Úloha CD64 (CD 169) v rozlišení virové a bakteriální etiologie sepse u pacientů s COVID19

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Holy Grail

Průkaz infekce

- Zlatý standard – přímý průkaz z ložiska nebo hemokultur
- Posledních 20 let přineslo pokroky zejména v oblasti molekulární diagnostiky

- Průkaz infekce na podkladě imunitní odpovědi
- Bakteriální infekce
- Virová infekce

Diagnostika infekce - sepse

- **Přímý a nepřímý průkaz infekce**
- BIOMARKERY SEPSE
- „Statimový režim“
- Dostupnost pokud možno 24 hod/7dnů v týdnu
- „Smysluplnost“ prováděných vyšetření (finanční náročnost)
- **Diagnostické a terapeutické konsekvence**

- **Ideální biomarker - 100% negativní predikce a sensitivita**
  > 85% pozitivní predikce a sensitivita

- **Přímý průkaz infekce : „speciálnosti“ u dětí (novorozenců) …množství krve, provádění anaerobních kultivací**

CD64- neutrofily

- The high-affinity Fc-IgG receptor (CD64) is expressed upon activation on neutrophils, macrophages, and some dendritic cell subsets, with different effector functions as opsonization and antibody-dependent cellular cytotoxicity.
- The IFN-gamma induces the CD64 expression on neutrophils in vitro, driving to a cellular immune response.

REVIEW ARTICLE

Neutrophil CD64 a Diagnostic and Prognostic Marker of Sepsis in Adult Critically Ill Patients: A Brief Review

Rupali Patnaik[1], Afzal Azim[2], Vikas Agarwal[3]

Abstract

Introduction: Sepsis is a life-threatening organ dysfunction with increased incidence of morbidity and mortality. Early diagnosis and prompt therapeutic intervention is the cornerstone of sepsis care. Biomarkers play an important role in sepsis having both diagnostic and prognostic implications. Neutrophil CD64 (nCD64) is a useful candidate biomarker for sepsis. Neutrophil CD64 also known as Fc receptor 1 (FcR1), is a high-affinity receptor present on neutrophils for Fc part of immunoglobulin-G (IgG) heavy chain. Its expression gets strongly upregulated in response to proinflammatory cytokines of infection within 4–6 hours. Neutrophil CD64 integrates function involving both innate and adaptive immune responses. The aim of this review is to present literature about nCD64 as a diagnostic and prognostic marker in patients with sepsis/septic shock.

Background: The authors searched articles over 13 years, i.e., from 2006 to 2019. They included articles written in English only and further reviewed the reference list of selected articles to obtain potentially relevant articles. Reviews, letters, commentaries, correspondences, case reports, conference abstracts, expert opinions, editorials, and animal experiments were excluded. Articles involving pediatric patients (≤18 years) were also excluded.

Review results: Several studies have indicated that nCD64 is a highly sensitive and specific marker for the diagnosis of sepsis. Various combinations of biomarkers have been used with nCD64 for a better diagnostic value. Neutrophil CD64 as a prognostic marker in critically ill patients needs to be explored more. Most of the existing literatures have highlighted its prognostic utility based on single value at enrolment. There are limited literatures on prognostic implications of serial trend and kinetics of nCD64.

Conclusion: Neutrophil CD64 is a useful diagnostic and prognostic marker of sepsis in critically ill patients. Additional studies are needed on nCD64 in sepsis based on sepsis-3 criteria. Further trials with large sample size are needed to establish prognostic implications of serial nCD64 trend.

Keywords: Fc receptor 1, Immunoglobulin-G, Neutrophil CD64, Sepsis, Septic shock.

Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23558

Table 2: Characteristic of studies using combination of neutrophil CD64 and other biomarkers for diagnosis of sepsis

Author	Gibot	Dimoula	Bauer	Jamsa
Year	2012	2014	2016	2017
Place	France	Belgium	USA	Finland
Clinical setting	ICU	ICU	ICU	ICU
Study population	Adult	Adult	Adult	Adult
Sample size	79	548	219	27
Disease severity	Sepsis, sever sepsis, septic shock	Sepsis, sever sepsis, septic shock	SIRS, sepsis	SIRS, sepsis
Control	No	No	99 (no SIRS, no infection source)	15 healthy controls
Measurement time	Within 12 hours of admission then on day 2	Within 24 hours of admission then daily	At enrolment	At admission
Number of times measured	Twice	Daily till death or discharge	Single time	Single time
CD64 assay	Flow cytometry	Flow cytometry	Flow cytometry	Flow cytometry
Unit of measurement	CD64 index	MFI	CD64 molecules per neutrophil and CD64% positive neutrophils	MESF
Cutoff	1.62	CD64: 230 MFI CRP: ≥3.5 mg/dL	≥1040.5 CD64 molecules/neutrophil and ≥49.96% positive neutrophils	9172 MESF
Other biomarkers	PCT, sTREM-1	CRP	CRP, PCT, APACHE IV	CRP, PCT
AUROC	Combination: 0.95 CD64: 0.93	CD64: 0.94	Combination: 0.90, CD64 molecules/neutrophil: 0.83, CD64% positive neutrophils: 0.81	
Sensitivity	CD64: 84.4%	Combination: 76%, CD64: 89%	CD64: 76.4%	
Specificity	CD64: 95.2%	Combination: 98%, CD64: 87%	CD64: 76.7%	

Table 3: Characteristic of studies using single value of neutrophil CD64 and prognosis of sepsis

Author	Livaditi	Cid	Chen	Olivgeris	Muzlovic
Year	2006	2011	2014	2015	2016
Place	Greece	Spain	China	Greece	Slovenia
Clinical setting	ICU	ED	ICU	ICU	ICU
Study population	Adult	Adult	Adult	Adult	Adult
Sample size	47	132	797	67	32
Disease severity	Sepsis, severe sepsis, septic shock	With (115) and without (17) bacterial infection	Infectious (381) and non-infectious disease (416)	SIRS (infectious and non-infectious)	VAP with or without sepsis
Control	12 healthy controls	No	No	No	No
Measurement time	First 24 hours of sepsis onset	One day after admission	First day within admission	Day 1 of SIRS	When temperature rises
CD64 assay	Flow cytometry	Flow cytometry	Flow cytometry	Flow cytometry	Flow cytometry
Unit of measurement	CD64 molecules per cell	CD64 index	Relative CD64 ratio {MFI (mean fluorescence intensity) on granulocytes ÷ MFI on lymphocytes}	Neutrophils expressing CD 64% and MFI (mean fluorescence intensity)	CD64 index
Cutoff	Severe sepsis prediction: 2566. Septic shock: 6512. 28-day mortality prediction: 6252	Survival prediction: CD64 index ≥1.5	For predicting ICU mortality value ≥1.835	Predicting infection in SIRS patient CD64%: >8, MFI of CD64 expression on neutrophils: >1.39	1.58 for possible bacterial infection
AUROC	Severe sepsis: 0.98, septic shock: 0.92, 28-day mortality: 0.75	0.71	0.752		0.92
Sensitivity	Severe sepsis: 94.6%, septic shock: 100%, 28-day mortality: 66.7	85%	For predicting ICU mortality: 60.55%	Predicting infection in SIRS patient CD 64%: 83%, MFI: 83%	100%
Specificity	Severe sepsis: 100%, septic shock: 86.7%, 28-day mortality: 73.9%	33%	For predicting ICU mortality: 80.23%	CD64%: 68%, MFI: 92%	85.7%

CD169- monocyty

- The Siglec-1 or sialoadhesin (CD169) is constitutively expressed on macrophages and has been associated with anti-viral and anti-tumor responses and with regulatory function.
- The CD169 ligand is modified-sialic acid and has been involved in removing exosomes by subcapsular macrophages in lymph nodes.
- The expression of CD169 on monocytes is induced after the type-I interferon (IFN) treatment in vitro.

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ORIGINAL ARTICLE

MIFlowCyt

ISAC CYTOMETRY Journal of Quantitative Cell Science PART A

CD169 and CD64 could help differentiate bacterial from CoVID-19 or other viral infections in the Emergency Department

Pénélope Bourgoin[1,2] | Thomas Soliveres[3] | Alexandra Barbaresi[3] | Anderson Loundou[4] | Inès Ait Belkacem[1,5] | Isabelle Arnoux[6] | Denis Bernot[6] | Marie Loosveld[6] | Pierre-Emmanuel Morange[2,6] | Pierre Michelet[2,3] | Fabrice Malergue[1] | Thibaut Markarian[2,3]

ISAC CYTOMETRY Journal of Quantitative Cell Science PART A

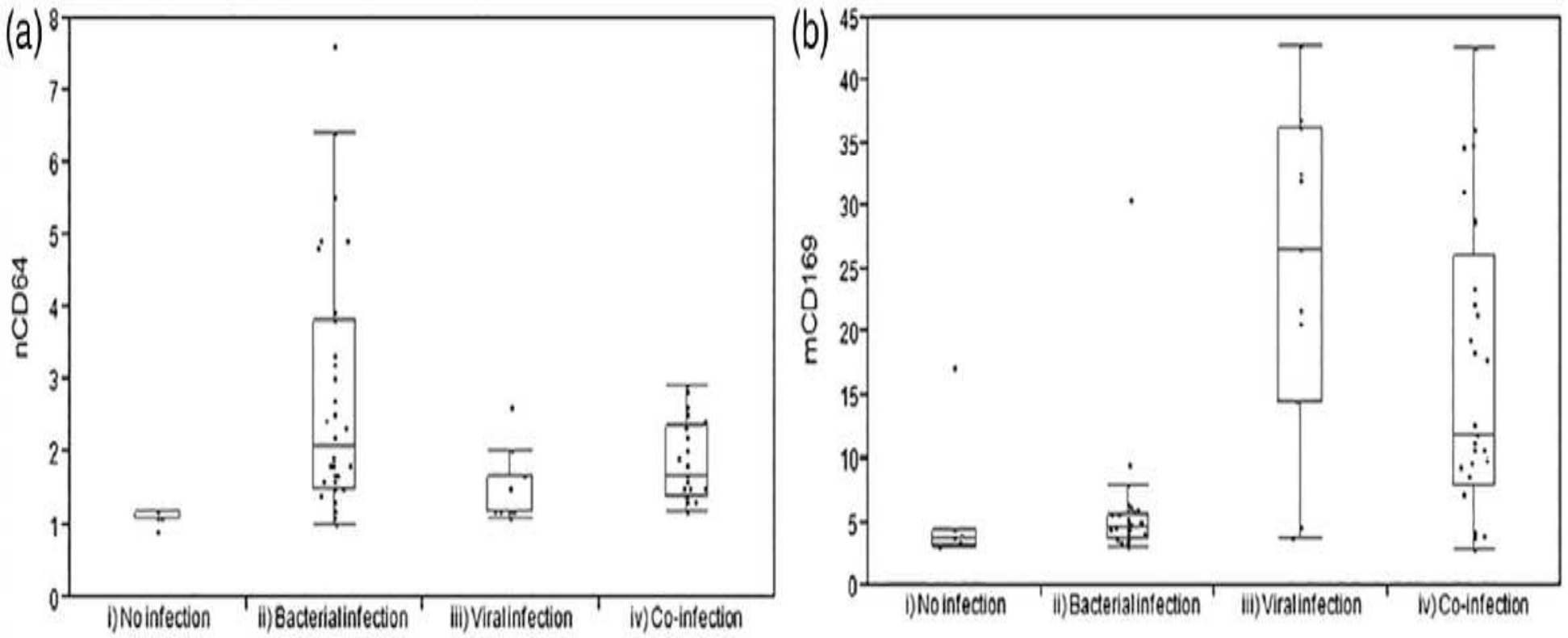
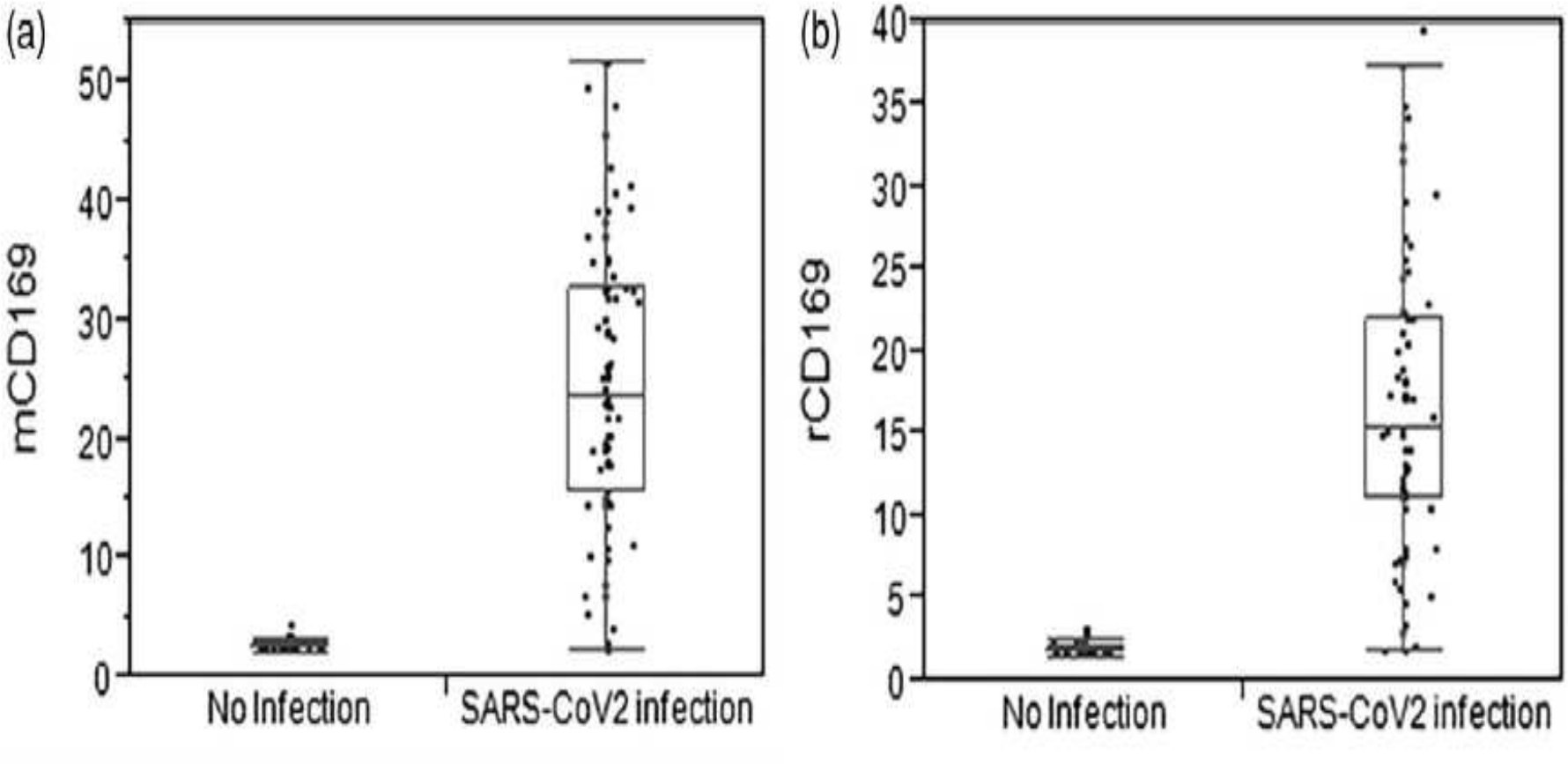


FIGURE 2 Biomarker levels for the four groups of patients. (A) nCD64 and (B) mCD169 levels of expression in patients with (i) no infection (control group), (ii) bacterial infection, (iii) viral infection, or (iv) co-infection

CD 64 **CD 169**


(a)
mCD169
50
40
30
20
10
0
No Infection
SARS-CoV2 infection
(b)
rCD169
40
35
30
25
20
15
10
5
0
No Infection
SARS-CoV2 infection

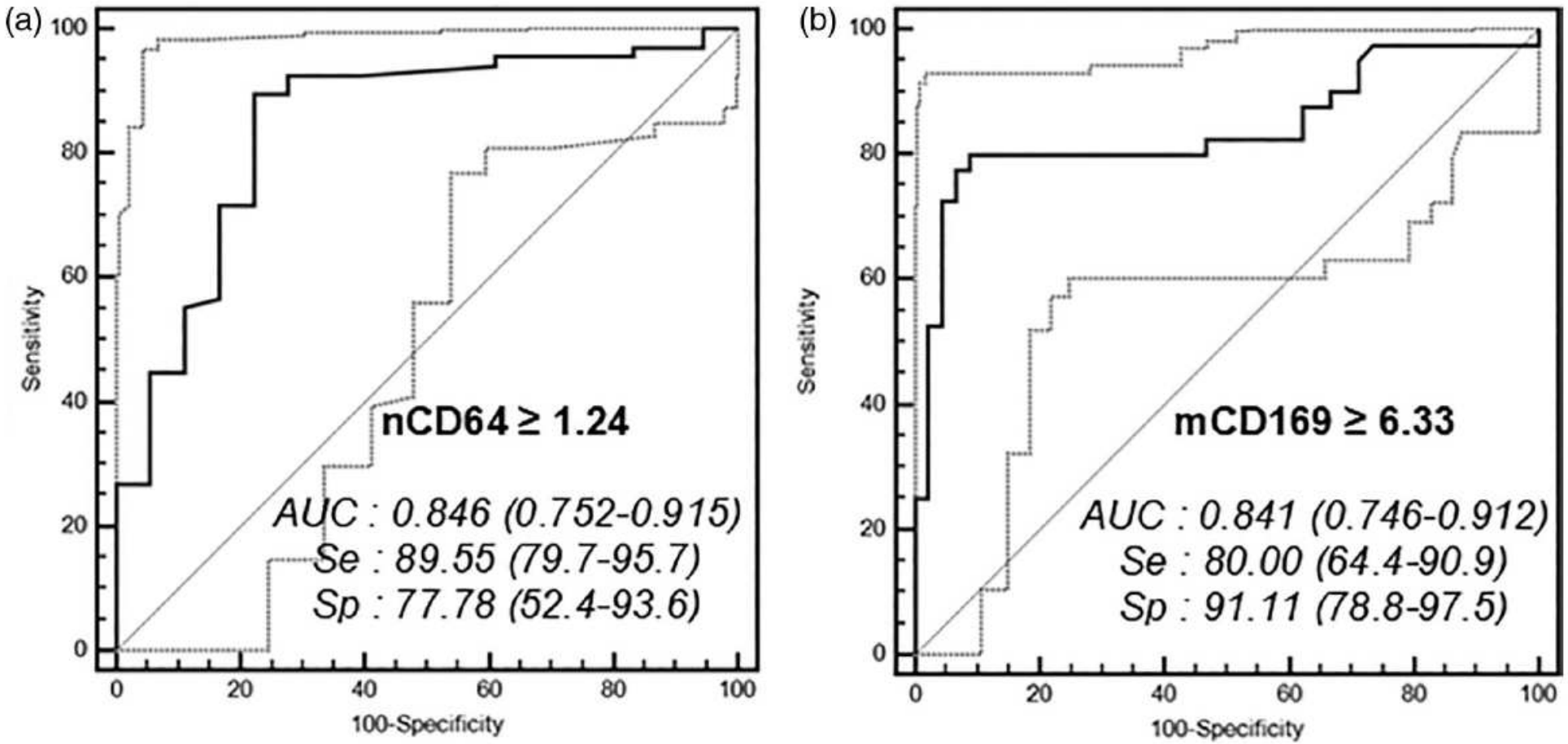


FIGURE 3 ROC analysis. ROC curves for the discrimination of bacterial infections with (A) nCD64 and of viral infections with (B) mCD169. Optimal thresholds for each biomarker are indicated with calculated values of specificity (Sp) and sensitivity (Se). Area under the curve (AUC) and 95% confidence interval are also given for each ROC analysis. Confidence interval curves are shown as light gray dotted lines

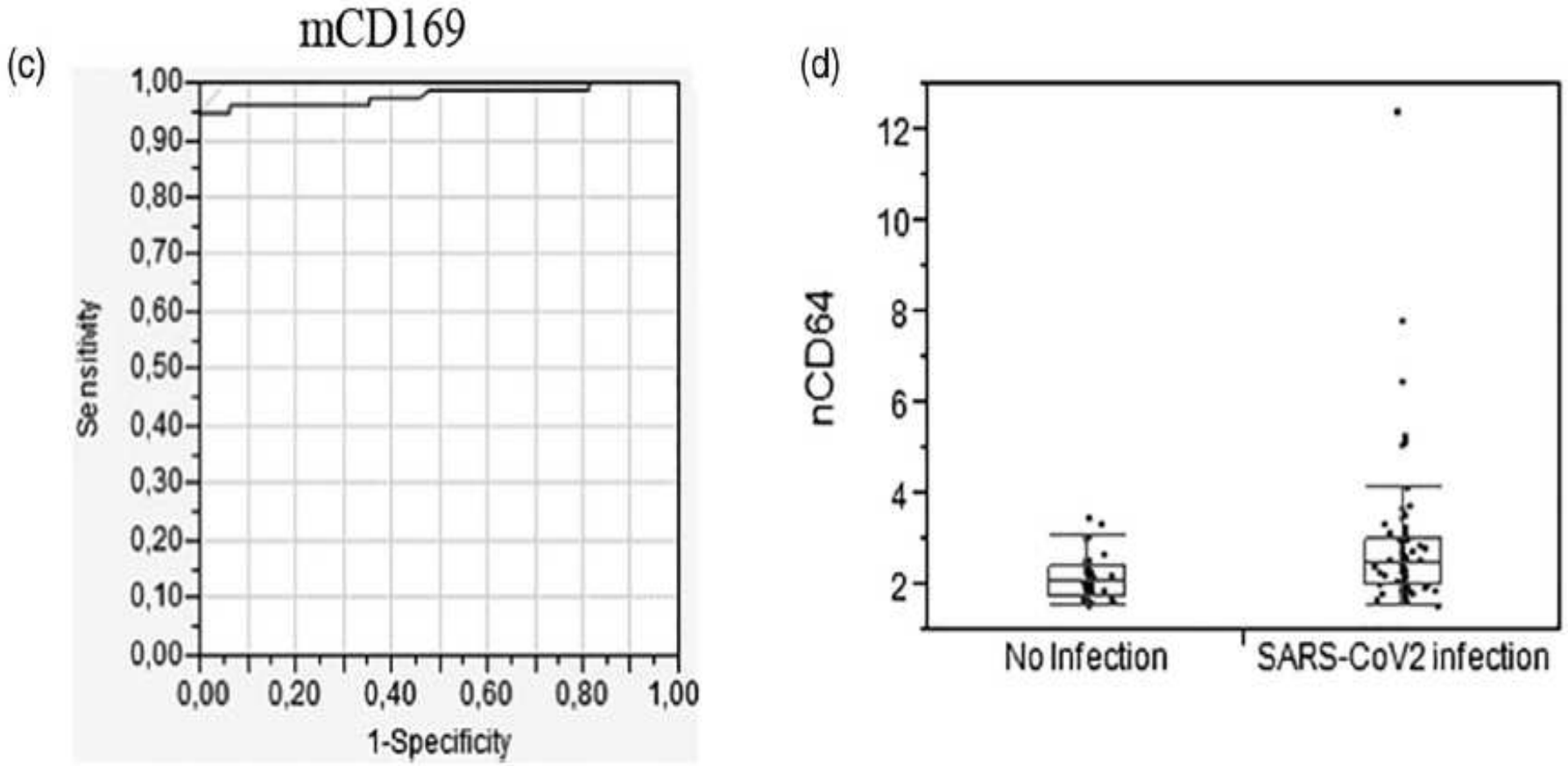


FIGURE 4 Biomarker levels and ROC analysis for SARS-CoV-2 infections. mCD169 (A) level, (B) ratio, and (C) ROC analysis for patients with SARS-CoV-2 infections, in comparison to healthy volunteers. (D) nCD64 level for the same patients

Original Article

Diagnostic Accuracy of CD64 for Sepsis in Emergency Department

Silvana Teixeira Dal Ponte, Ana Paula Alegretti[1], Diogo André Pilger[2], Gabriela Petitot Rezende[3], Giordanna Andrioli, Helena Cocolichio Ludwig[3], Luciano Diogo[4], Luciano Zubaran Goldani[3], Melina Loreto[3], Pauline Simas Machado[3], Renato Seligman

Departments of Emergency Medicine, [1]Clinical Pathology, [2]Hematology, [3]Internal Medicine and [4]Infectology, Clinical Hospital of Porto Alegre, Porto Alegre, Brazil

Abstract

Introduction: Sepsis is a systemic inflammatory response to suspected or confirmed infection. Clinical evaluations are essential for its early detection and treatment. Blood cultures may take as long as 2 days to yield a result and are not always reliable. However, recent studies have suggested that neutrophil CD64 expression may be a sensitive and specific alternative for the diagnosis of systemic infection. **Objective:** The objective of the study was to analyze the difference in CD64 values between subjects with systemic inflammatory response syndrome (SIRS), suspected or confirmed sepsis, who meet diagnostic criteria for SIRS upon arriving at an emergency department. **Materials and Methods:** This was a prospective observational cohort study, an accuracy study of CD64 prospectively evaluated. The sample consisted of 109 patients aged 18 years with criteria for SIRS on arrival to emergency department. CD64 expression was measured within 6 h of hospital admission and once again after 48 h. **Results:** ROC curve analysis suggested that a cutoff of 1.45 for CD64 expression could diagnose sepsis with a sensitivity of 0.85, a specificity of 0.75, an accuracy of 82.08%, a positive predictive value of 0.96, a negative predictive value of 0.38 and a positive likelihood ratio of 3.33. The area under the curve was 0.83. **Conclusion:** CD64 seems to be a useful, sensitive, and specific biomarker in discriminating between SIRS and sepsis.

Keywords: CD64 index, sepsis, systemic inflammatory response syndrome

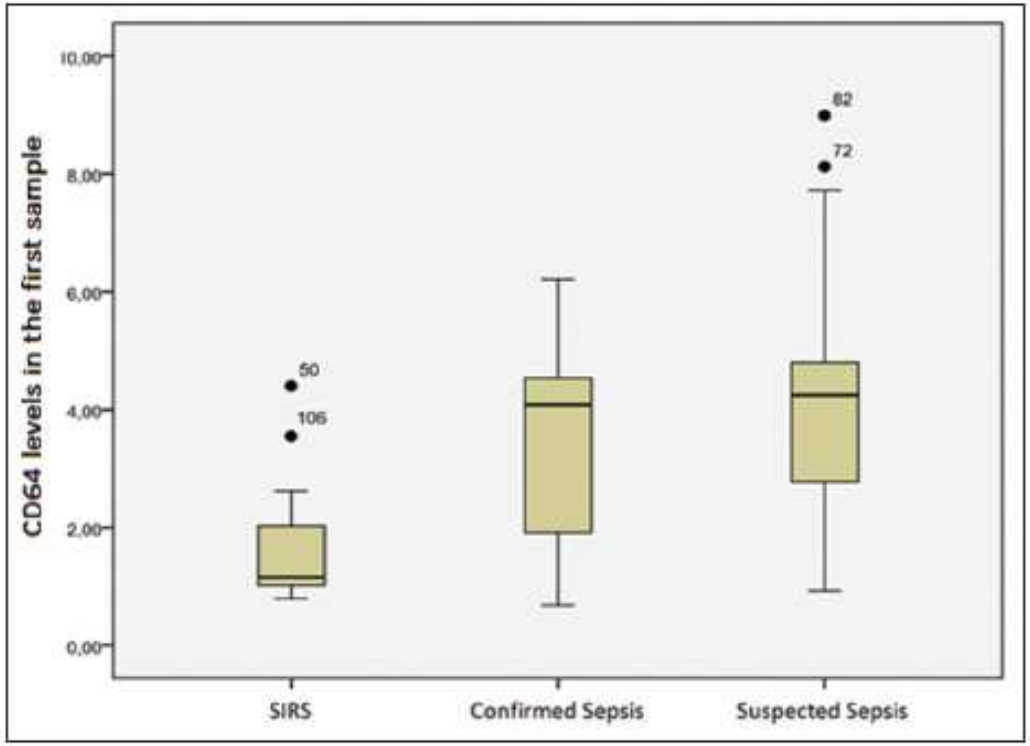


Figure 1: CD64 levels in the first sample for systemic inflammatory response syndrome, confirmed sepsis and suspected sepsis

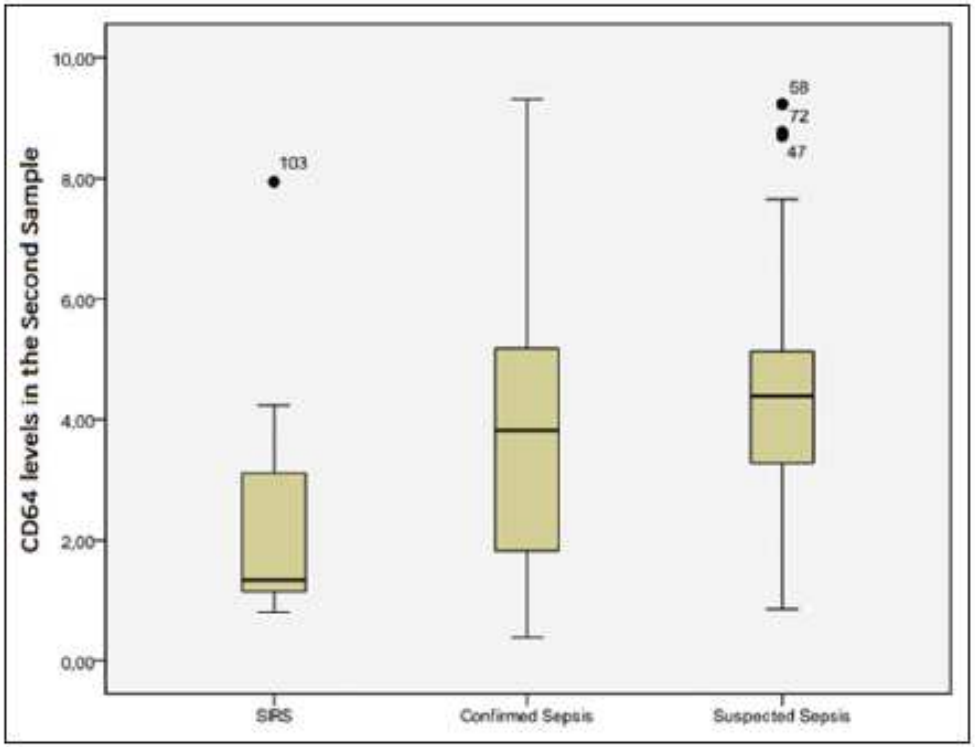


Figure 2: CD64 levels in the second sample for systemic inflammatory response syndrome, confirmed sepsis and suspected sepsis

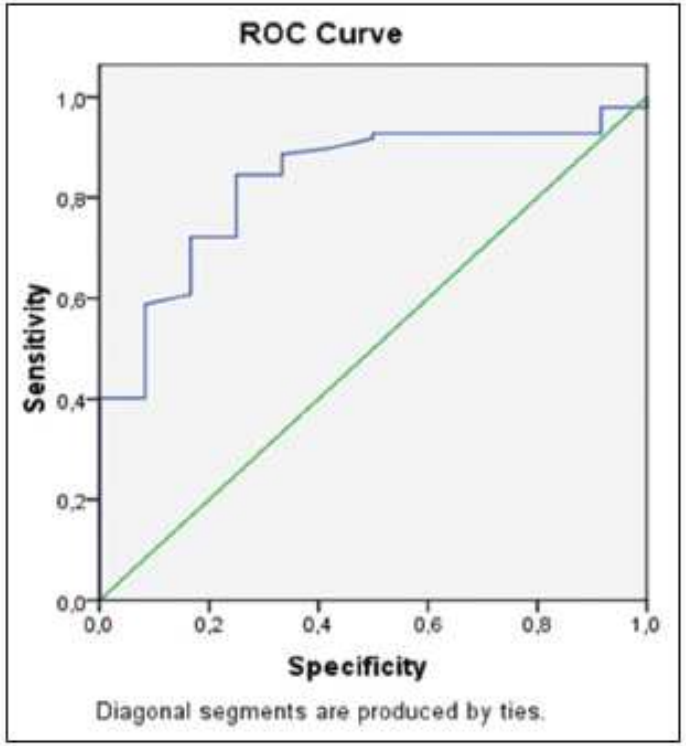


Figure 3: The receiver operating characteristic curve

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https://doi.org/10.1186/s44158-023-00090-x

Journal of Anesthesia,
Analgesia and Critical Care

ORIGINAL ARTICLE Open Access

Kinetics of CD169, HLA-DR, and CD64 expression as predictive biomarkers of SARS-CoV2 outcome

Arianna Gatti[1*], Paola Fassini[2], Antonino Mazzone[3], Stefano Rusconi[4], Bruno Brando[1] and Giovanni Mistraletti[2]

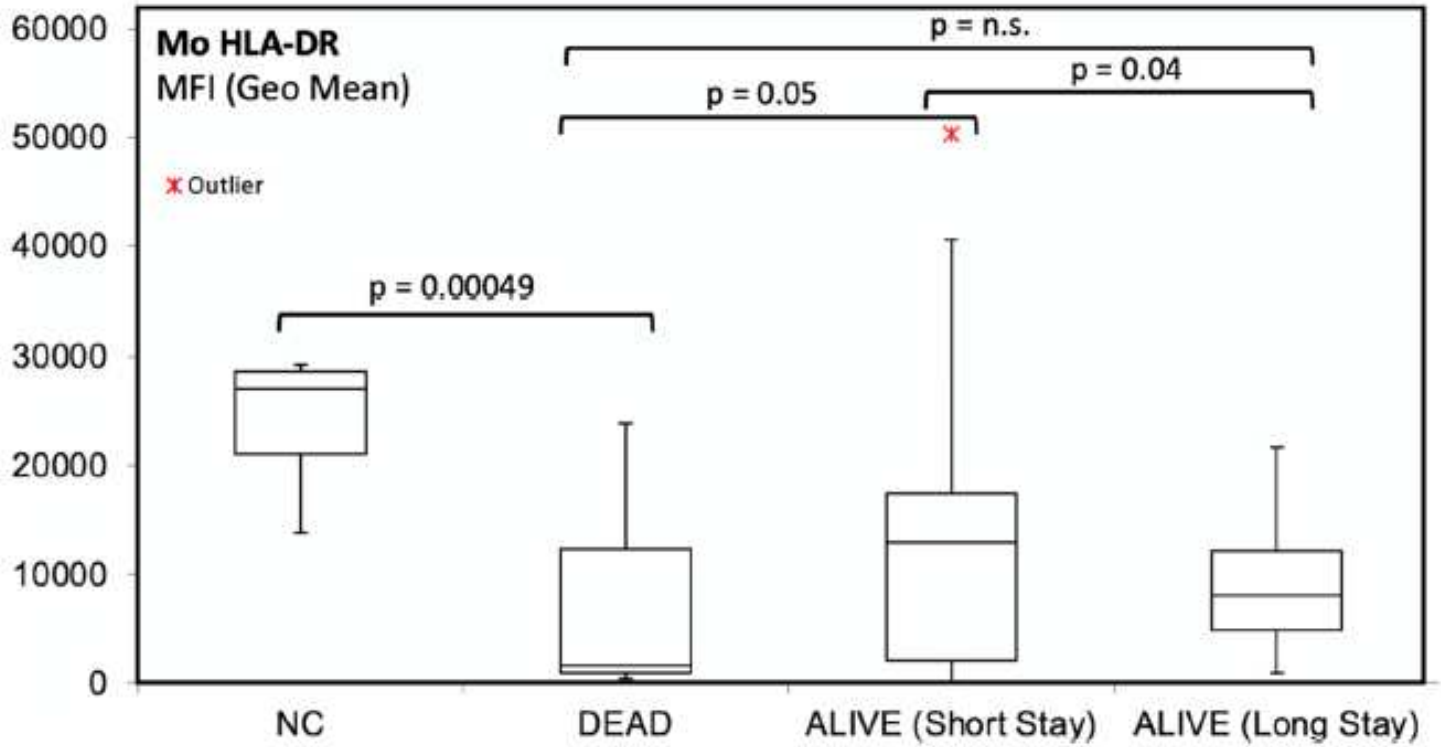

Fig. 3 Expression of monocyte HLA-DR as an indicator of immune competence in SARS-CoV2 infected patients. The lowest level of expression was observed in patients who died for multiple complications, whereas patients with prolonged hospital stay showed a lower HLA-DR expression level, as compared with patients with shorter and more favorable clinical course and normal control (NC) subjects

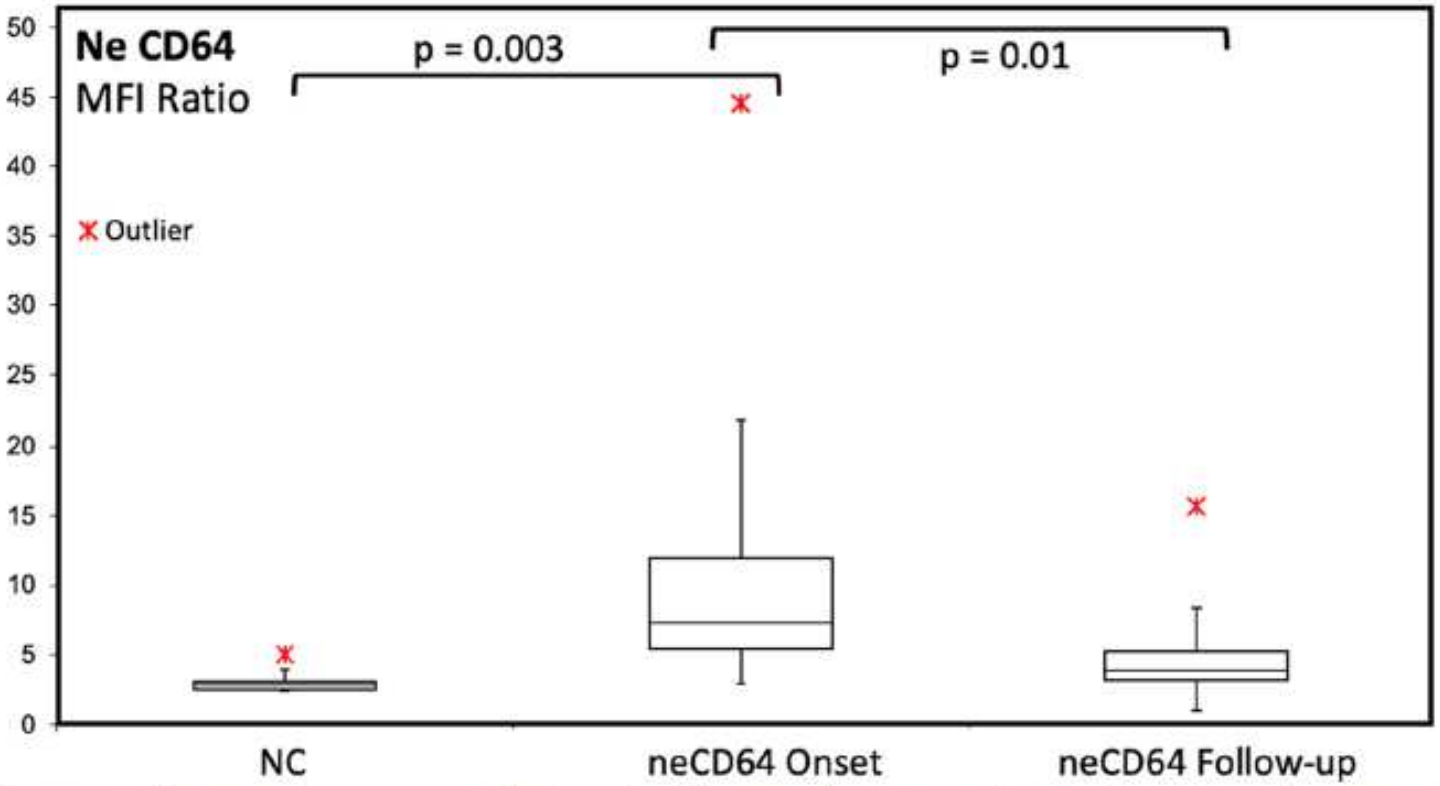

Fig. 2 Expression of neutrophil CD64 at disease onset and during the follow-up. A mild upregulation of neCD64 is observed in the majority of patients, while very high values were detectable only in patients with overt bacteremia and sepsis

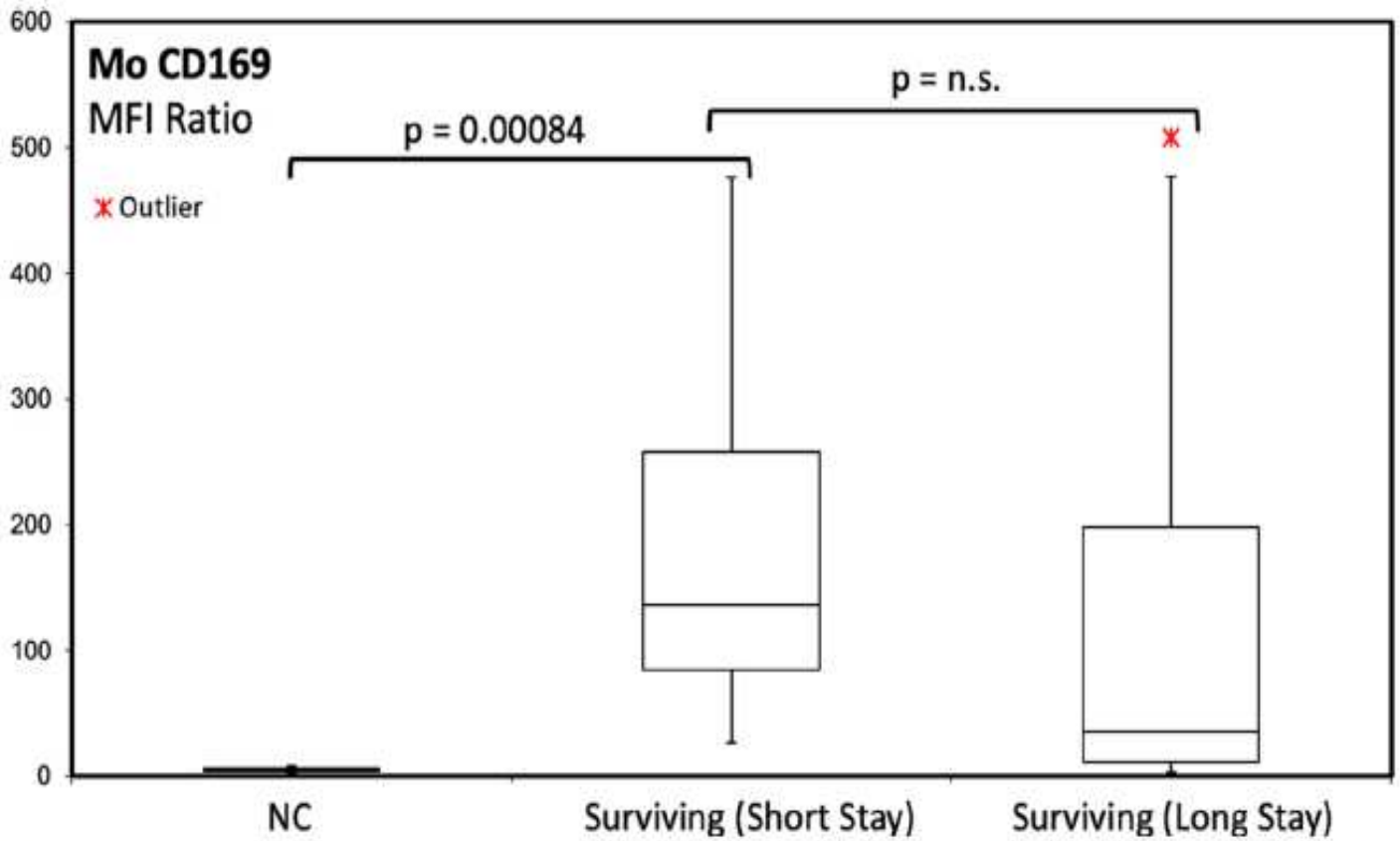

Fig. 1 Expression of monocyte CD169 in acutely SARS-CoV2-infected patients in the early phase of the disease and during the follow-up, according to the length of hospital stay. The overall trend to moCD169 downregulation in the long-term did not reach statistical significance, due to some patients with persistent positive swabs for SARS-CoV2

Meta-Analysis > BMC Infect Dis. 2021 Apr 26;21(1):384. doi: 10.1186/s12879-021-06064-0.

Diagnostic value of neutrophil CD64, procalcitonin, and interleukin-6 in sepsis: a meta-analysis

Shan Cong [1], Tiangang Ma [1], Xin Di [1], Chang Tian [1], Min Zhao [1], Ke Wang [2]

Affiliations + expand

PMID: 33902476 PMCID: PMC8072745 DOI: 10.1186/s12879-021-06064-0

Free PMC article

Results: Fifty-four articles were included in the study. The pooled sensitivity, specificity, and AUC of neutrophil CD64 for the diagnosis of sepsis were 0.88 (95% confidence interval [CI], 0.81-0.92), 0.88 (95% CI, 0.83-0.91), and 0.94 (95% CI, 0.91-0.96), respectively. The pooled sensitivity, specificity, and AUC of PCT for the diagnosis of sepsis were 0.82 (95% CI, 0.78-0.85), 0.78 (95% CI, 0.74-0.82), and 0.87 (95% CI, 0.83-0.89), respectively. Subgroup analysis showed that the AUC for PCT diagnosis of intensive care unit (ICU) sepsis was 0.86 (95% CI, 0.83-0.89) and the AUC for PCT diagnosis of non-ICU sepsis was 0.82 (95% CI, 0.78-0.85). The pooled sensitivity, specificity, and AUC of IL-6 for the diagnosis of sepsis were 0.72 (95% CI, 0.65-0.78), 0.70 (95% CI, 0.62-0.76), and 0.77 (95% CI, 0.73-0.80), respectively.

Conclusions: Of the three biomarkers studied, neutrophil CD64 showed the highest diagnostic value for sepsis, followed by PCT, and IL-6. On the other hand, PCT showed a better diagnostic potential for the diagnosis of sepsis in patients with severe conditions compared with that in patients with non-severe conditions.

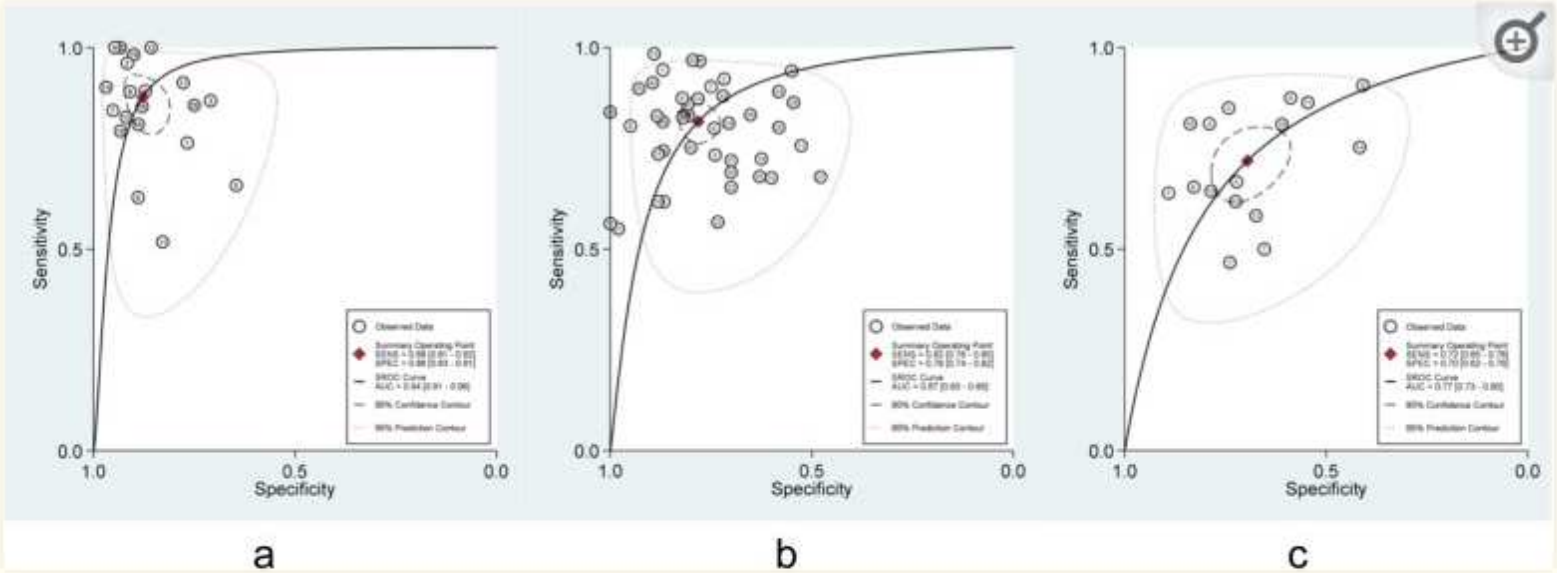

Fig. 3

Summary receiver operator characteristic (SROC) of CD64 (**a**) across 20 studies, PCT (**b**) across 43 studies, and IL-6 (**c**) across 16 studies

SOUHRN

- CD 64 na neutrofilech a CD 169 na monocytech představují velmi dobré biomarkery pro diagnózu sepse a rozlišení virové a bakteriální etiologie systémové zánětlivé odpovědi

- Technologie je běžně dostupná- průtoková cytometrie a dostatečným způsobem validovaná