ΒΙΟΔΕΙΚΤΕΣ ΣΕ ΕΙΔΙΚΟΥΣ ΠΛΗΘΥΣΜΟΥΣ

Γαρυφαλλιά Πουλάκου
Λοιμωξιολόγος
Γ’ Πανεπιστημιακή Παθολογική Κλινική
ΓΝΝΘΑ «Η ΣΩΤΗΡΙΑ»

ΠΑΡΑΔΟΧΕΣ

- ✓ **Βιοδείκτες σήψης/λοίμωξης**
- ✓ **Ειδικοί Πληθυσμοί**
  - Εμπύρετη Ουδετεροπενία
  - Ανοσοκατεσταλμένοι-ογκολογικοί-αιματολογικοί
  - Μεταμοσχευθέντες
  - Καρδιακή ανεπάρκεια, Νεφρική δυσλειτουργία
  - Ασθενής μετά από Χειρουργείο και Τραύμα

Ποιος είναι ο ρόλος των βιοδεικτών

- **Να αποδείξουν ή να αποκλείσουν τη σήψη**
- **Να υποδείξουν τους ασθενείς που δυνητικά θα ωφεληθούν από κάποια θεραπευτική παρέμβαση**
- **Να αποτελέσουν έναν αξιόπιστο δείκτη παρακολούθησης της θεραπευτικής παρέμβασης**
- **Να πληροφορήσουν εγκαίρως για την πρόγνωση του ασθενή**

Ποια είναι τα χαρακτηριστικά του ιδανικού βιοδείκτη;

- **Να έχει ικανή ευαισθησία και ειδικότητα, ώστε να μπορεί να διαγνώσει τη σήψη λοιμώδους αιτιολογίας και να τη διαχωρίσει από άλλα παρεμφερή φλεγμονώδη σύνδρομα άλλης αιτιολογίας**
- **Να συνδέεται με κάποιες από τις υποκείμενες διεργασίες**
  - **Ιστική βλάβη**
  - **Ιστική αναγέννηση**
  - **Φλεγμονή**
  - **Πήξη**
- **Να είναι παρών στην αρχή της σηπτικής διεργασίας ή ακόμη και να προηγείται της εμφάνισης των κλινικών συμπτωμάτων**
- **Να μετριέται με ευχέρεια, ακρίβεια, αναπαραγωγιμότητα και ασφάλεια για τον πάσχοντα και το περιβάλλον**
- **Να υπάρχει βιολογική εξήγηση για τις πιθανές διακυμάνσεις του και να είναι κατανοητή και ερμηνεύσιμη η κινητική του**

Categories of Biomarkers

- **According to pathophysiology, the biomarkers of sepsis can be classified into the following seven categories:**

(1) **acute phase reactants, e.g., C-reactive protein (CRP), erythrocyte sedimentation rate, and procalcitonin;**

(2) **proinflammatory cytokines, e.g., interleukin, tumor necrosis factor (TNF), and monocyte chemoattractant protein;**

(3) **biomarkers of activated neutrophils and monocytes, e.g., presepsin, cluster of differentiation (CD), and receptor for advanced glycation end products;**

(4) **infectious organisms and related protein, e.g., high-mobility group box 1 and myeloid-related protein;**

(5) **receptors, e.g., toll-like receptors, TNF receptors, triggering receptor expressed on myeloid cell 1 (TREM-1);**

(6) **anti-inflammatory markers, e.g., monocyte human leukocyte antigen-DR expression, cytotoxic T-lymphocyte-associated protein 4; and**

(7) **biomarkers for organ dysfunction, e.g., liver function test, coagulation, and renal function**

Πώς αποτιμάται η συνεισφορά ενός βιοδείκτη στην κλινική πράξη;

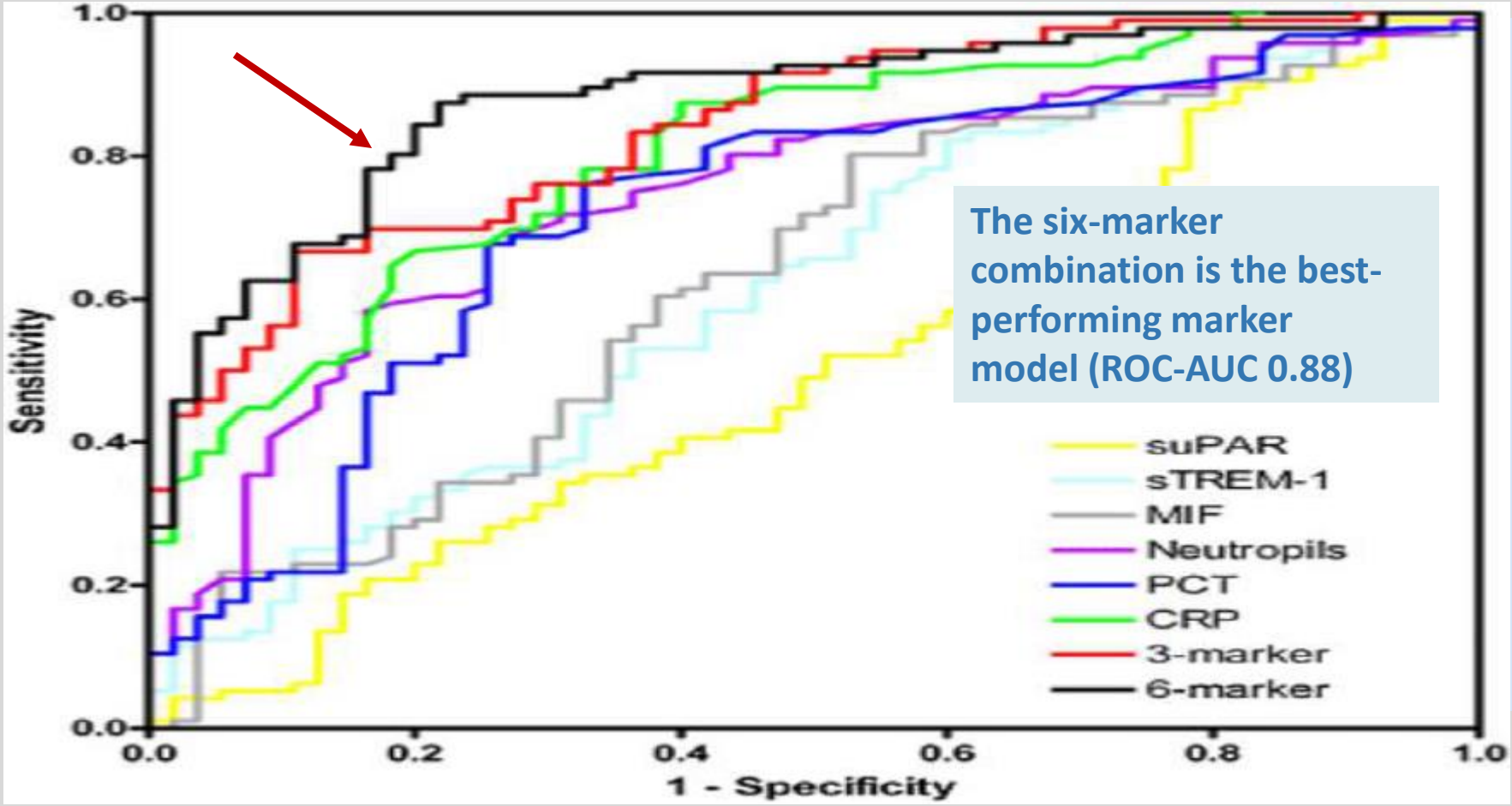
- **Βοηθά στη διάγνωση;**
- **Προσθέτει προγνωστική πληροφορία;**
  - **Για την τελική έκβαση**
  - **Για πιθανή επιδείνωση ή ευνοϊκή εξέλιξη**
- **Προσθέτει κάτι επιπλέον από τα διάφορα scores που μπορεί να έχουν προταθεί;**

Πόσοι είναι οι μέχρι τώρα προταθέντες βιοδείκτες;

- **Acute phase proteins**
  - CRP
  - Procalcitonin
  - Pentraxin 3 (PTX3)
  - Lipopolysaccharide binding protein (LBP)
- **Cytokines & chemokines**
  - IL-1RA, IL-1β, IL-2, IL-6, MCP-1
  - TNF-α, TNFR1/2
  - HMGBP1
- **Cell surface markers**
  - Soluble CD14 (presepsin)
  - Neutrophil CD64 index (CD64in)
  - mHLA-DR (monocyte HLA-DR levels)
  - CD-163
- **Receptor markers**
  - VEGF
  - Soluble VEGF-receptor 1 (sFLT)
  - Soluble urokinase plasminogen activator (suPAR)
  - sTREM-1
  - RAGE (soluble receptor for advanced glycation end products)
- **Coagulation**
  - Activated partial thromboplastin time (aPTT) waveform analysis
  - Protein C receptor
  - Thrombomodulin
- **Endothelial damage**
  - Heparin binding protein
  - E-selectin
  - Neopterin
  - ICAM-1, VCAM-1
  - Angiopoietin-1 and -2
  - Syndecan-1 and -2
- **Vasodilation**
  - Copeptin (AVP precursor)
- **Cell damage**
  - MicroRNA
  - Microparticles
- **Cell repair**
  - Procollagen III amino propeptide

Εξ' αυτών πολύ λίγοι είχαν την τύχη να υιοθετηθούν στην κλινική πράξη

The ROC curve



The six-marker combination is the best-performing marker model (ROC-AUC 0.88)

Use of plasma C-reactive protein, procalcitonin, neutrophils, macrophage migration inhibitory factor, soluble urokinase-type plasminogen activator receptor, and soluble triggering receptor expressed on myeloid cells-1 in combination to diagnose infections

Kofoed K, Crit Care 2007; 11: R38.

Procalcitonin (PCT)

- **PCT is a prohormone synthesized and rapidly released by many cell types during period s of generalized inflammation.**
- **Plasma levels are usually highest during episodes of severe bacterial infection, but noninfectious injury such as major surgery, severe trauma, and some virus infections can also elevate PCT levels**

Am J Health Syst Pharm, Volume 77, Issue 10, 15 May 2020, Pages 745–758,

Procalcitonin (PCT)

- **Serial measurement of PCT levels might prove to be useful in antibiotic stewardship programs to encourage clinicians to withdraw empiric antibiotics if PCT levels were never elevated or were low and drop precipitously.**
- **The clinical usefulness of applying PCT levels as a guide to discontinue antibiotics, if no objective evidence of bacterial infection is found, remains the subject of considerable debate**

Am J Health Syst Pharm, Volume 77, Issue 10, 15 May 2020, Pages 745–758,

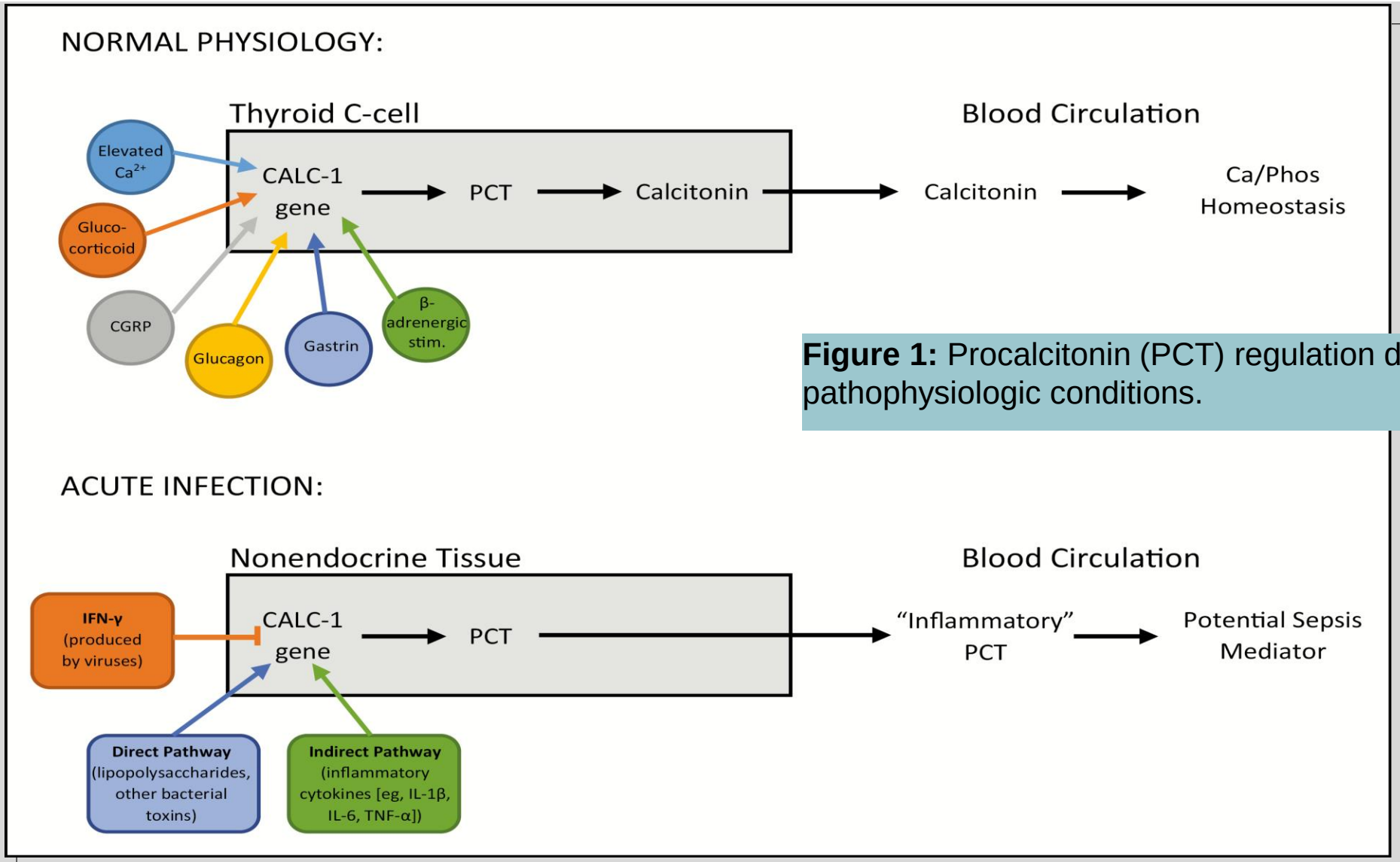


Figure 1: Procalcitonin (PCT) regulation during physiologic and pathophysiologic conditions.

Am J Health Syst Pharm, Volume 77, Issue 10, 15 May 2020, Pages 745–758, https://doi.org/10.1093/ajhp/zxaa089

ΕΜΠΥΡΕΤΗ ΟΥΔΕΤΕΡΟΠΕΝΙΑ

Assessment of Procalcitonin as a Diagnostic Marker of Underlying Infection in Patients with Febrile Neutropenia FREE

Evangelos J. Giamarellos-Bourboulis ✉, Paraskevi Grecka, Garyfallia Poulakou, Konstantinos Anargyrou, Nikolaos Katsilambros, Helen Giamarellou

Clinical Infectious Diseases, Volume 32, Issue 12, 15 June 2001, Pages 1718–1725,

- **Blood samples were obtained from 115 patients with febrile neutropenia for determination of PCT levels before onset of fever and daily until the resolution of fever.**
- **A dramatic decrease in PCT levels was documented after resolution of the infection; PCT levels were elevated when the infection worsened.**
- **Pronounced PCT levels were also found in patients with fever of unknown origin who were responding to antimicrobial chemotherapy, compared with those not responding to treatment with antibiotics.**
- **PCT levels were particularly elevated in patients with bacteremia and severe sepsis.**

Table 2 Daily follow-up of procalcitonin levels in 39 patients with neutropenia who presented with bacteremia or with localized bacterial infection

	Procalcitonin levels, ng/mL				
	Patients with bacteremia		Patients with localized bacterial infection		
Time	Median (no. observations)	Range	Median (no. observations)	Range	*P*
Before chemotherapy	0.16 (28)	ND–0.80	ND (11)	ND–0.69	
Afebrile on neutropenia	0.05 (28)	ND–0.97	0.12 (11)	ND–0.28	
Days of fever					
1	8.23 (28)[a,b]	0.09–297.63	0.86 (11)[c]	ND–6.71	.017
2	6.68 (24)[a,b]	ND–269.36	0.24 (8)[c]	ND–1.42	.018
3	2.95 (18)[a,b]	ND–181.23	0.23 (8)[c]	ND–1.16	.033
4	1.68 (14)[b,d]	ND–129.81	0.63 (6)[e]	ND–1.95	NS
Resolution of fever	0.37 (20)	ND–6.91	0.39 (11)	ND–1.0	

NOTE. ND, nondetectable; NS, not significant.

[a] $P < .001$ compared with the values of the same patients in the status of neutropenia before the onset of fever.
[b] P = NS compared with patients with severe sepsis.
[c] P = NS compared with patients with clinical localized infections.
[d] $P < .01$ compared with the values of the same patients in the status of neutropenia before the onset of fever.
[e] $P < .05$ compared with the values of the same patients in the status of neutropenia before the onset of fever.

The median PCT level on the first day of fever was 8.23 ng/mL in patients with bacteremia, compared with 0.86 ng/mL in patients with localized bacterial infections (P = .017).

Giamarellos-Bourboulis EJ, Clin Infect Dis. 2001 Jun 15;32(12):1718-25

Table 3 Daily follow-up of procalcitonin levels in 34 patients with neutropenia who presented with severe sepsis or localized infections

Time	Procalcitonin level, ng/mL: Patients with severe sepsis — Median (no. observations)	Range	Patients with clinical localized infections — Median (no. observations)	Range	*P*
Before chemotherapy	ND (11)	ND–1.25	0.05 (23)	ND–1.07	
Afebrile on neutropenia	0.35 (11)	ND–.54	0.15 (23)	ND–0.80	
Days of fever					
1	2.62 (11)[a]	0.63–43.47	0.57 (23)[b]	ND–16.17	<.001
2	5.28 (10)[a]	0.19–37.45	0.60 (21)[c]	ND–8.09	.003
3	4.64 (8)[b]	0.38–21.98	0.45 (19)[c]	ND–3.08	.005
4	1.25 (8)[b]	0.94–7.55	0.25 (13)[d]	ND–0.45	.007
Resolution of fever	0.25 (5)	ND–3.25	0.77 (22)	ND–1.44	

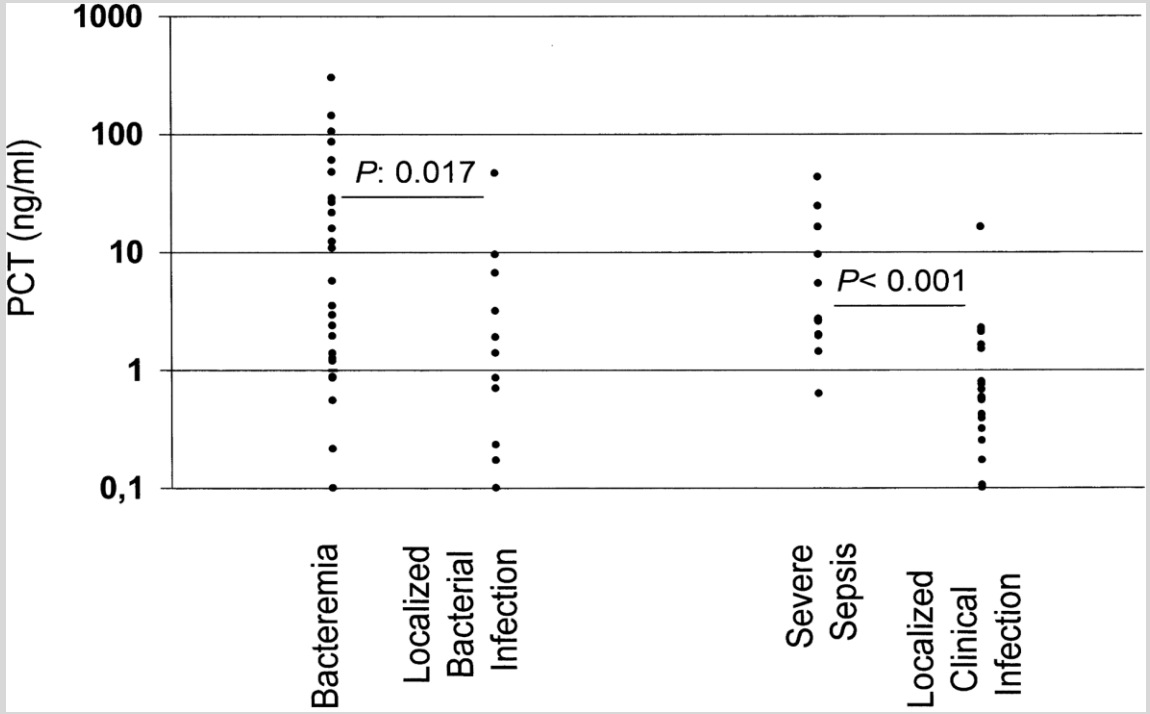
NOTE. ND, nondetectable; NS, not significant.

[a] $P < .001$ compared with the values of the same patients in the status of neutropenia before the onset of fever.
[b] $P < .01$ compared with the values of the same patients in the status of neutropenia before the onset of fever.
[c] $P < .05$ compared with the values of the same patients in the status of neutropenia before the onset of fever.
[d] P = NS compared with the values of the same patients in the status of neutropenia before the onset of fever.

The median PCT level on the first day of fever was 2.62 ng/mL in patients with severe sepsis, compared with 0.57 ng/mL in patients with clinically localized infections ($P < .001$).

Giamarellos-Bourboulis EJ, Clin Infect Dis. 2001 Jun 15;32(12):1718-25

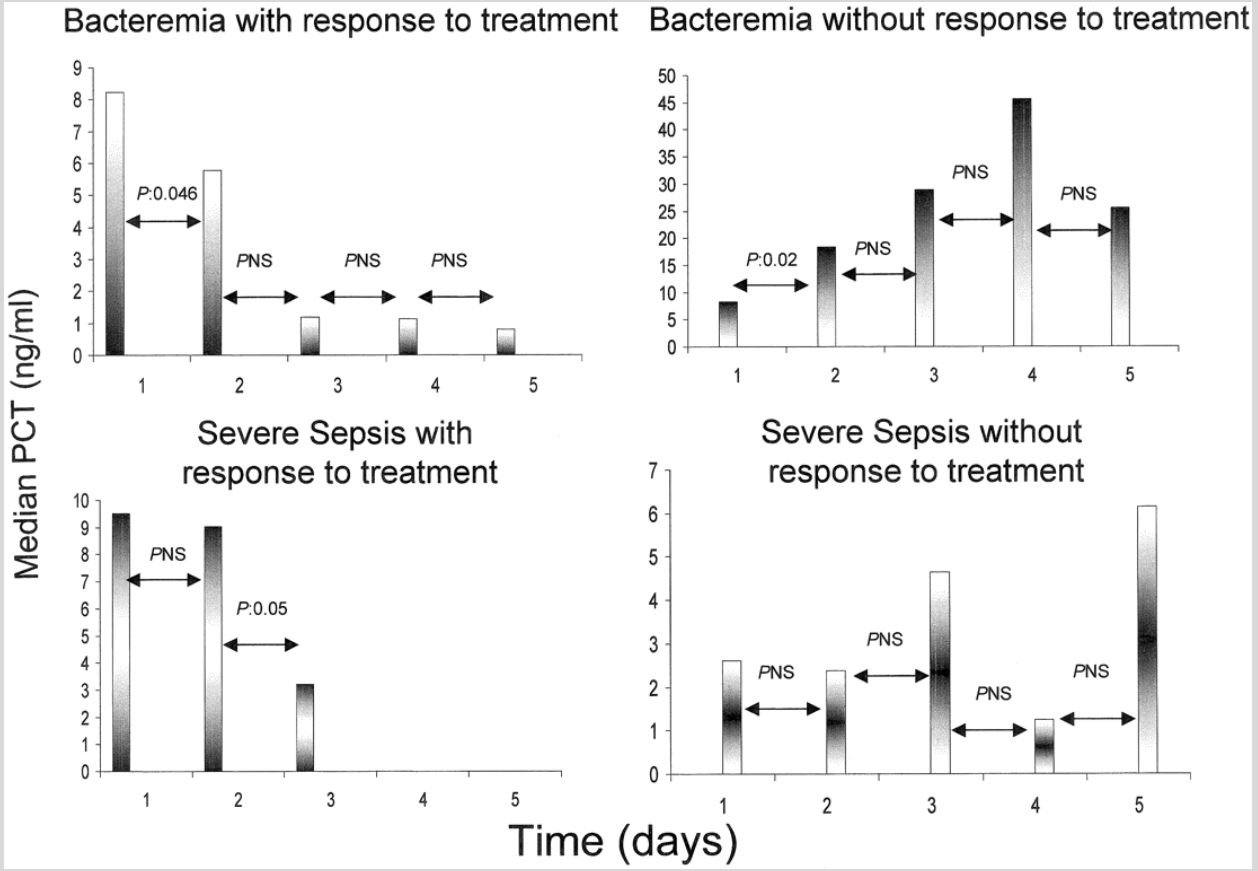
Figure 1 Distribution of values of procalcitonin (PCT) on the first day of fever among patients who presented with bacteremia, severe sepsis or localized infections



The median PCT level on the first day of fever was 2.62 ng/mL in patients with severe sepsis, compared with 0.57 ng/mL in patients with clinically localized infections (P < .001).

Giamarellos-Bourboulis EJ, Clin Infect Dis. 2001 Jun 15;32(12):1718-25

Figure 2 Follow-up of procalcitonin (PCT) over time in patients with bacteremia and with severe sepsis in relation to response to treatment



Giamarellos-Bourboulis EJ, Clin Infect Dis. 2001 Jun 15;32(12):1718-25

OXFORD UNIVERSITY PRESS

Giamarellos-Bourboulis EJ, Clin Infect Dis. 2001 Jun 15;32(12):1718-25

Table 5 Definitions of sensitivity, specificity, and positive predictive values of different concentrations of procalcitonin determined on the first day of febrile neutropenia for the diagnosis of bacteremia

	Patients with bacteremia		Patients with localized infections				
Procalcitonin, ng/mL	No. of true positive results	No. of false negative results	No. of false positive results	No. of true negative results	Sensitivity, %	Specificity, %	PPV, %
>0.5	26	2	6	5	92.9	45.5	81.3
>1.0	22	6	4	7	78.6	63.6	84.6
>1.5	19	9	4	7	67.9	63.6	82.6

NOTE. PPV, positive predictive value.

Table 6 Definitions of sensitivity, specificity, and positive predictive values of different concentrations of procalcitonin determined on the first day of febrile neutropenia for the diagnosis of severe sepsis

	Patients with severe sepsis		Patients with localized infections				
Procalcitonin, ng/mL	No. of true positive results	No. of false negative results	No. of false positive results	No. of true negative results	Sensitivity, %	Specificity, %	PPV, %
>0.5	10	1	14	9	90.9	39.1	41.7
>1.0	10	1	7	16	90.9	69.5	58.8
>1.5	10	1	5	18	90.9	78.3	66.7
>2.0	10	1	3	20	90.9	86.9	76.9
>2.5	5	6	1	22	45.5	95.6	83.3

NOTE. PPV, positive predictive value.

Does procalcitonin, C-reactive protein, or interleukin-6 test have a role in the diagnosis of severe infection in patients with febrile neutropenia? A systematic review and meta-analysis

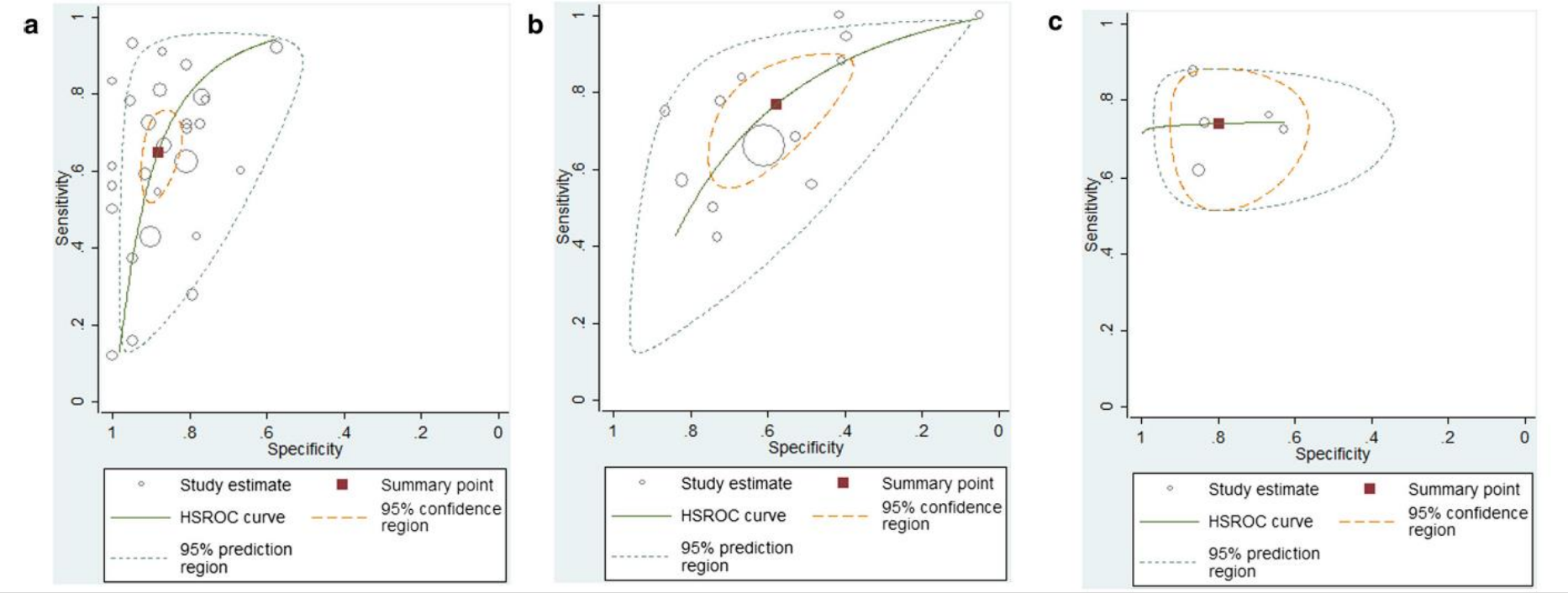
Chun-Wei Wu · Jiunn-Yih Wu · Chun-Kuei Chen · Shiau-Ling Huang · Shou-Chien Hsu · Meng-tse Gabriel Lee · Shy-Shin Chang · Chien-Chang Lee

- **Twenty-seven studies were included (1960 febrile episodes) for PCT analysis, 13 (1712 febrile episodes) for C reactive protein (CRP) analysis, and five (314 febrile episodes) for interleukin (IL)-6 analysis (1966-2012)**
- **Increased PCT levels (odds ratio [OR] 11.5; 95% CI 7.6 to 17.3), raised CRP levels (3.3; 2.7 to 4.2), and raised IL-6 levels (10.0; 5.5 to 18.0) were significantly associated with bacterial infection.**
- **Overall positive likelihood ratio was 5.49 (4.04–7.45) for PCT, 1.82 (1.42–2.33) for CRP, and 3.68 (2.41–5.60) for IL-6.**
- **Overall negative likelihood ratio was 0.40 (0.31–0.51) for PCT, 0.40 (0.26–0.61) for CRP, and 0.33 (0.23–0.46) for IL-6.**

Wu CW, Support Care Cancer. 2015 Oct;23(10):2863-72

Fig. 3 Receiver operating curve analysis of PCT (a), CRP (b), or IL-6 (c) for the detection of systemic bacterial infection among patients with FN.

Summary receiver operating characteristic (SROC) curve: solid line; bivariate summary estimate: solid square; 95 % confidence ellipse:inner dashed line; 95% prediction ellipse: outer dotted line. Symbol area is proportional to study size



Wu CW, Support Care Cancer. 2015 Oct;23(10):2863-72

Does procalcitonin, C-reactive protein, or interleukin-6 test have a role in the diagnosis of severe infection in patients with febrile neutropenia? A systematic review and meta-analysis

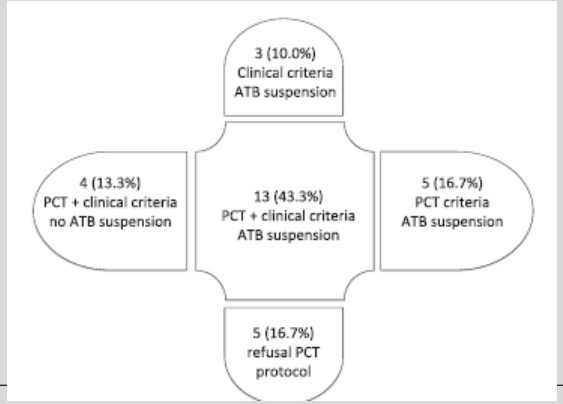
Chun-Wei Wu · Jiunn-Yih Wu · Chun-Kuei Chen · Shiau-Ling Huang · Shou-Chien Hsu · Meng-tse Gabriel Lee · Shy-Shin Chang · Chien-Chang Lee

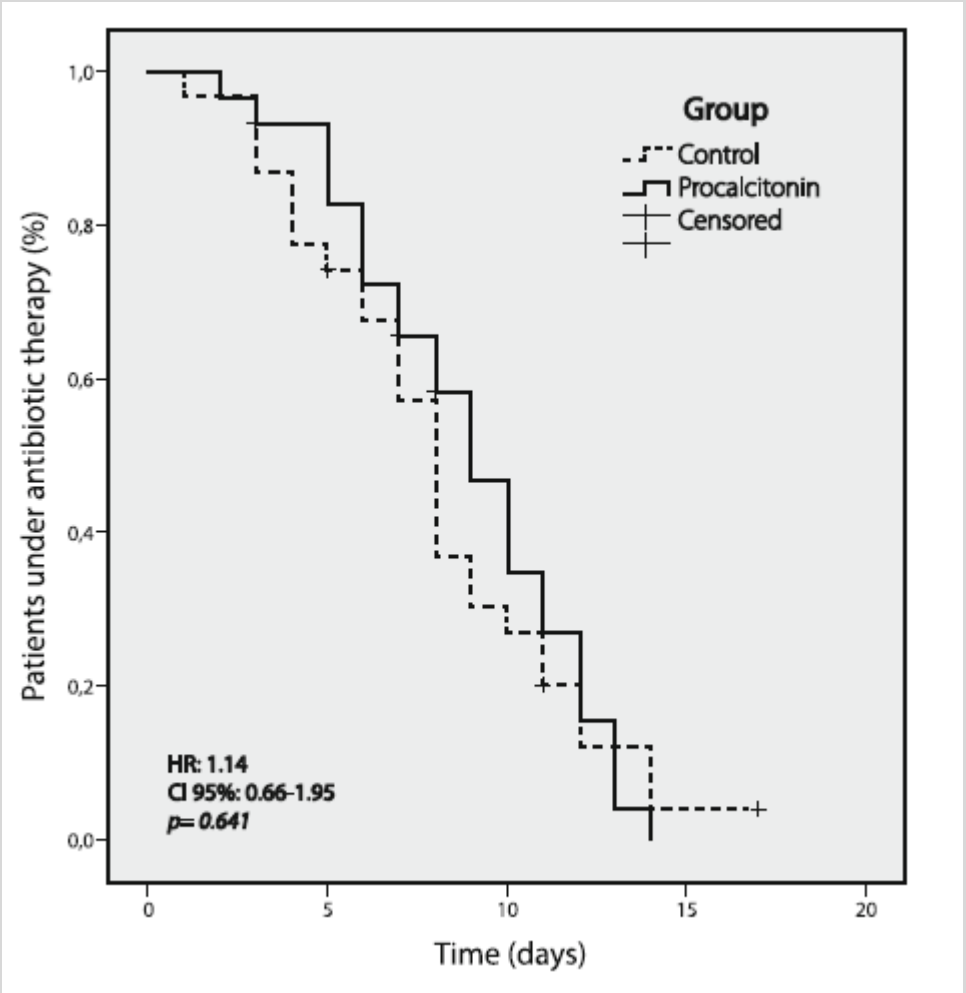
- **In conclusion, this meta-analysis found that the PCT test has higher diagnostic value than CRP or IL-6 for the detection of bacterial infection in patients with FN.**
- **Our data suggest that PCT is a more specific than sensitive test and helps to confirm bacterial infections rather than rule them out.**
- **Initial decision making on empirical antimicrobial treatment based on PCT in this high-risk population may not be possible.**
- **Future studies should examine whether PCT may help to early de-escalate antibiotics if it remains low.**
- **Further studies may also be needed to address whether multi-marker approach or a clinical diagnostic score that incorporates the information of PCT may improve mortality and morbidity**

Wu CW, Support Care Cancer. 2015 Oct;23(10):2863-72

Febrile neutropenia

- A total of 62 hematological adult patients with FN were randomized, in 1:1 ratio, into
- two groups: (1) PCT group: length of ATB guided by institutional protocol plus PCT dynamics, and (2) control group:duration of ATB in accordance with institutional protocol
- Considering the cut-off of 0.5 ng/ml, PCT was correlated with bacteremia (sensitivity of 51.9 % and specificity of 76.5 %).
- In this randomized controlled trial, adding a PCT guided protocol to the standard recommendations did not reduce the use of antibiotics in febrile neutropenia, although no apparent harm was caused.



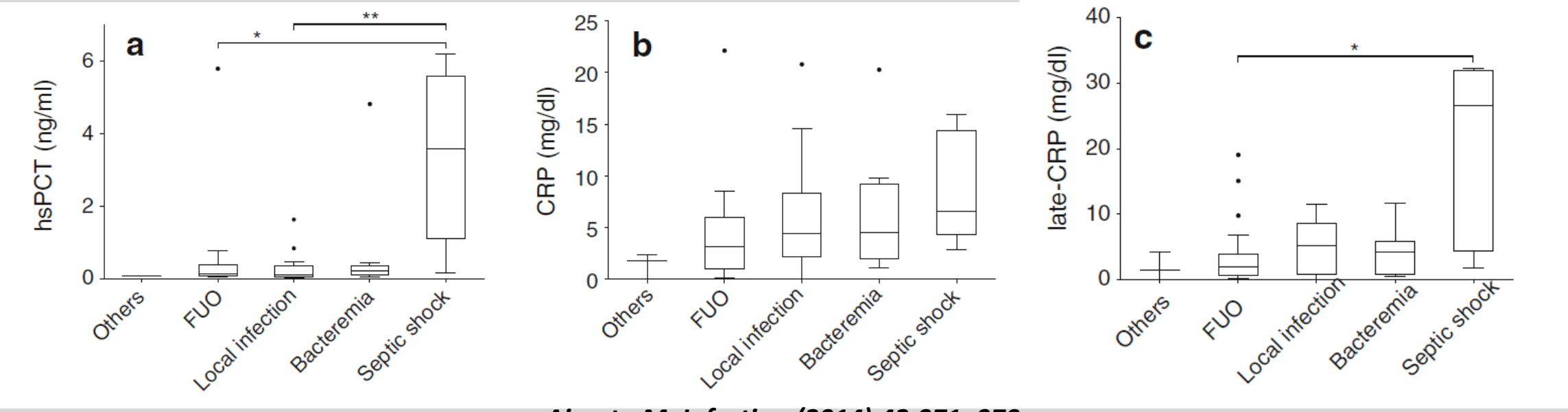


Kaplan–Meier curve of the first antibiotic therapy duration in procalcitonin and control group.
PCT procalcitonin. Cox model adjusted for bacteremia. Censure: antibiotic suspension due to death

Lima SSS, Ann Hematol
DOI 10.1007/s00277-016-2639-5

Diagnostic performance of serum high-sensitivity procalcitonin and serum C-reactive protein tests for detecting bacterial infection in febrile neutropenia

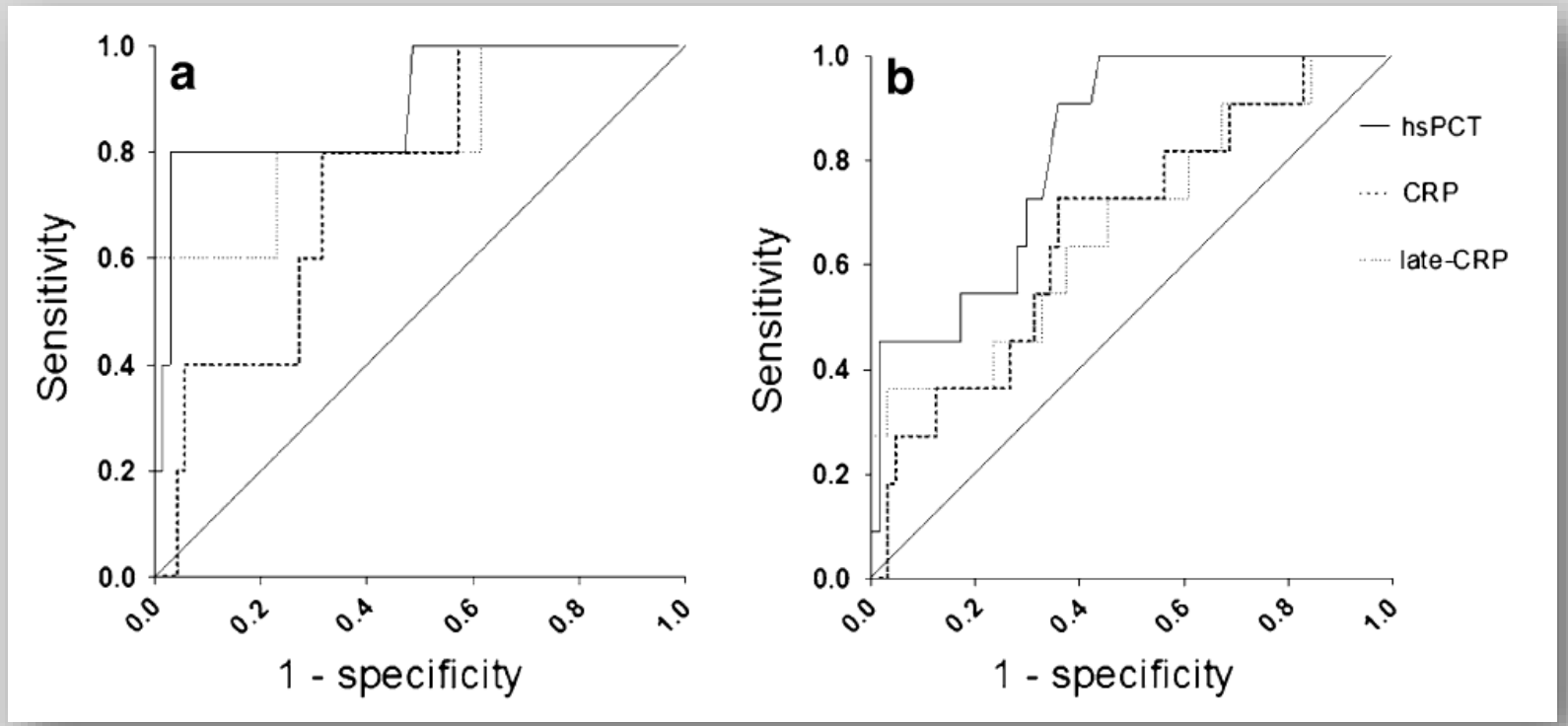
- **Prospective study, 75 patients**
- **FN after intensive chemotherapy or hematopoietic cell transplantation (HCT)**
- **hsCRP detection limit 0.02 ng/ml**



Aimoto M, Infection (2014) 42:971–979

Conclusions

- **Serum hsPCT test may be more useful than the CRP test in the detection of life-threatening infection at an early phase after the onset of FN.**
- **In contrast, serum CRP test may be more useful in diagnosing the degree of infection severity.**
- **However, neither of these tests was able to differentiate among FUO, local infection, and bacteremia caused by CNS in patients with FN.**
- **No correlation was found between PCT\72 h levels and leukocytes, neutrophils, and monocytes. However, both CRP\72 h and late-CRP were moderately correlated with each component of leukocytes.**



ROC curves; AUC were: hsPCT 0.889 late-CRP 0.831 and CRP 0.74

Discrimination of septic shock from the other groups (a)

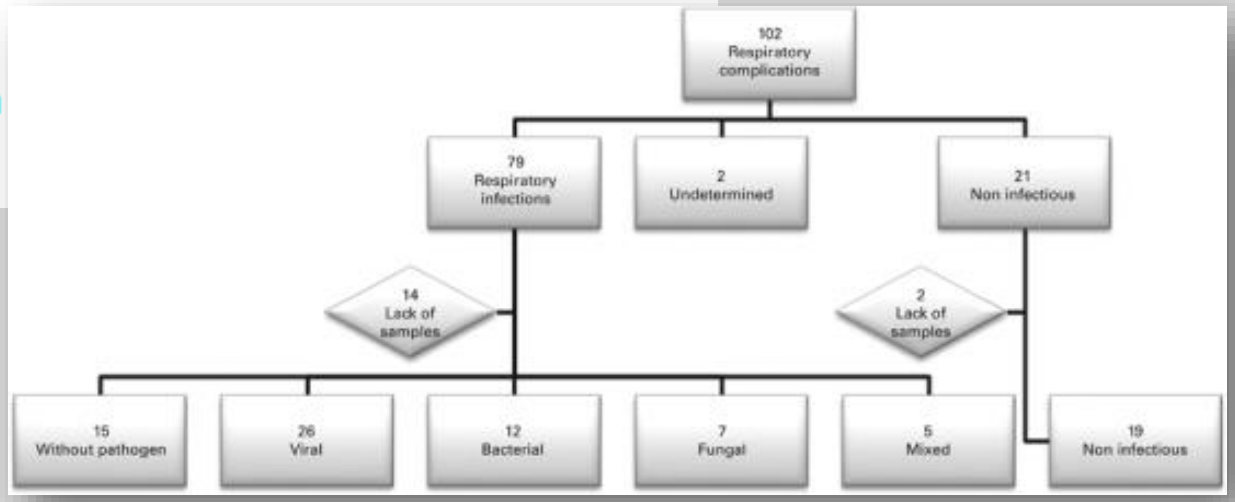
hsPCT, 0.824 CRP0.673 and late-CRP 0.678

Discrimination of life-threatening infection (septic shock or bacteremia caused by non-coagulase negative staphylococcus) from the other groups (b).

Aimoto M, Infection (2014) 42:971–979

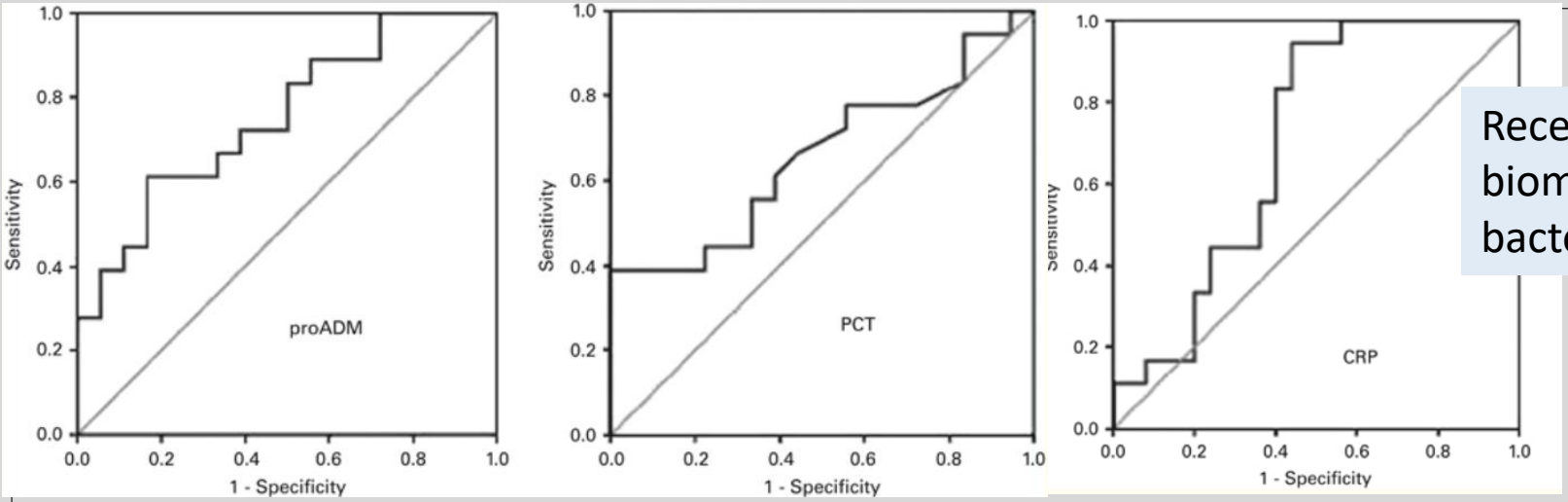
The clinical value of biomarkers in respiratory complications in hematopoietic SCT

C M Lucena [1 2 3], M Rovira [2 4], A Gabarrús [2], X Filella
A Torres [1 2 3 6], C Agustí [1 2 3]



- **Prospectively evaluated a cohort of 175 patients followed-up for 1 year after HSCT.**
- **Excluded both unidentified respiratory infections (RI) and mixed RI.**
- **A total of 64 RC were included.**
- **Plasma levels of C-reactive protein (CRP), procalcitonin (PCT) and proadrenomedullin (proADM) were measured at diagnosis and on day 3 and 7. Different cytokines were evaluated in serum on the first day**
- **Engraftment syndrome (26%), pulmonary edema (21%) and underlying disease progression (21%) were the most common non-infectious etiologies**

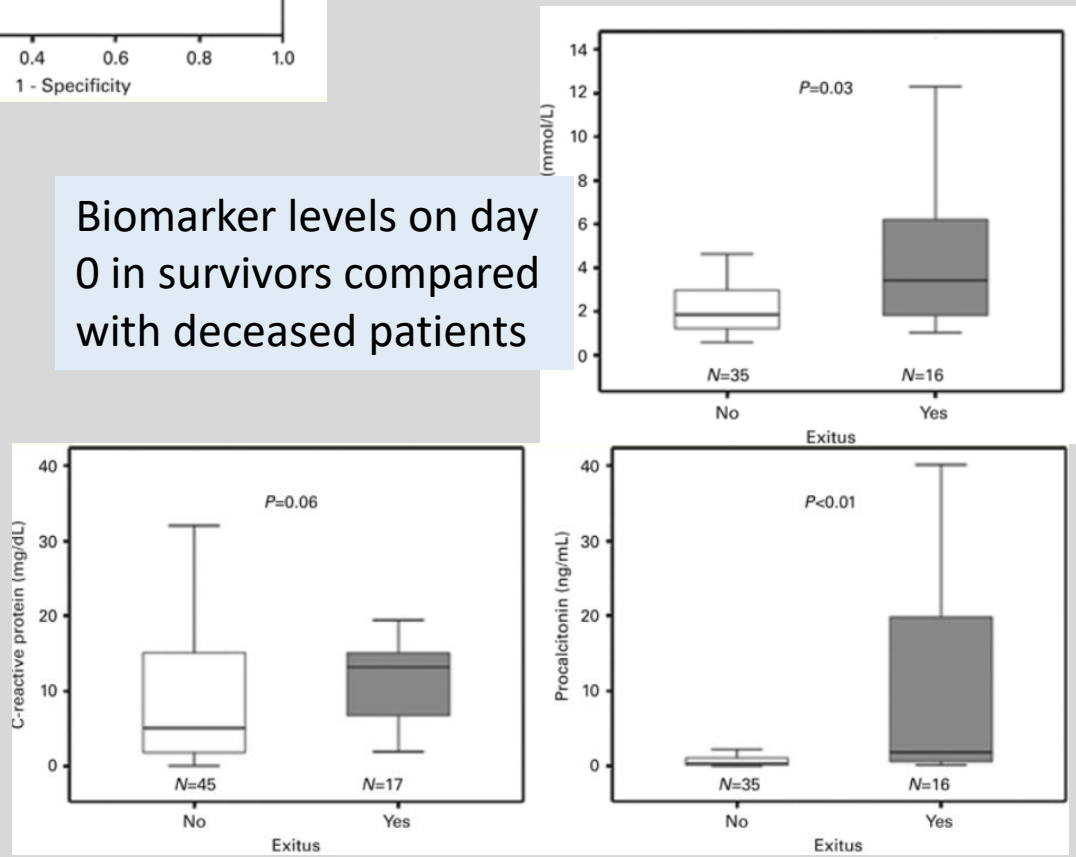
Lucena CM Bone Marrow Transplant. 2017; 52(3): 415–422.



Receiver operating characteristic curves for biomarker levels on day 0 for predicting bacterial–fungal respiratory infections

- **Biomarkers cannot differentiate between infectious and non-infectious complications in HSCT recipients; they still can be useful from a clinical standpoint.**
- **Levels of CRP, PCT and proADM on day 0 reflect the severity of the Respiratory Complications and have prognostic relevance.**
- **Moreover, persistent low levels of these biomarkers suggest a viral infection and may help to tailor the therapeutic regime.**

Biomarker levels on day 0 in survivors compared with deceased patients



Lucena CM Bone Marrow Transplant. 2017; 52(3): 415–422.

Η προκαλσιτονίνη ως βιοδείκτης λοίμωξης σε νεφρικη δυσλειτουργία

Clinical Condition	Effect on PCT	Recommendation(s)[a]	PCT Threshold
Chronic kidney disease	• Inconsistent increase in PCT reported • Proposed hypothesis: proinflammatory metabolites stimulate nonneuroendocrine pathway of PCT production	• Consider a higher PCT threshold for ruling in bacterial infection	• >0.85-1.5 ng/mL[24,25]
Acute kidney injury	• Inconsistent increase in PCT reported • PCT levels also associated with disease severity in patients with AKI	• Consider a higher PCT threshold for ruling in bacterial infection	• >0.42-2 ng/mL[28,29] • 7.13 ng/mL with failure per RIFLE criteria[29]
Chronic RRT (HD or PD)	• Baseline PCT levels higher in ESRD but increase reliably with infection • PCT levels high prior to each HD or PD session and PCT cleared to varying degrees	• Consider a higher PCT threshold for ruling in bacterial infection • Measure PCT level prior to HD	• >1.5 ng/mL in detecting severe infection or sepsis[20]
Continuous RRT	• PCT removed by convection (primarily) and adsorption • Effect on plasma PCT levels is limited with conventional modes of CRRT • Significant PCT clearance with high-cutoff CRRT membranes	• Must be aware of specific CRRT parameters to assess potential impact on PCT utility • With conventional CRRT, PCT may remain a useful diagnostic marker	• No specific threshold recommended[23,35-37]

Susan E Smith, American Journal of Health-System Pharmacy, Volume 77, Issue 10, 15 May 2020, Pages 745–758

Η προκαλσιτονίνη ως βιοδείκτης λοίμωξης σε καρδιακή δυσλειτουργία

Clinical Condition	Effect on PCT	Recommendation(s)[a]	PCT Threshold
Cardiac arrest	• PCT is higher in cardiac arrest; PCT correlates to survival and neurological outcomes	• Consider measuring PCT for predicting survival and neurological outcomes	• 0.291-1.36 µg/L for 12-month outcome[39] • 0.5 ng/mL for poor outcomes[41] • 0.05 ng/mL for mortality[43] • 1 ng/mL for ventilator-associated pneumonia[48] and neurological outcome[42]
Cardiogenic shock	• Elevated PCT is associated with infection, sepsis, and mortality	• Consider measuring PCT to predict infection, sepsis, and mortality	• ≥2 ng/mL for infection[50] • >10 ng/mL for sepsis[52] • >10 ng/mL for mortality in patients receiving ECMO[53]
Cardiac surgery	• Elevated PCT is associated with infection and postoperative complications	• Consider measuring PCT to predict infection and postoperative complications	• 1-9.4 ng/mL for infection[54,55,57,60,66,67] • 2.95-5 ng/mL for complications[56,58]
Heart failure	• Elevated PCT is associated with death, rehospitalization, and infection	• Consider measuring PCT to predict death, rehospitalization, and infection	• ≥0.2 ng/mL for death and rehospitalization[71] • 0.086-0.657 ng/mL for infection[75]

Susan E Smith, American Journal of Health-System Pharmacy, Volume 77, Issue 10, 15 May 2020, Pages 745–758

Η προκαλσιτονίνη ως βιοδείκτης λοίμωξης σε χειρουργείο και τραύμα

Clinical Condition	Effect on PCT	Recommendation(s)[a]	PCT Threshold
Surgery	• Elevated PCT is associated with infection and mortality • PCT-guided antibiotic therapy led to shorter duration of antibiotic therapy and reduced antibiotic costs without increase in negative outcomes	• Consider measuring PCT to predict infection and mortality • Consider using PCT-guided antibiotic therapy	• >1.5 ng/mL for postoperative infection[55] • 1.44 ng/mL for mortality; 0.75 ng/mL for morbidity and mortality[77] • PCT-guided antibiotic treatment resulted in shorter length of treatment and reduced costs without increase in negative outcomes[78]
Burns	• Elevated PCT is associated with infection and sepsis	• Consider measuring PCT to predict infection and sepsis	• Variable (0.5-3 ng/mL) for sepsis and infection[79,81,82,84,85-89,91] • 5.12 ng/mL for bloodstream infection[90]
Trauma	• Elevated PCT is associated with sepsis, complications, and poor outcomes	• Consider using PCT as a marker for infection, sepsis, and risk for complications	• 0.1-0.29 ng/mL for sepsis and infection[103,104] • 1-2 ng/mL for complications and poor outcomes[96,98] • >5 ng/mL for increased mortality[95] • 0.6-5 ng/mL[107]

Susan E Smith, American Journal of Health-System Pharmacy, Volume 77, Issue 10, 15 May 2020, Pages 745–758

Biomarkers in Burn Patients

Biomarker	Diagnostic contribution to infection and sepsis	Comments
CRP	Non discriminative	
Procalcitonin	Non discriminative	Probably other thresholds
Cytokines (TNF-α, IL-6, IL-8, IL10	Promising	
Prepepsin	Very promising	Not alone
Neutrophil function, immature granulocyte count and plasma cell-free DNA levels	Very promising	
Mid-regional pro-atrial natriuretic peptide	Very promising	Along with PCT
Micro RNAs (i.e. miR-495)		Significantly downregulated in patients with sepsis and negatively correlated with CRP and PCT

Zhang P, Burns Trauma. 2021 Jan; 9: tkaa047

Soluble urokinase plasminogen activator receptor informs on the progression course after multiple injuries

Maria Patrani [1], Thomas Tsaganos [2], Katerina Kotzampassi [3], Michael Paraschos [1], Chrysostomos Katsenos [1], Evangelos J Giamarellos-Bourboulis [2], Konstantinos Mandragos [1]

Patrani M, Biomarkers. 2016 Nov;21(7):660-4.

- **Serum suPAR was measured within the first 24 h after multiple injuries in 85 patients.**
- **Measurements were repeated after 4 d or at sepsis onset.**
- **Results: Odds ratio for trauma-associated MOF was 4.09 (p: 0.026) with admission suPAR greater than8 ng/ml.**
- **More than 40% increases of suPAR were associated with odds ratio 9.33 (p: 0.047) for severe sepsis.**

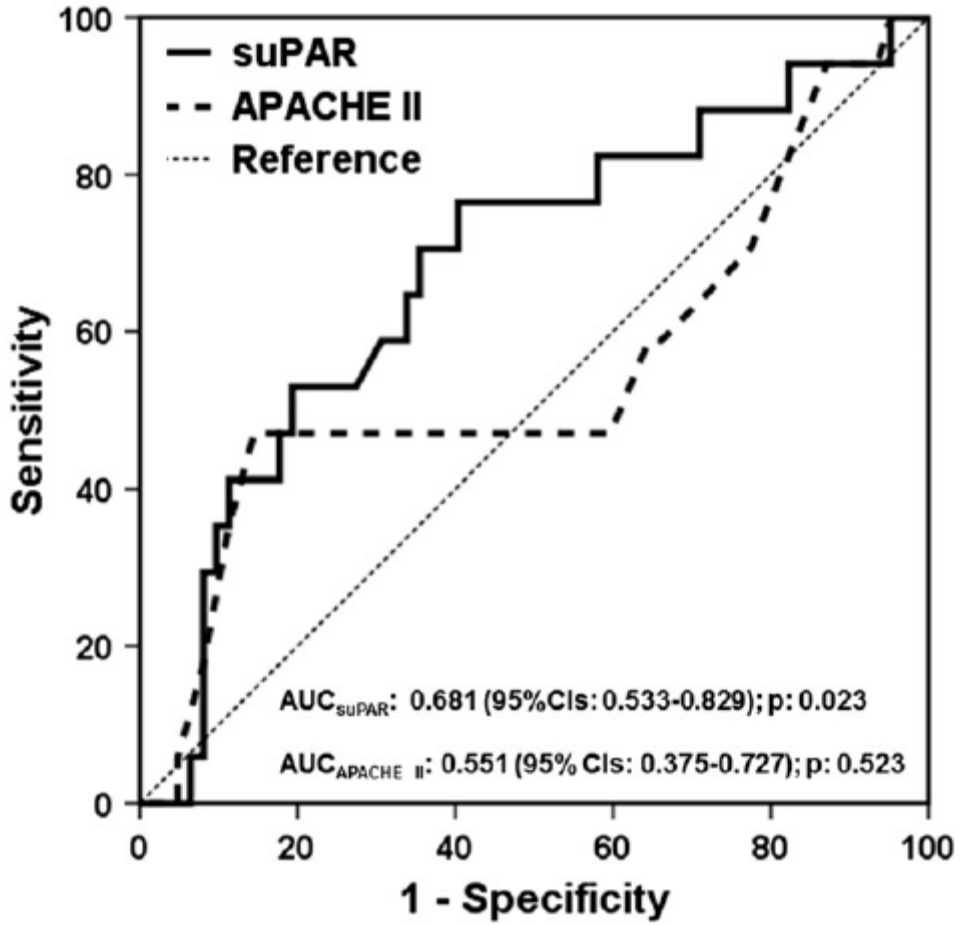
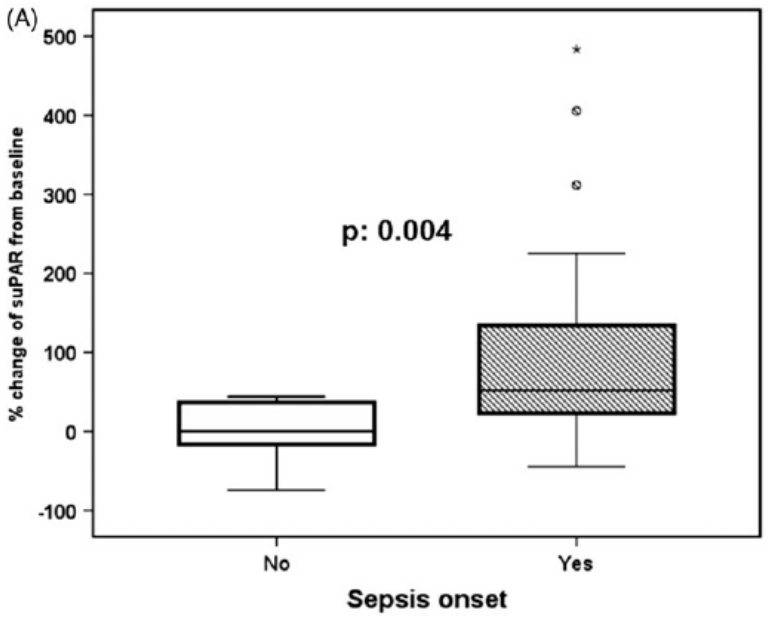


Figure 2. Receiver operator characteristics curve of suPAR to predict development of multi-organ failure. AUC: area under the curve.

Patrani M, Biomarkers. 2016 Nov;21(7):660-4.



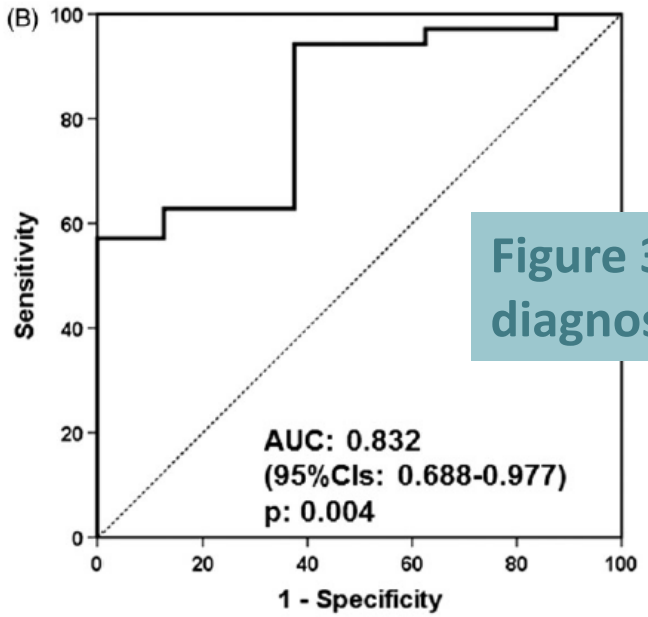


Figure 3. Changes of baseline suPAR for the diagnosis of severe sepsis development.

(C)

	Severe sepsis	No sepsis
≥40% increase	20 (57.1)	5 (10.0)
<40% increase	15 (42.9)	45 (90.0)
Total	35	50

(A) Comparison of changes between patients who did not develop severe sepsis and patients who developed severe sepsis;
(B) ROC curve analysis of the change of suPAR from the baseline for the diagnosis of advent of severe sepsis in patients with multiple injuries; and
(C) (C) association between patients who develop severe sepsis and increase of suPAR more than or equal to 40% from the baseline admission concentrations.

p values indicate the level of significance. AUC: area under the curve; CI: confidence intervals

Τραύμα και sUPAR

Soluble urokinase plasminogen activator receptor informs on the progression course after multiple injuries

Maria Patrani [1], Thomas Tsaganos [2], Katerina Kotzampassi [3], Michael Paraschos [1], Chrysostomos Katsenos [1], Evangelos J Giamarellos-Bourboulis [2], Konstantinos Mandragos [1]

- **suPAR is an accurate and independent biomarker for the prognosis of the development of MOF in critically ill non-septic patients admitted with multiple traumas in the ICU.**
- **Increase more than 40% from the baseline admission levels is diagnostic of the progression into severe sepsis**

Patrani M, Biomarkers. 2016 Nov;21(7):660-4.

Η προκαλσιτονίνη ως βιοδείκτης λοίμωξης σε ασθενείς με κακοήθεια και μεταμόσχευση

Clinical Condition	Effect on PCT	Recommendation(s)[a]	PCT Threshold
Hematologic malignancy	• PCT level not expected to be significantly affected by malignancy • Elevations with engraftment syndrome and GVHD after HSCT, T cell–directed therapies	• Avoid using PCT for management of antimicrobials if a confounding condition/medication is present • Consider using along with clinical criteria to facilitate antimicrobial discontinuation during febrile neutropenia	• >0.5 ng/mL for bacterial infection in febrile neutropenia[115] • >2 ng/mL for risk of severe sepsis or septic shock[117]
Solid tumors	• Elevations with medullary thyroid cancer, small cell lung cancer	• Avoid using PCT for management of antimicrobials if a confounding oncologic condition is present • Consider using along with clinical criteria to facilitate antimicrobial discontinuation during febrile neutropenia	• >0.5 ng/mL for bacterial infection in febrile neutropenia[115]
Solid organ transplantation	• Elevations with T cell–directed therapies	• Avoid using PCT early after receipt of alemtuzumab or antithymocyte globulin • Consider using along with clinical criteria to facilitate antimicrobial discontinuation in the setting of suspected infection	• Variable cutoffs for bacterial infection (0.14-8.18 ng/mL)[119]

Susan E Smith, American Journal of Health-System Pharmacy, Volume 77, Issue 10, 15 May 2020, Pages 745–758

Συμπεράσματα: βιοδείκτες σε ειδικούς πληθυσμούς

- **Στους «ειδικούς πληθυσμούς» κατά κανόνα δεν υπάρχουν «ειδικοί βιοδείκτες»**
- **Οι συνήθεις βιοδείκτες που έχουν αναπτυχθεί για την αναγνώριση της σήψης, χρησιμοποιούνται και στους ειδικούς πληθυσμούς**
- **Ο βιοδείκτης κατά κανόνα διατηρεί τα βασικά χαρακτηριστικά του και στους ειδικούς πληθυσμούς (πχ προγνωστικός δείκτης)**
- **Μέχρις ώρας η CRP και PCT έχουν την ευρύτερη εφαρμογή**
  - **Υποσχόμενες η presepsin, pro adrenomedullin, sUPAR**
- **Αλλάζουν πιθανώς τα όρια λήψης αποφάσεων, υπάρχουν περισσότεροι ερμηνευτικοί περιορισμοί**
- **Όταν στον ειδικό πληθυσμό συνυπάρχει οργανική δυσλειτουργία πρέπει να λαμβάνεται υπόψιν πιθανή αλλαγή στη φαρμακοκινητική των γνωστών βιοδεικτών**
- **Οι παθολογικές διεργασίες που διέπουν τους «ειδικούς» πληθυσμούς μπορεί να αποτελούν εκλυτικό παράγοντα για αύξηση των βιοδεικτών χωρίς παρουσία λοιμώδους αιτίου**
- **Σε εξαιρετικά ευάλωτους πληθυσμούς (πχ μεταμοσχευμένους μυελού ή ουδετεροπενικούς, σπανίως ο βιοδείκτης από μόνος του θα αποτελέσει κριτήριο έναρξης ή μη έναρξης αντιμικροβιακής αγωγής**
- **Χρειάζονται ερευνητικά δεδομένα με προοπτικές ή/και τυχαιοποιημένες**