517 bolnikov, razvrščeni glede na Sepsis-2 ali Sepsis-3 kriterije
AUROC za diagnozo sepse (Sepsis-2) pri MDW 0.81; pri MDW + WBC 0,86
AUROC za diagnozo sepse (Sepsis-3) pri MDW 0.82
AUROC CRP 0,85, PCT 0,78

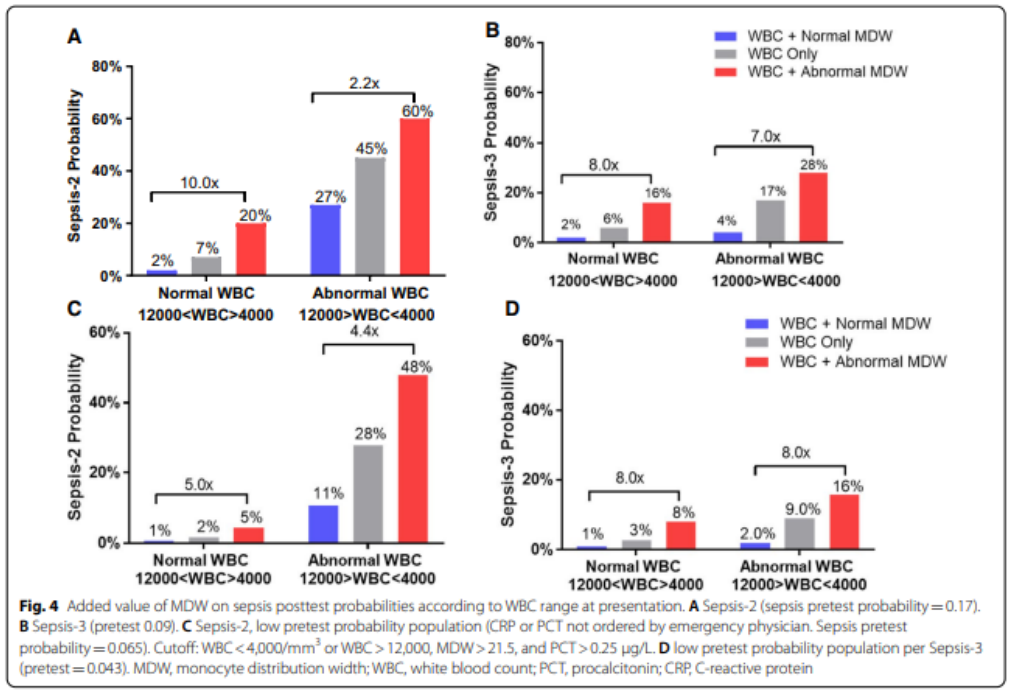


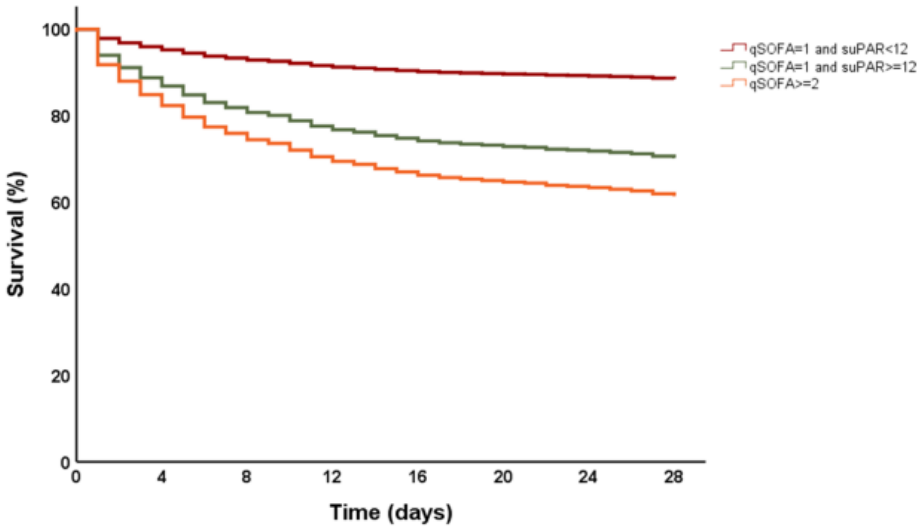
Fig. 4 Added value of MDW on sepsis posttest probabilities according to WBC range at presentation. **A** Sepsis-2 (sepsis pretest probability = 0.17). **B** Sepsis-3 (pretest 0.09). **C** Sepsis-2, low pretest probability population (CRP or PCT not ordered by emergency physician. Sepsis pretest probability = 0.065). Cutoff: WBC < 4,000/mm^3 or WBC > 12,000, MDW > 21.5, and PCT > 0.25 µg/L. **D** low pretest probability population per Sepsis-3 (pretest = 0.043). MDW, monocyte distribution width; WBC, white blood count; PCT, procalcitonin; CRP, C-reactive protein

Zaključek: MDW v kombinaciji z WBC ima diagnostično vrednosti pri dokazovanju sepse, predvsem pri nizki pred-testni verjetnosti; **MDW bi lahko uporabili v kombinaciji s qSOFA točkovnikom za namen izboljšanja zgodnje diagnoze sepse**

Gremo še korak naprej…

qSOFA combined with suPAR for early risk detection and guidance of antibiotic treatment in the emergency department: a randomized controlled trial

Maria Evangelia Adami[1], Antigone Kotsaki[1], Nikolaos Antonakos[1], Efthymia Giannitsioti[1], Stamatios Chalvatzis[1], Maria Saridaki[1], Christina Avgoustou[1], Karolina Akinosoglou[2], Konstantina Dakou[3], Georgia Damoraki[1], Konstantina Katrini[1], Panagiotis Koufargyris[1], Vasileios Lekakis[1], Antonia Panagaki[1], Asimina Safarika[1], Jesper Eugen-Olsen[4] and Evangelos J. Giamarellos-Bourboulis[1,3*]



večje tveganje za smrt ob qSOFA≥1 in suPAR>12

Ali zgodnja antibiotična terapija pri bolnikih s qSOFA=1 in suPAR>12 ng/ml vpliva na klinični potek okužbe?

-> randomizacija bolnikov, ki so prišli v UA (meropenem vs. placebo)

-> primarni izid: zgodnje poslabšanje = porast SOFA za vsaj 1 točko v 24 urah

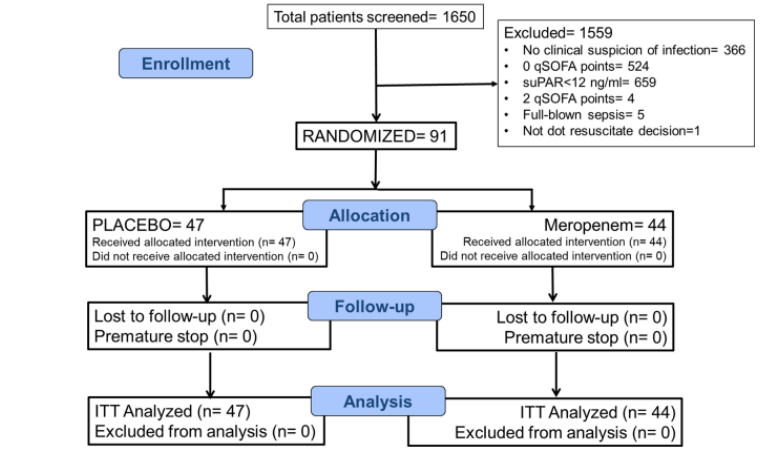
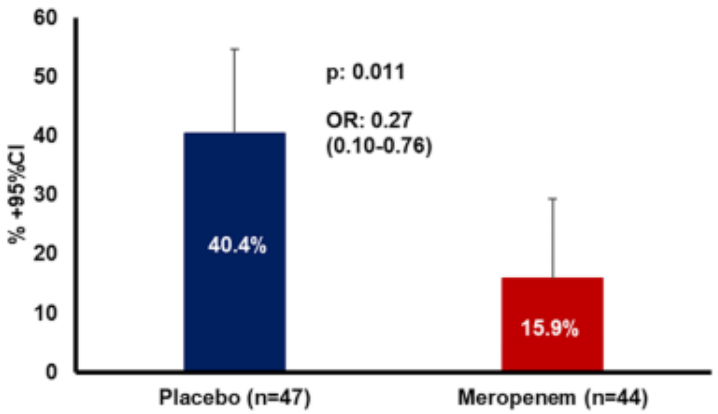


Fig. 2 Flowchart of the SUPERIOR trial. *ITT* Intent-to-treat, *n* number of patients, *qSOFA* Quick Sequential Organ Failure Assessment Score, *suPAR* soluble urokinase plasminogen activator receptor



Rezultati: študija prezgodaj ustavljena zaradi pandemije COVID-19, primarni cilj dosežen pri 40,4% (19) vs. 15,9% (7) bolnikov; pri bolnikih, zdravljenih z meropenemom, večji delež ozdravitve in krajši čas do le-te

Adami et al. Crit Care. 2024

Nadaljevanje…

Table 2 Endpoints of the SUPERIOR study

	Placebo ($n=47$)	Meropenem ($n=44$)	% Difference (95% CIs)	Odds ratio (95% CI s)	*p* value
Primary endpoint: early worsening, *n* (%)	19 (40.4)	7 (15.9)	24·5 (5.9 to 40.8)	0.28 (0.10 to 0.76)	0.011
Secondary endpoints					
At least 2-point SOFA increase the first 24 h, *n* (%)	10 (21.3)	2 (4.5)	16·7 (2.7 to 30.8)	0.18 (0.04 to 0.86)	0.028
Early worsening per quartile of the admission SOFA score, n/patients at the respective quartile (%)					
SOFA = 0-1 points	5/15 (33.3)	0/6 (0)	33.3 (−0.09 to 0.58)	*	0.262
SOFA = 2–3 points	6/10 (60.0)	7/20 (35.0)	25.0 (−0.11 to 53.7)		0.255
SOFA = 4 points	5/12 (41.7)	0/8 (0)	41.7 (2.2 to 68.1)	*	0.055
SOFA > 4 points	3/10 (30·0)	0/10 (0)	30.0 (−7.7 to 60.3)	*	0.211
Resolution of infection, *n* (%)	29 (61.7)	37 (84.1)	22.4 (4.0 to 38.7)	3·28 (1.21 to 8.91)	0.020
Time to infection resolution, days, median (Q1-Q3)	13.0 (9 to 60)	12 (8 to 15.8)	NA	NA	0.018
7-day mortality, *n* (%)	2 (4.3)	0 (0)	4.3 (−4.3 to 14.3)	*	0.494
28-day mortality, *n* (%)	8 (17·0)	4 (9.1)	7·9 (−6.6 to 22.2)	0.49 (0.14 to 1.75)	0.357
60-day mortality, *n* (%)	11 (23.4)	8 (18.2)	5.2 (−11.7 to 21.5)	0.73 (0.26 to 2.02)	0.611
90-day mortality, *n* (%)	15 (31.9)	9 (20.5)	11.5 (−6.7 to 28.5)	0.55 (0.21 to 1.43)	0.242
New infections the first 7 days, *n* (%)	4 (8.5)	3 (6.8)	1.7 (−10.8 to 13.9)	0.79 (0.17 to 3.73)	1.000
New infections the first 60 days, *n* (%)	18 (38.3)	14 (30.2)	6.5 (−12.8 to 25.0)	0.69 (0.29 to 2.68)	0.507
Change of antibiotics, *n* (%)	24 (51.1)	18 (40.9)	10.2 (−10 to 29.2)	0.66 (0.29 to 1.52)	0.402
Duration of hospitalization, days, median (range)	8 (5 to 14)	11 (6.3 to 17)	NA	NA	0.372

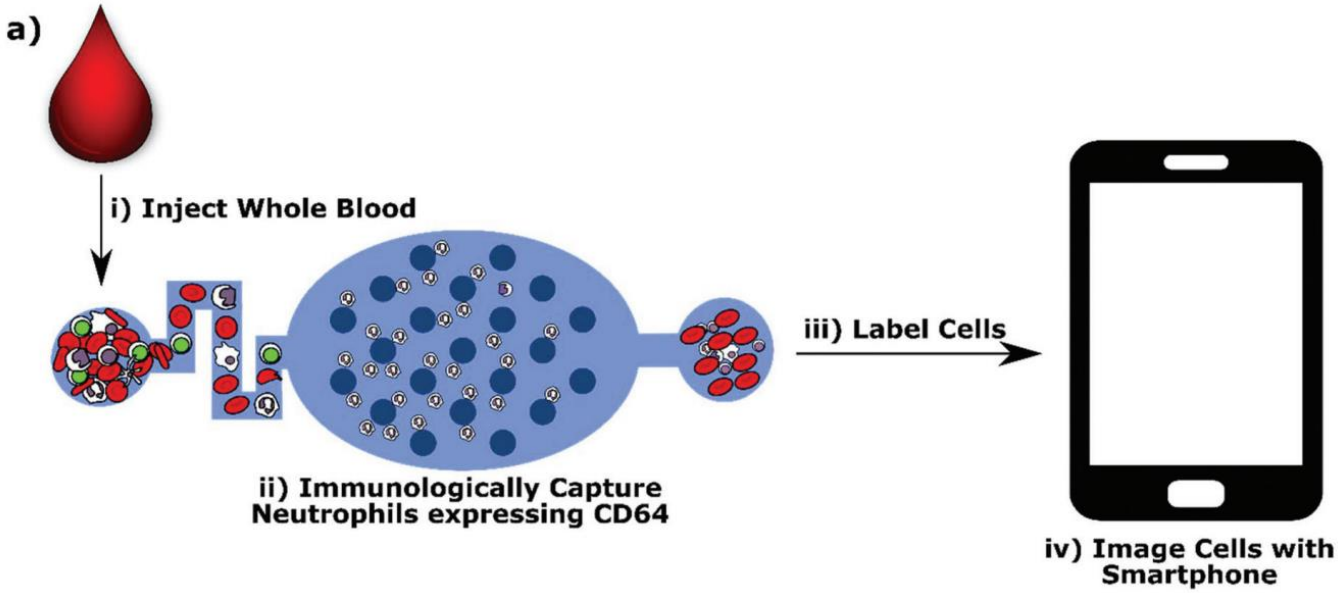
*Cannot be calculated because one value is zero

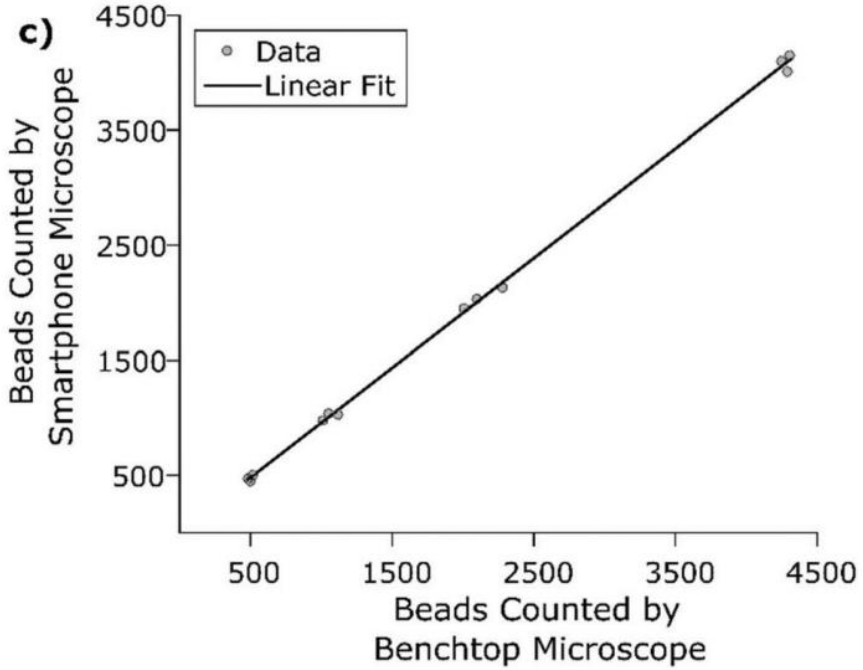
n Number of patients, *SD* standard deviation, *SOFA* Sequential Organ Failure

Pogled v prihodnost…

Smartphone-imaged microfluidic biochip for measuring CD64 expression from whole blood†

Tanmay Ghonge,[a,b,c] Hatice Ceylan Koydemir,[d] Enrique Valera,[a,b,c] Jacob Berger,[a,b,c] Carlos Garcia,[a,b,c] Noshin Nawar,[a,b,c] Justin Tiao,[a,b,c] Gregory L. Damhorst,[e] Anurup Ganguli,[a,b] Umer Hassan,[f] Aydogan Ozcan *[d,g,h] and Rashid Bashir *[a,b,c,i]





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Review

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Khalid Bindayna

Review

Personalizing Care for Critically Ill Adults Using Omics: A Concise Review of Potential Clinical Applications

Kay Choong See

Machine learning for the prediction of sepsis: a systematic review and meta-analysis of diagnostic test accuracy

Lucas M. Fleuren[1,2*], Thomas L. T. Klausch[3], Charlotte L. Zwager[1], Linda J. Schoonmade[4], Tingjie Guo[1], Luca F. Roggeveen[1,2], Eleonora L. Swart[5], Armand R. J. Girbes[1], Patrick Thoral[1], Ari Ercole[6,7], Mark Hoogendoorn[2] and Paul W. G. Elbers[1,7]

Uporabljajte biomarkerje.

Koncentracijo določite večkrat v poteku bolezni.

Vedno v sklopu kliničnega konteksta.

Hvala za pozornost!