



Immunomonitoring of CD64 and HLA-DR biomarkers in ICU patients with high risk of developing sepsis

Predictive, diagnostic and prognostic study

Ester Lucas Varas¹; Oriol Plans Galván²; Fernando Arméstar Rodríguez²; Bibiana Quirant Sánchez^{1, 3}, Eva M^a Martínez-Cáceres^{1, 3}

¹Immunology Department. Laboratori Clínic de la Metropolitana Nord, Hospital Germans Trias i Pujol, Badalona (Spain)

²Intensive Care Unit, Hospital Germans Trias i Pujol, Badalona (Spain)

³Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona, Bellaterra (Spain)





1. Introduction. Incidence and Mortality



About
31,5 millions
of people develop sepsis



Survivors
with increased
morbidity



5,3 millions
associated deaths



1. Introduction. Sepsis Definition

According to Sepsis-3¹:



Sepsis. Life-threatening organ dysfunction caused by a dysregulated host response to infection. Clinical diagnostic



Septic Shock. Subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are profound enough to substantially increase mortality

1. (Singer et al., 2016)



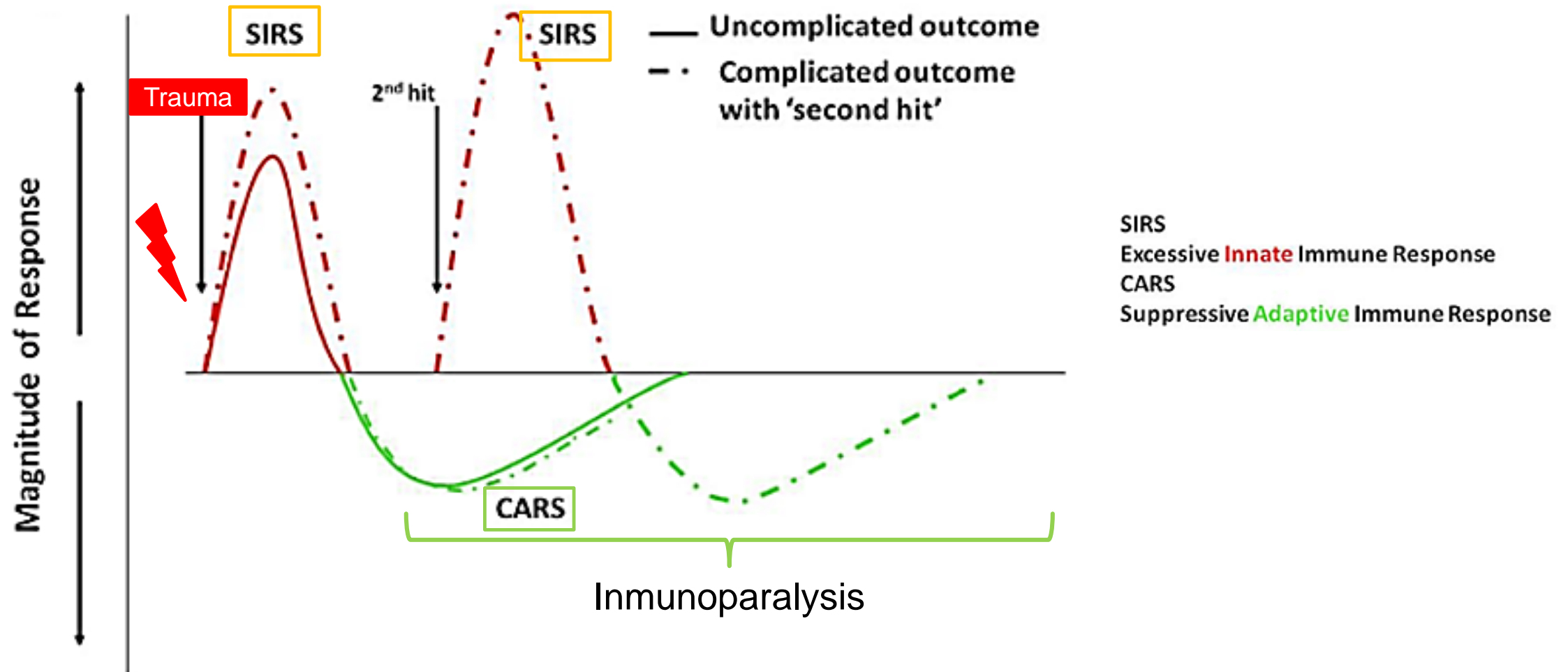
1. Introduction. Diagnostic Markers

Microbiological culture	CRP	PCT	Lactate
<ol style="list-style-type: none">1. Confirmatory infection test2. Response time3. False negatives4. The infection is rarely confirmed microbiologically	<ol style="list-style-type: none">1. High Sensibility Low Specificity2. Non specific acute phase protein3. Normality: CRP<10mg/ml	<ol style="list-style-type: none">1. High Specificity Low Sensibility2. Normality: <2ng/ml	<ol style="list-style-type: none">1. Reflects tissue hypoperfusion and anaerobic metabolism

CRP: C-Reactive Protein

PCT: Procalcitonin

1. Introduction. Immune response associated with the infection



(Gentile et al., 2012)



1. Introduction. Immunological markers

The immunological markers used for immunomonitoring:



HLA-DR

- § MHCII à APCs
- § Reports on **immunocompetent status**



CD64

- § Early marker of **infection**
- § CD64 is constitutively expressed in monocytes
 - ↑ [IL-6] à neutrophil activation à ↑ CD64 expression in neutrophils



2. Hypothesis

01

Immunological monitoring of the HLA-DR and CD64 biomarkers in risk patients allows early diagnostic of immunoparalysis and sepsis

02

Immunomonitoring allows the clinical evolution of these patients to be determined



3. Objectives

Preventive

Monitoring the immunocompetent status of patients at high risk of infections in the ICU using the **HLA-DR** biomarker

Diagnostic

Assessment of the sensibility and specificity of the **CD64** biomarker in critical patients who develop infection during follow-up

Prognostic

Serial monitoring of the immune response using **nCD64** and **mHLA-DR** to determine the proinflammatory and anti-inflammatory balance



4. Material

- | Prospective longitudinal study
(January 2018 - May 2018)
- | Collaboration ICU – Microbiology –
Immunology Hospital Germans Trias i
Pujol (Badalona)

Inclusion Criteria

- | >18 years admitted to the ICU
- | Hospitalization prognosis >15 days
- | Neurological pathology or Acute
pancreatitis

Exclusion Criteria

- | Admission in the study >24h of
hospitalization
- | Discharge or Exitus 72h after the inclusion
- | Corticosteroid therapy

5. Methods. Immunological Monitoring

Table. Immunological Monitoring

T0	T1	T2	T3	T4	T5
Day 0	Day 3	Day 6	Day 9	Day 12	Day 15

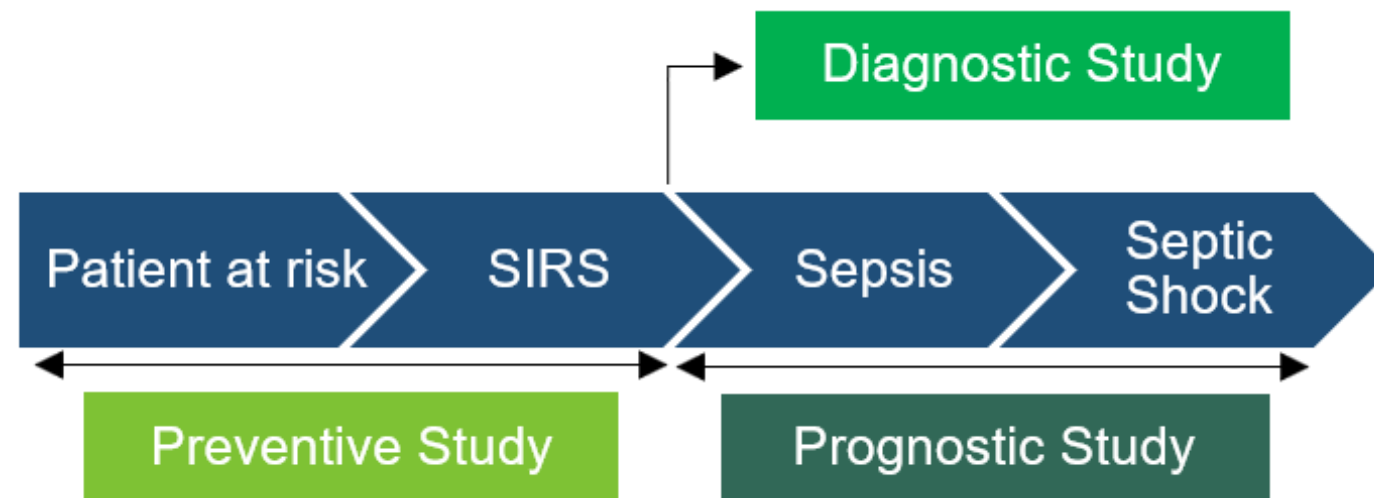


Figure. Monitoring of the preventive, diagnosis and prognosis study

5. Methods. Immunological Variables

Preventive Study

Evaluates the ability if the immune system to control the infection

mHLA-DR MFI

% mHLA-DR

$$\text{Index HLA-DR} = \frac{\text{mHLA-DR}}{\text{IHLA-DR}}$$

Diagnostic Study

Rapid and early detection of infection

nCD64 MFI

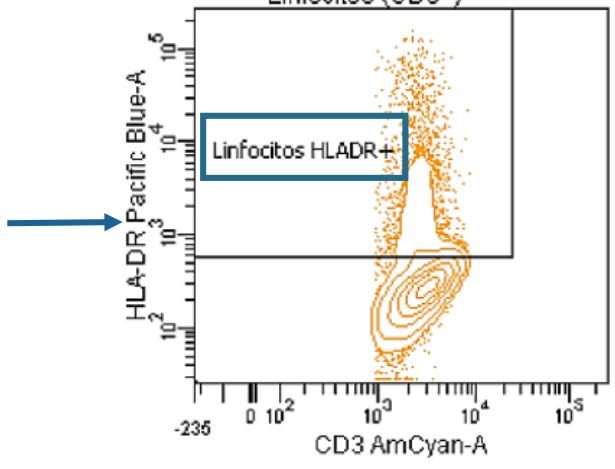
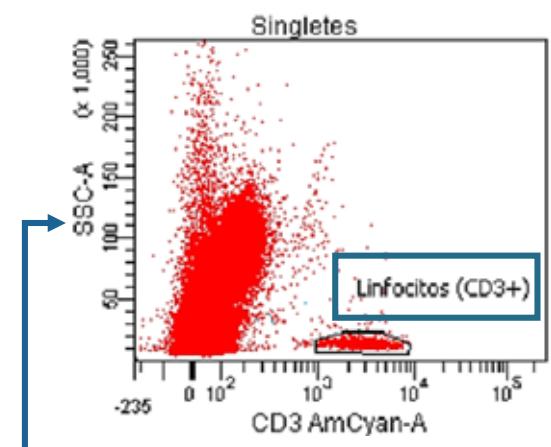
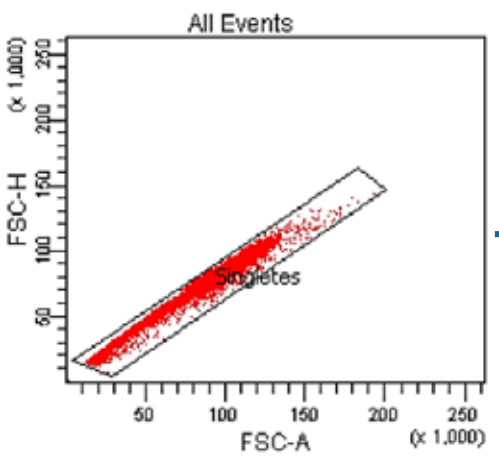
$$\text{Index CD64} = \frac{\text{nCD64}}{\text{mCD64}}$$

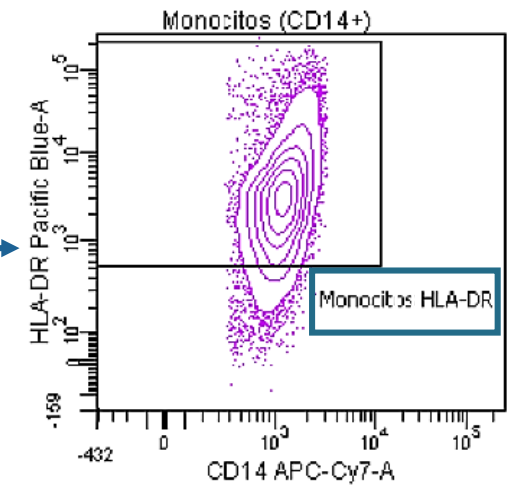
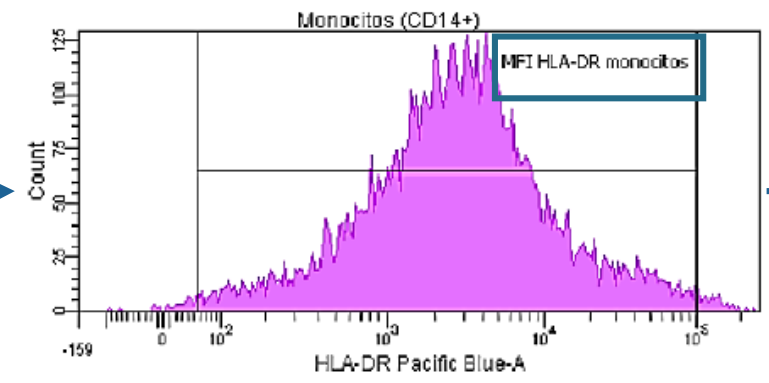
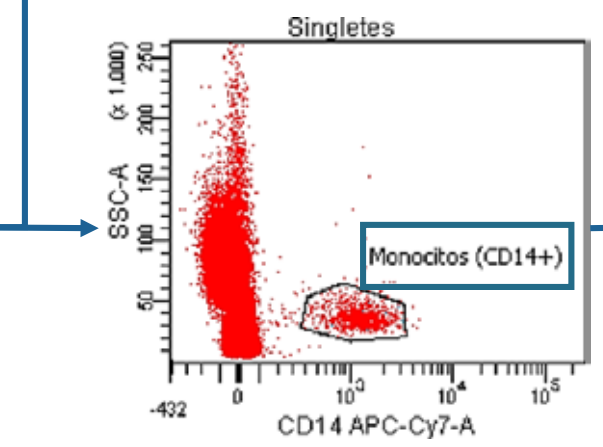
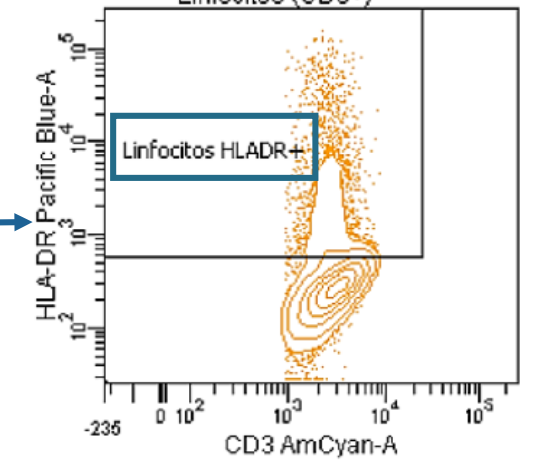
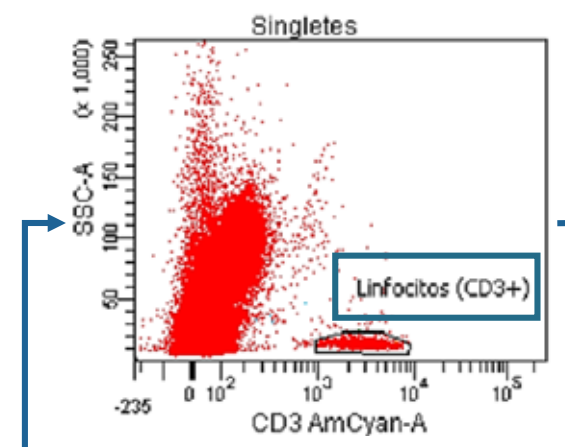
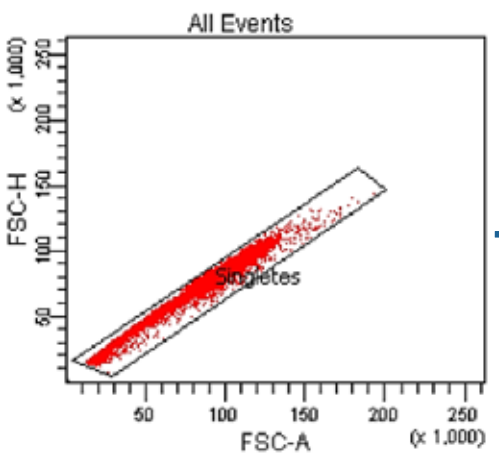
$$\text{Index Sepsis} = \frac{\text{nCD64}}{\text{mHLA-DR}}$$

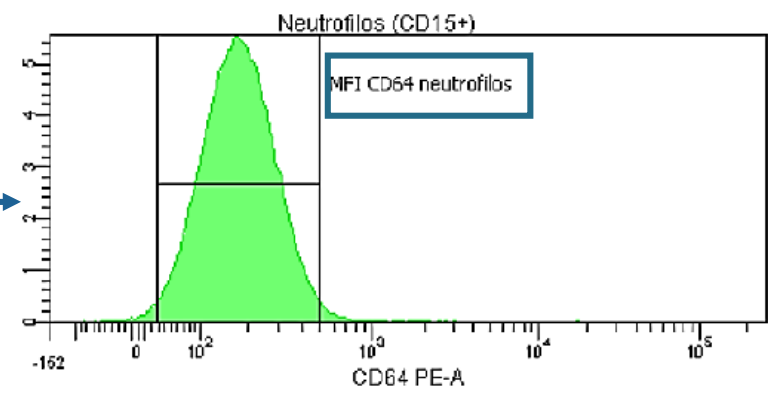
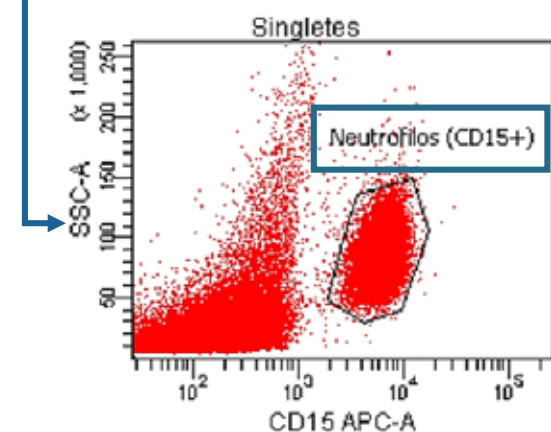
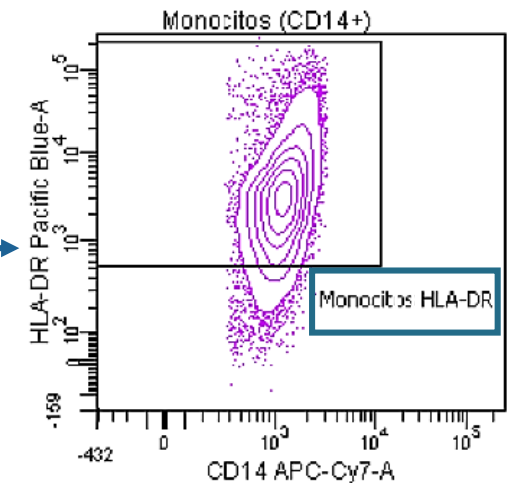
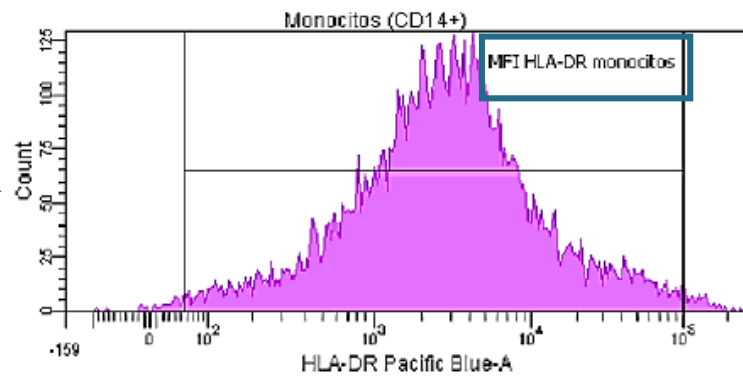
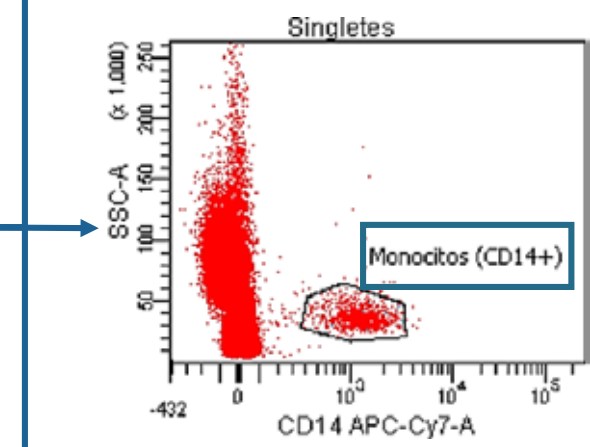
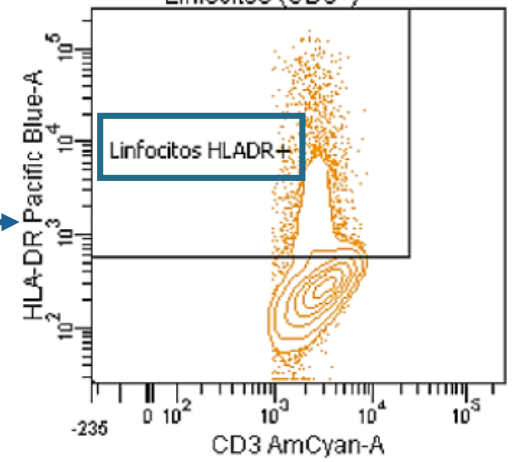
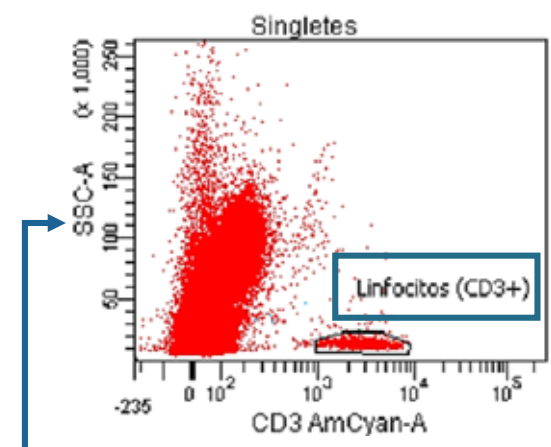
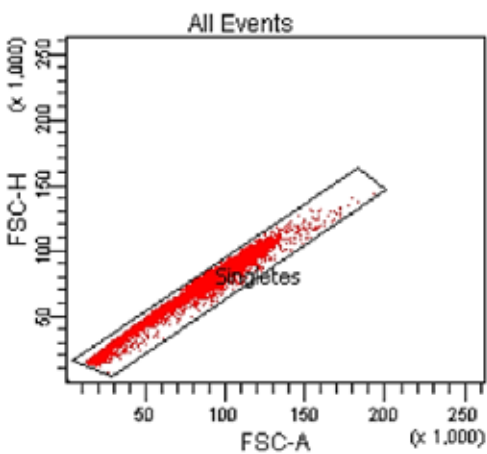
Prognostic Study

Monitoring of changes in proinflammatory and anti-inflammatory expression

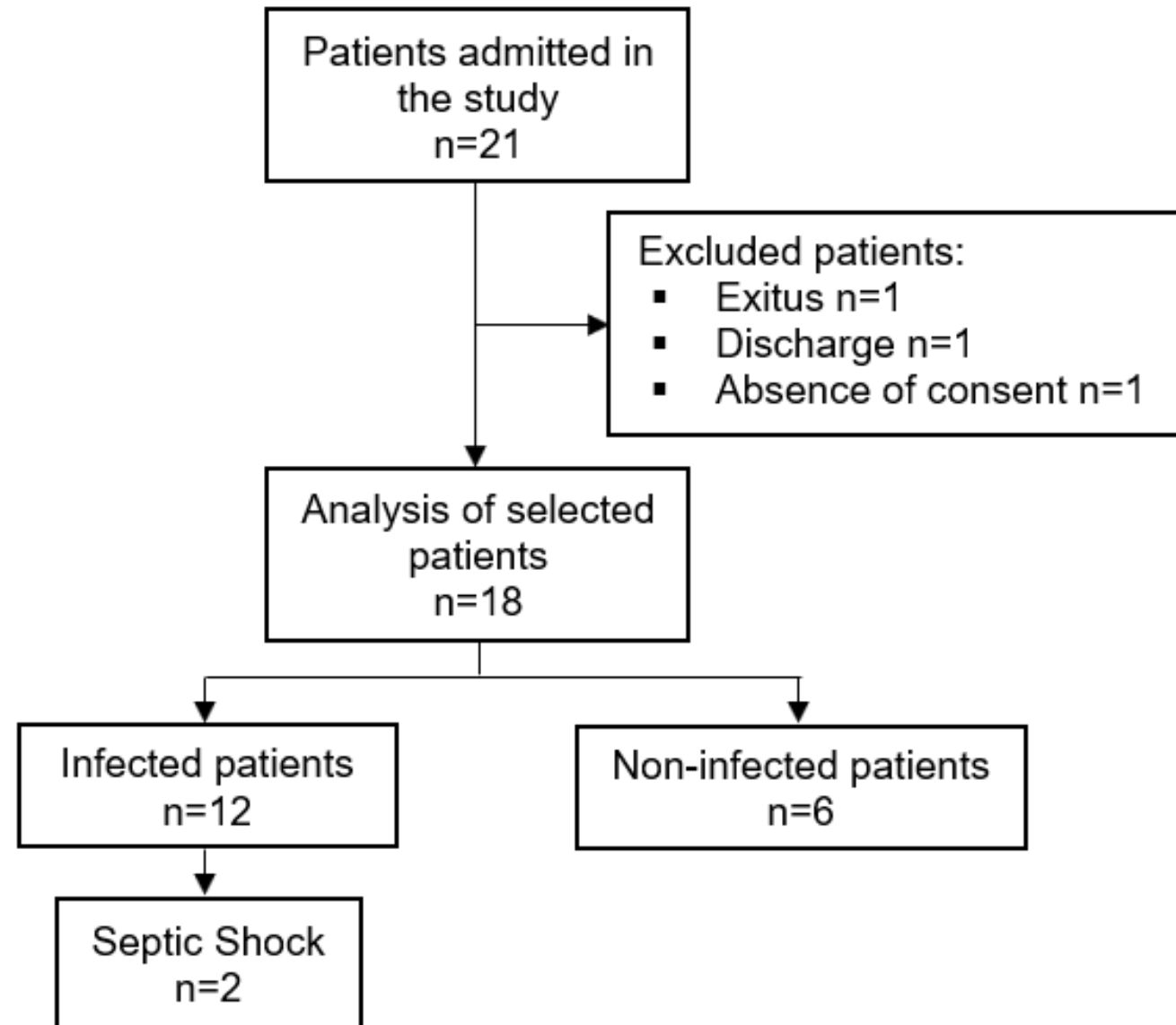
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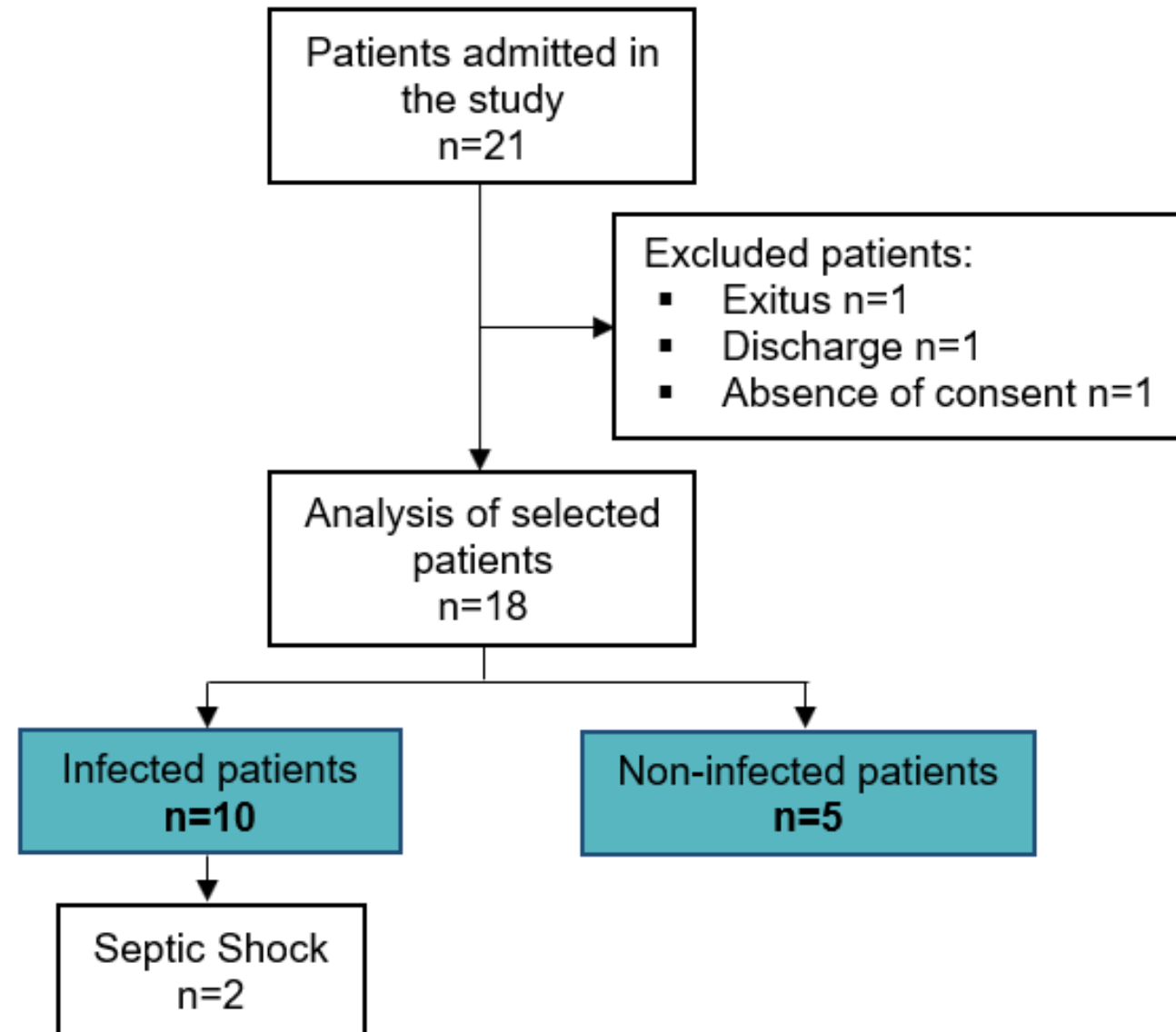




6. Results. Included Patients



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6. Results. Preventive Biomarkers

Expression of HLA-DR in monocytes

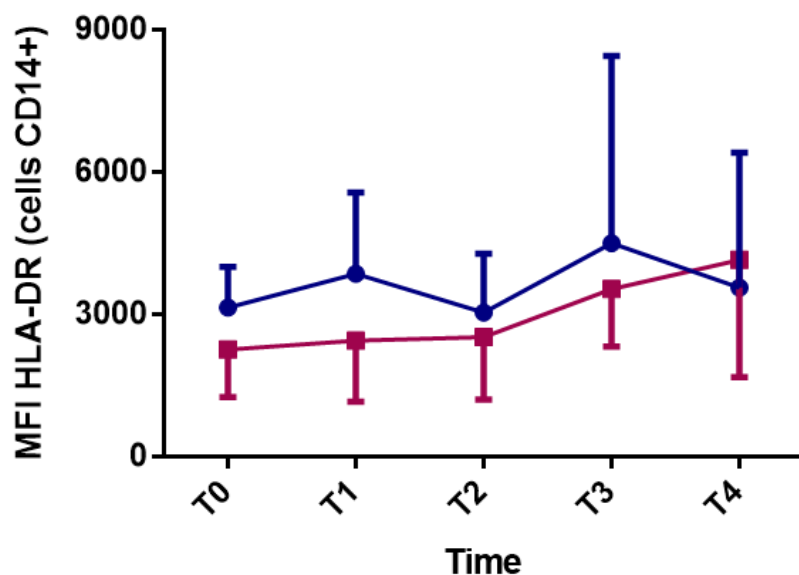


Figure. Comparison of the HLA-DR MFI in monocytes in serial determinations every 3 days between patients infected (n=10) and non-infected (n=5)

HLA-DR Index

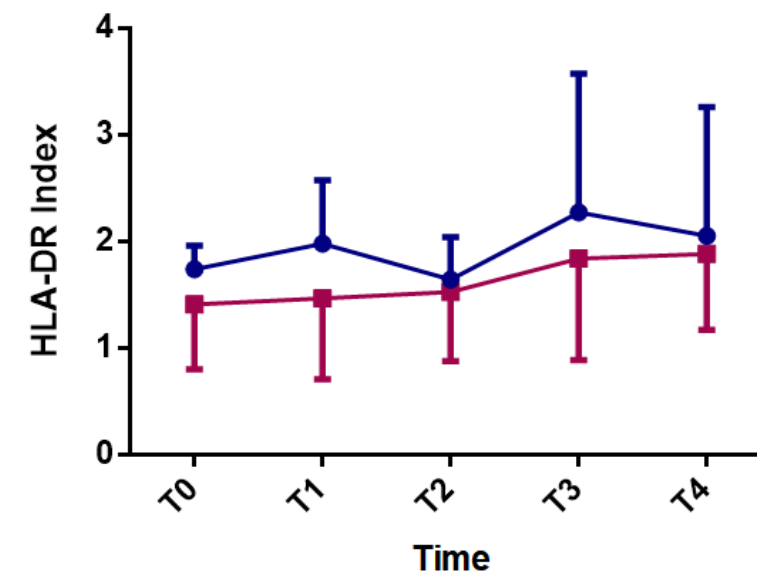
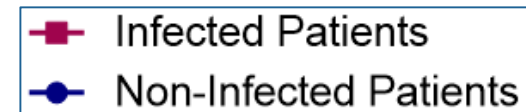


Figure. Comparison of HLA-DR Index in serial determinations every 3 days between patients infected (n=10) and non-infected (n=5)



6. Results. Preventive Biomarkers

Expression of HLA-DR in monocytes

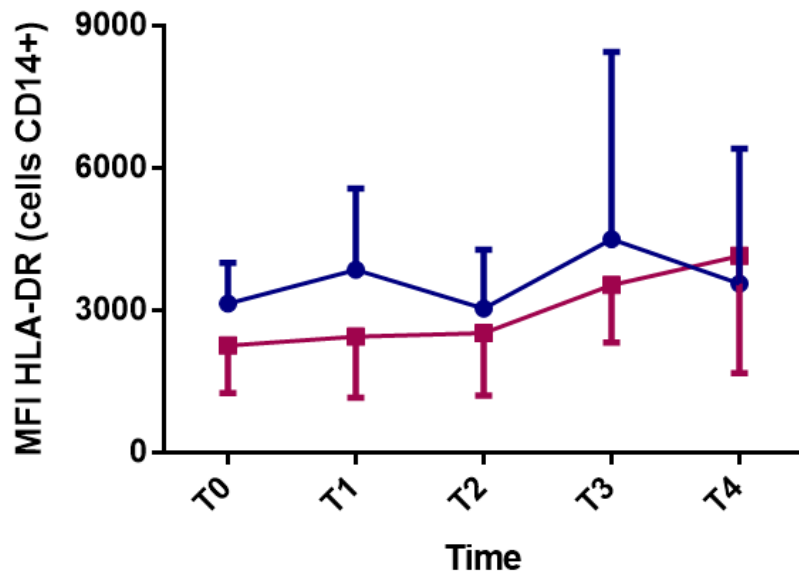


Figure. Comparison of the HLA-DR MFI in monocytes in serial determinations every 3 days between patients infected (n=10) and non-infected (n=5)

Percentage of monocytes expressing HLA-DR

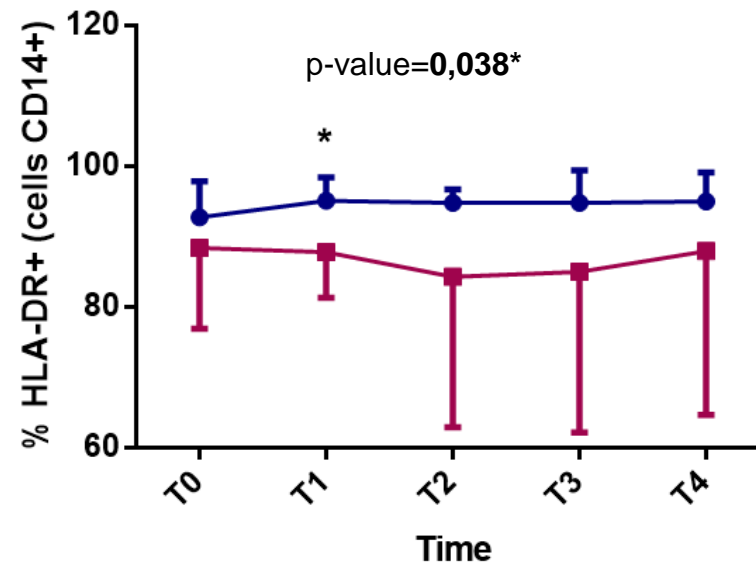


Figure. Comparison of the percentage of monocytes in serial determinations every 3 days between patients infected (n=10) and non-infected (n=5) *p-value<0,05

HLA-DR Index

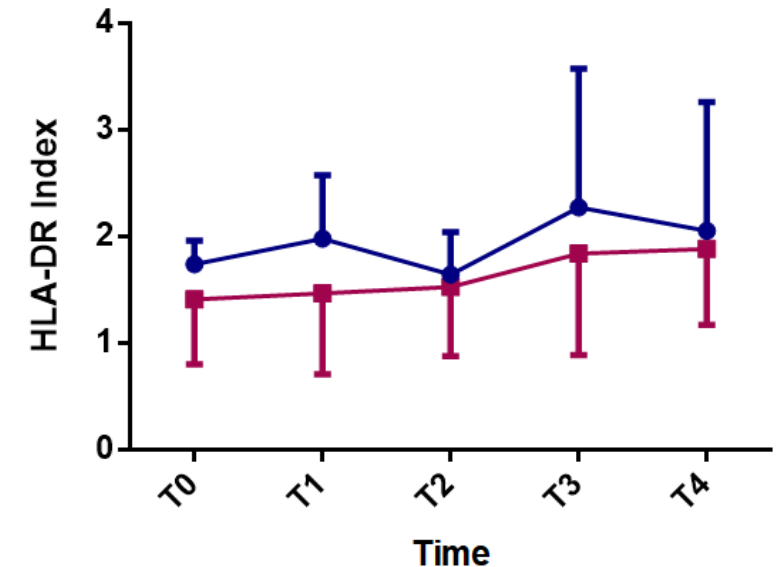
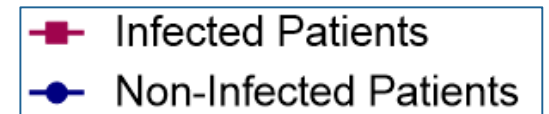


Figure. Comparison of HLA-DR Index in serial determinations every 3 days between patients infected (n=10) and non-infected (n=5)



6. Results. Diagnostic Biomarkers

Expression of CD64 in neutrophils

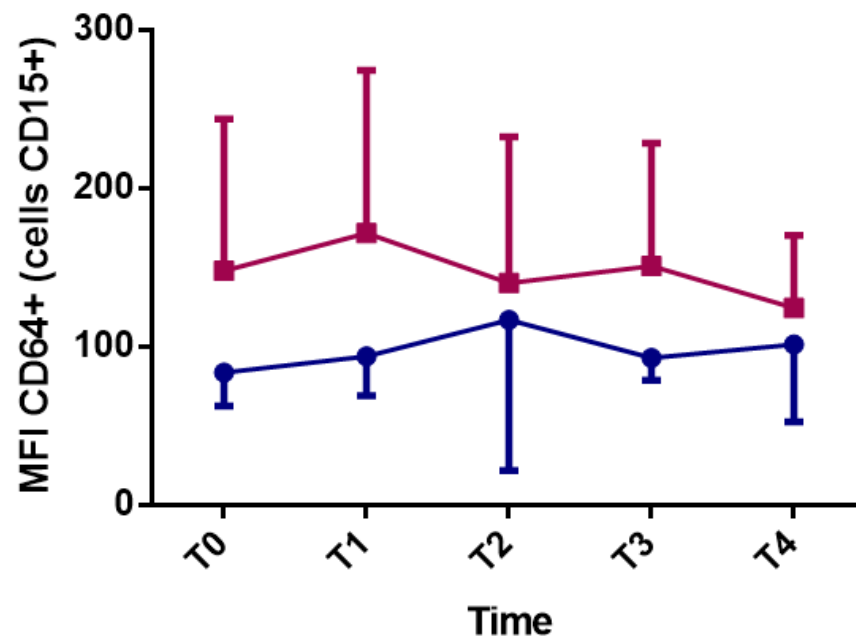


Figure. Comparison of CD64 MFI in neutrophils in serial determinations every 3 days between patients infected (n=10) and non-infected (n=5)

CD64 Index

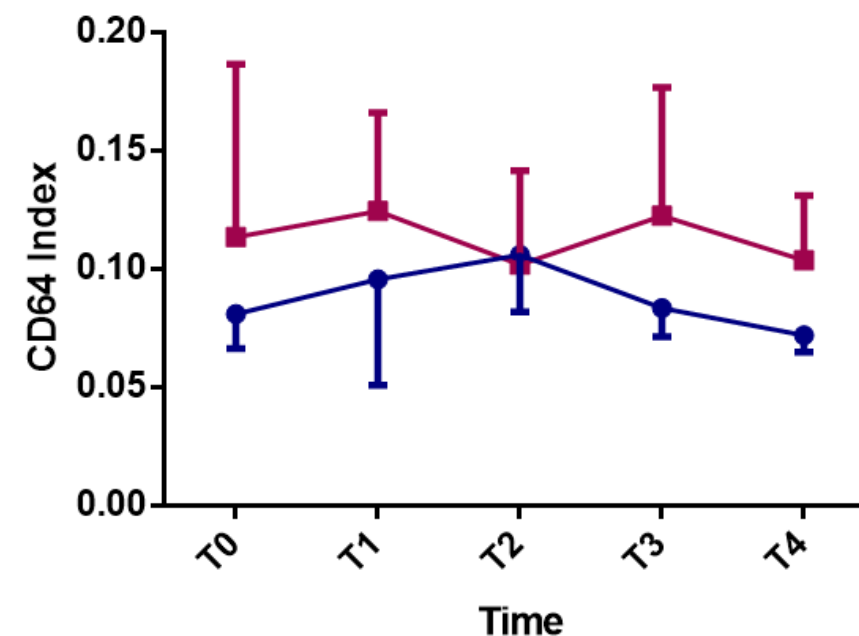
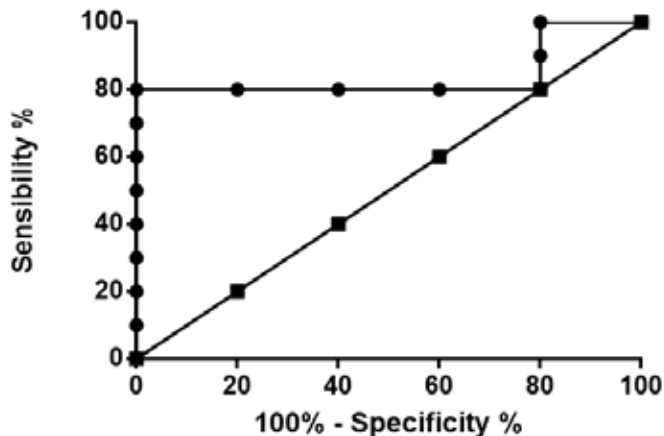


Figure. Comparison of CD64 Index in serial determinations every 3 days between patients infected (n=10) and non-infected (n=5)

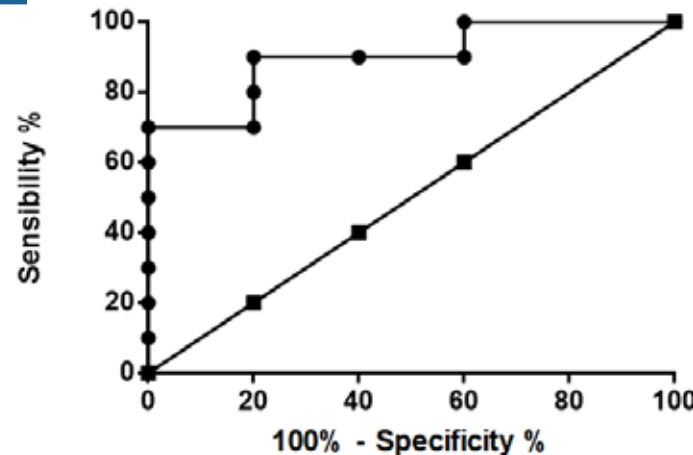


6. Results. Diagnostic Biomarkers



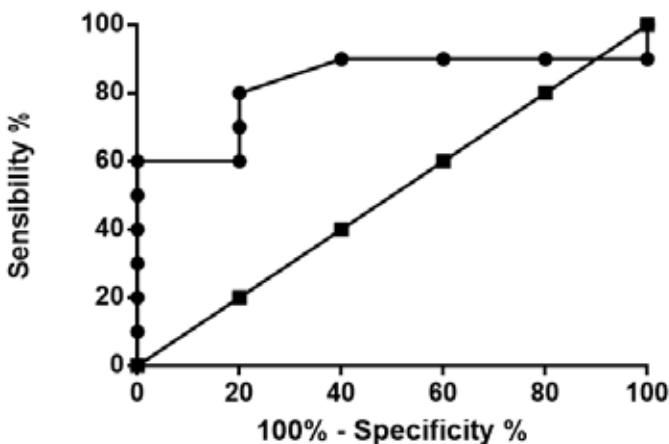
AUC	P-Value
0,840	0,037*
CRP >10,75 mg/ml (Sensibility:80% Specificity: 60%)	

Figure. ROC curve of CRP



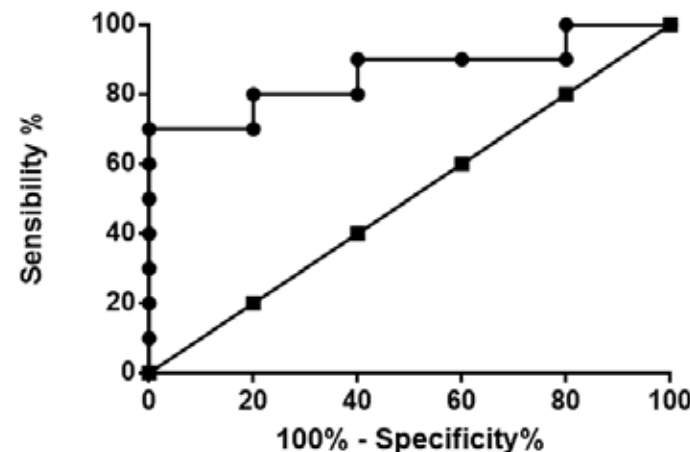
AUC	P-Value
0,900	0,014*
PCT >2,08 ng/ml (Sensibility:40% Specificity: 100%)	

Figure. ROC curve of PCT



AUC	P-Value
0,830	0,043*
nCD64 >98,5MFI (Sensibility:80% Specificity: 80%)	

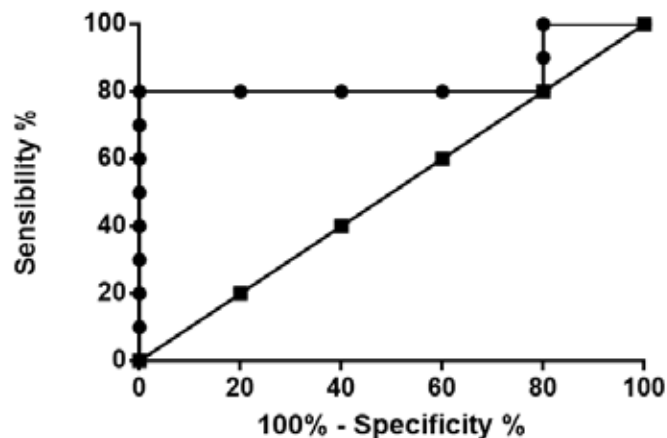
Figure. ROC curve of nCD64



AUC	P-Value
0,850	0,032*
Sepsis Index >0,035 (Sensibility:80% Specificity: 80%)	

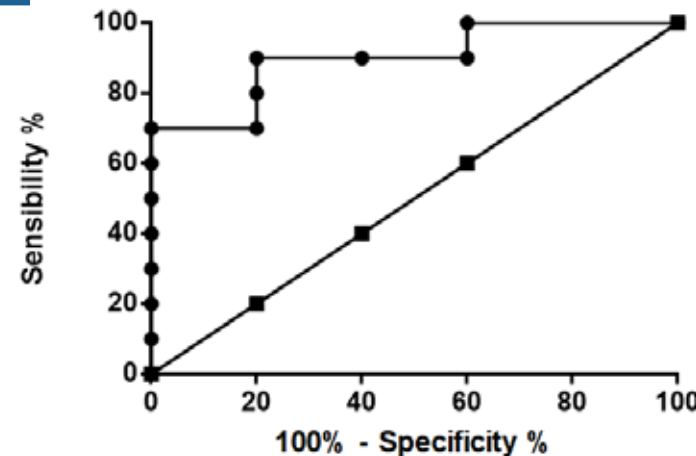
Figure. ROC curve of Sepsis Index

6. Results. Diagnostic Biomarkers



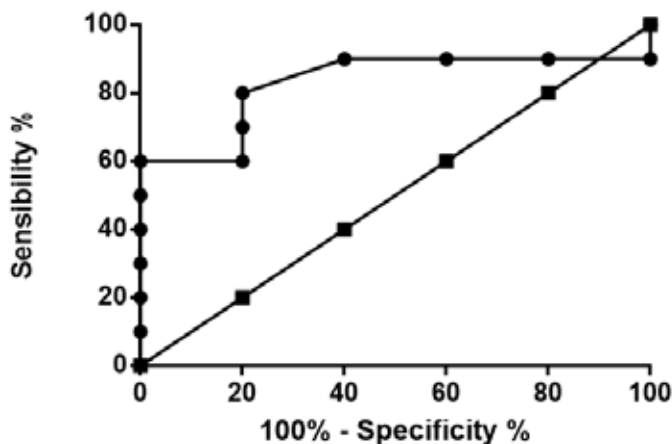
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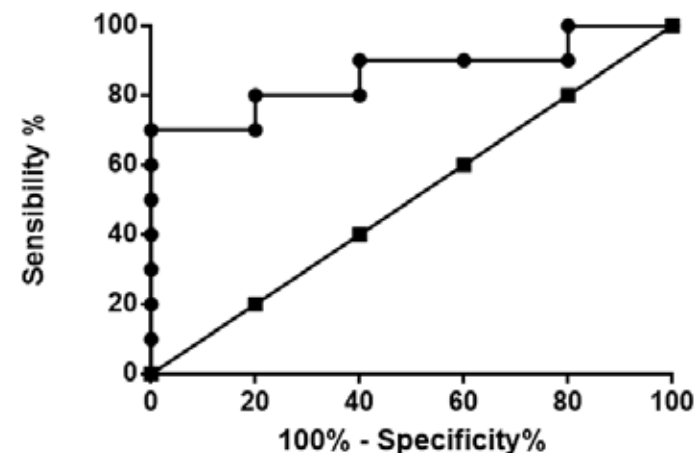
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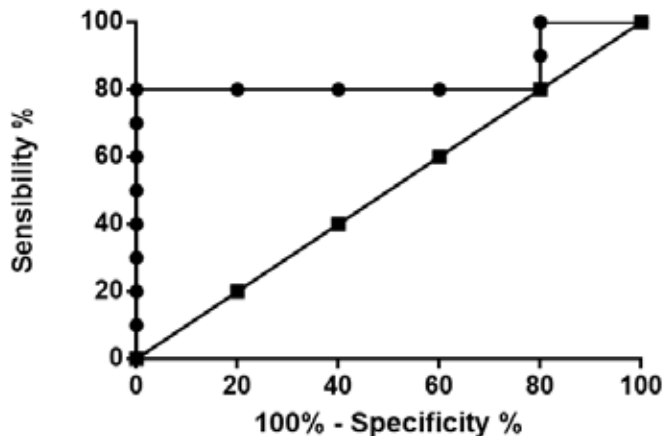
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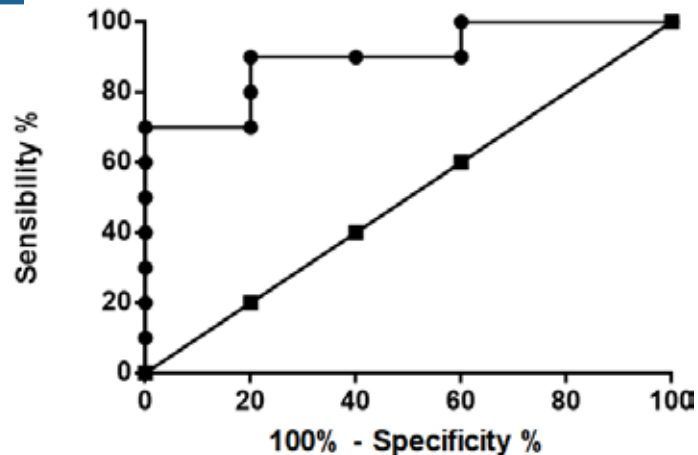
Figure. ROC curve of Sepsis Index

6. Results. Diagnostic Biomarkers



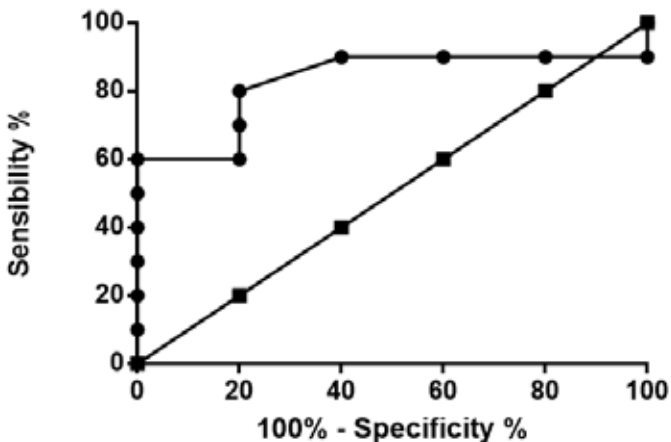
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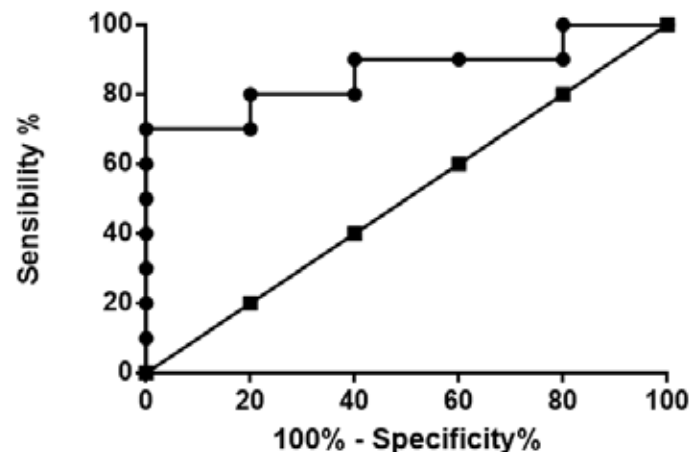
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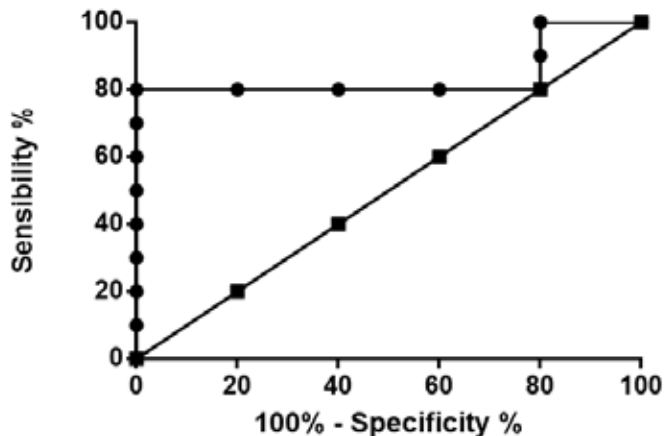
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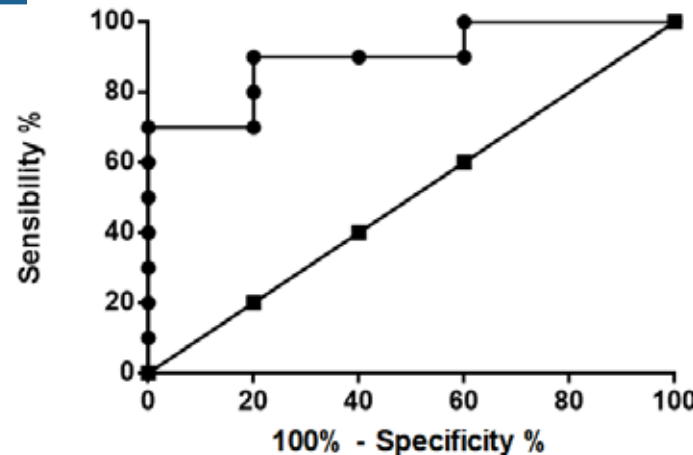
Figure. ROC curve of Sepsis Index

6. Results. Diagnostic Biomarkers



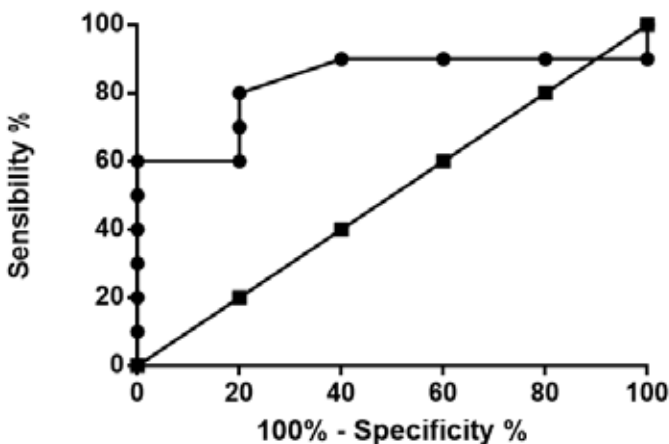
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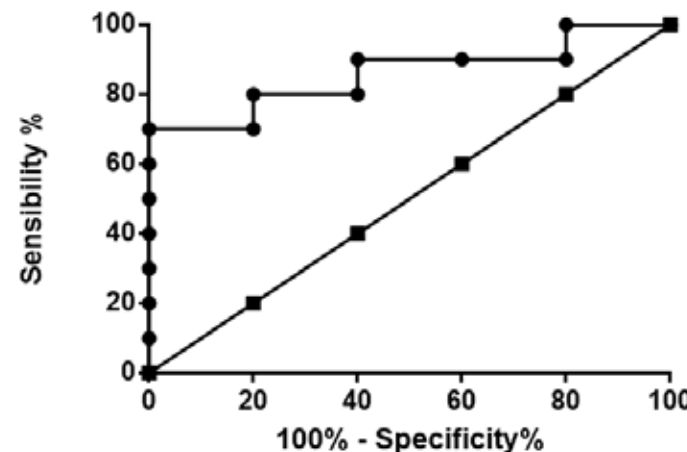
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6. Results. Diagnostic Biomarkers

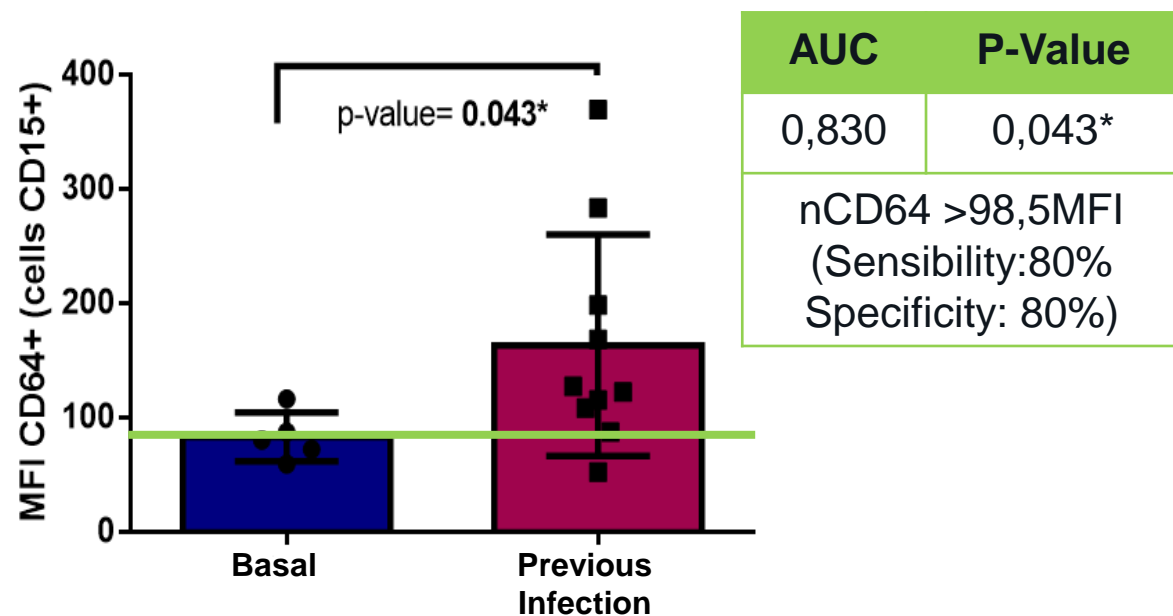


Figure. Comparative cut-off MFI nCD64 between infected patients (n=10) and non-infected (n=5)

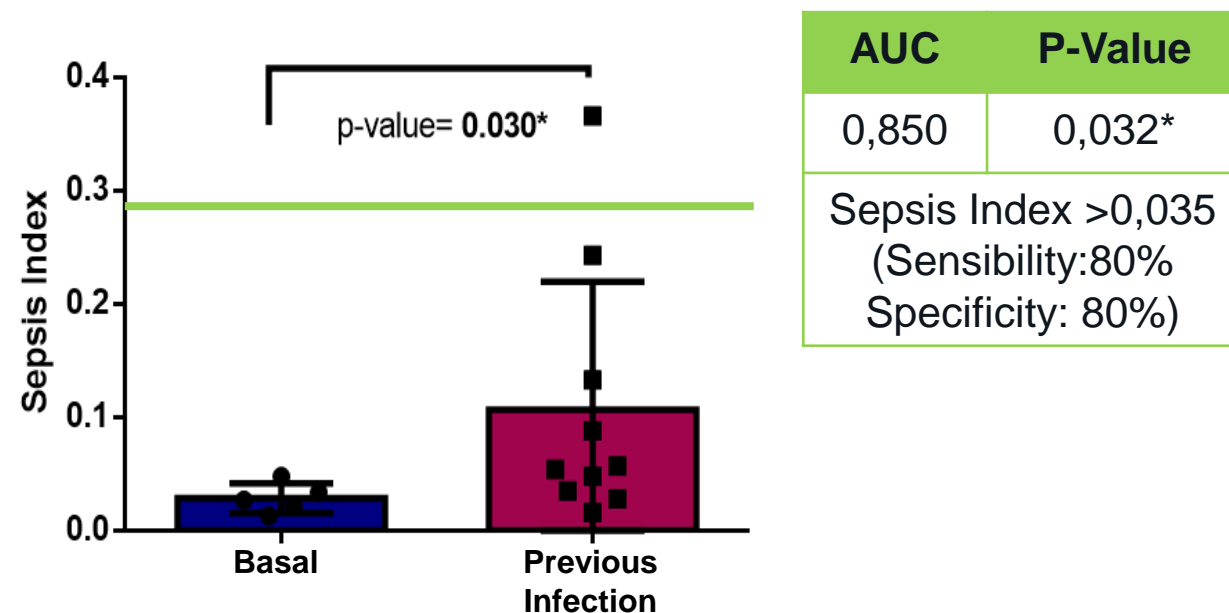


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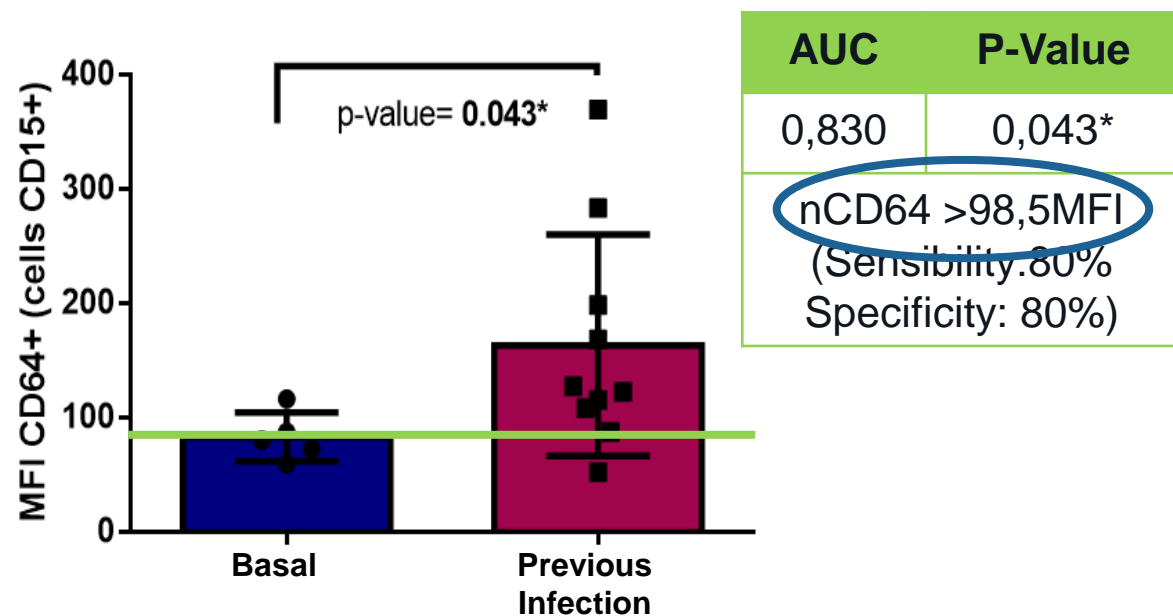


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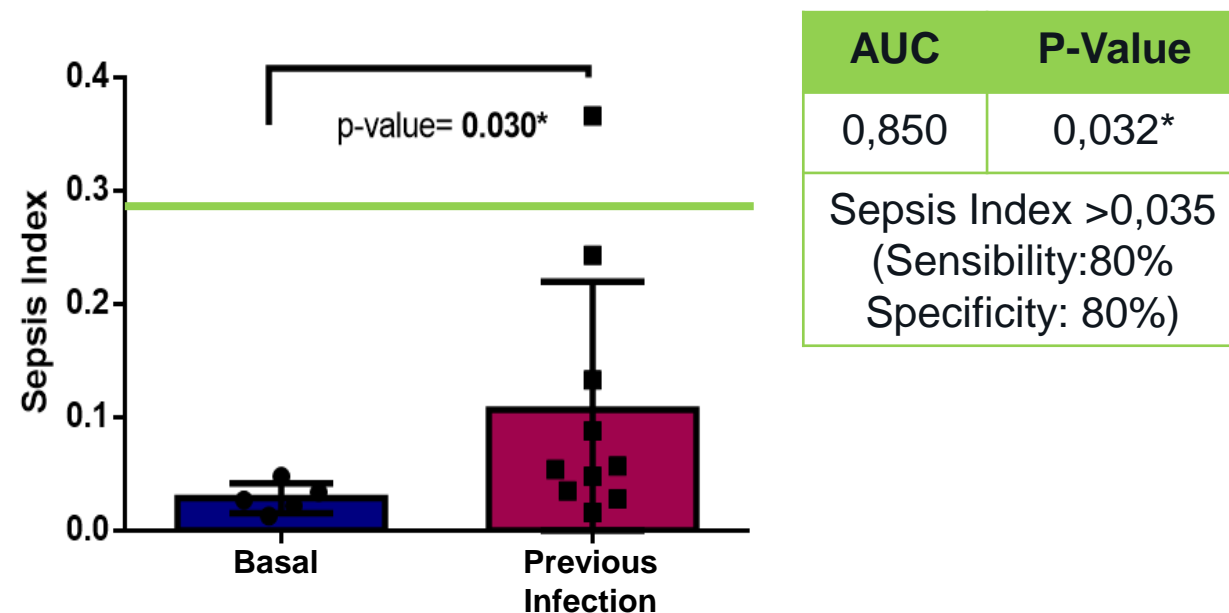


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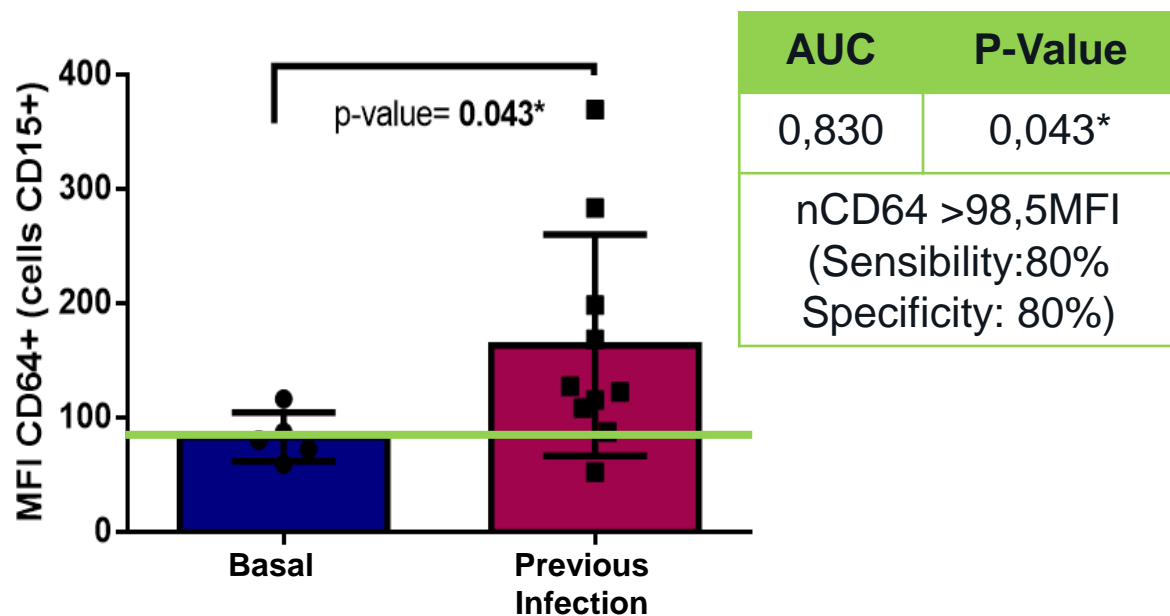


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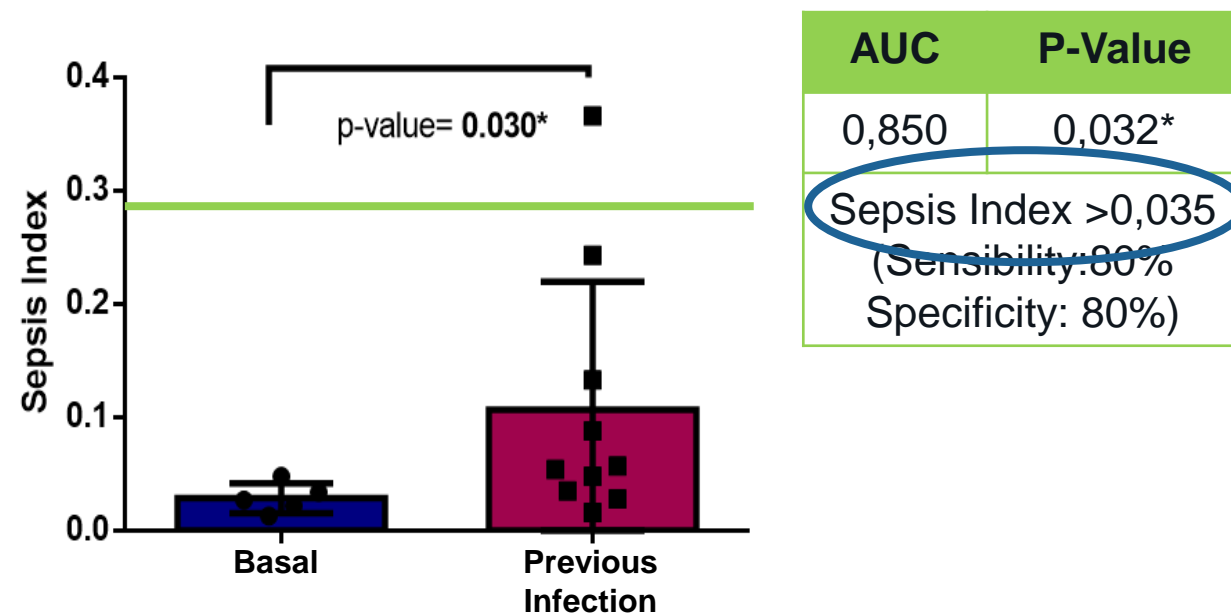


Figure. Comparative cut-off Sepsis Index between infected patients (n=10) and non-infected (n=5)

6. Results. Prognostic Biomarkers

Sepsis Index

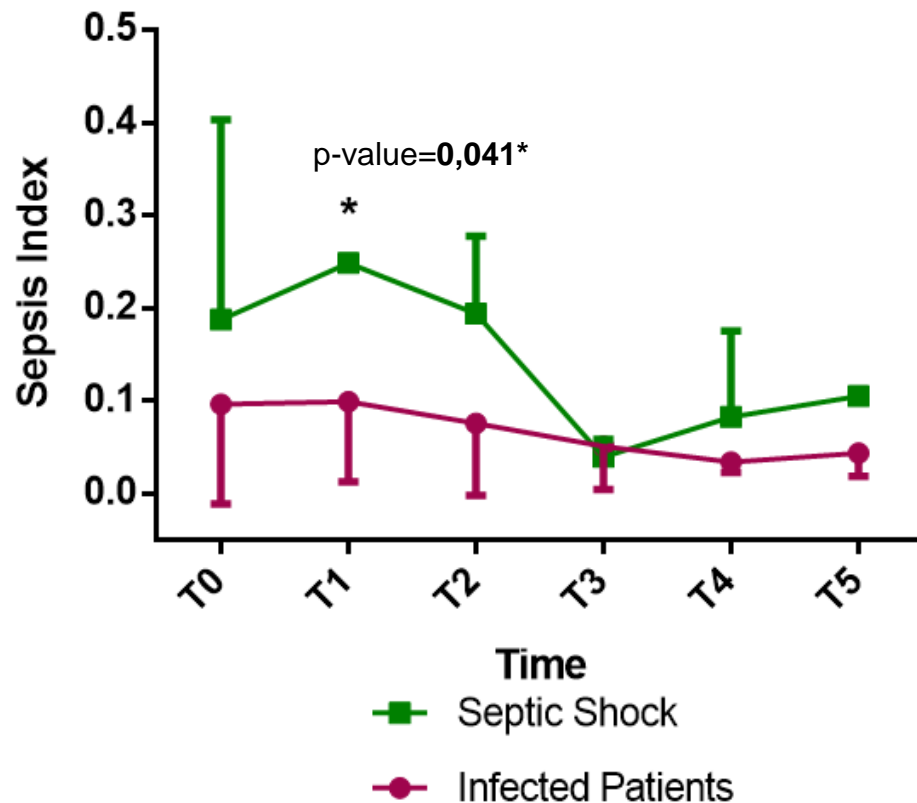


Figure. Comparison of the sepsis index in serial determinations every 3 days between infected patients (n=8) and patients with septic shock (n=2) *p-value<0,05

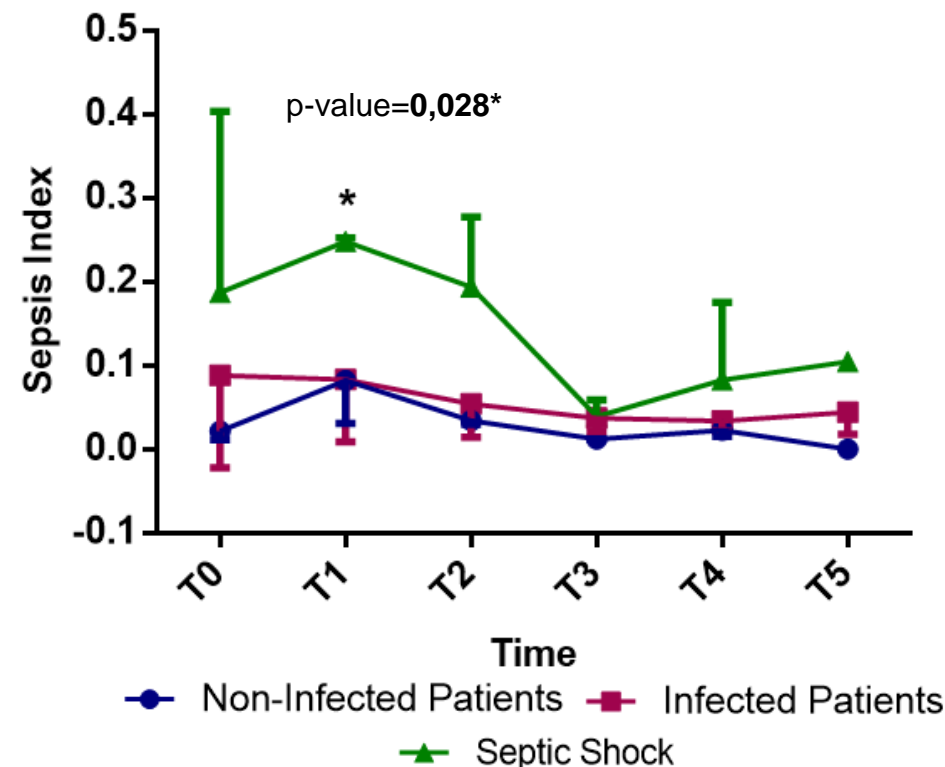


Figure. Comparison of the sepsis index in serial determinations every 3 days between non-infected patients (n=5), infected patients (n=8) and patients with septic shock (n=2) *p-value<0,05

6. Results. Prognostic Biomarkers

Correlation Sepsis Index vs. APACHE

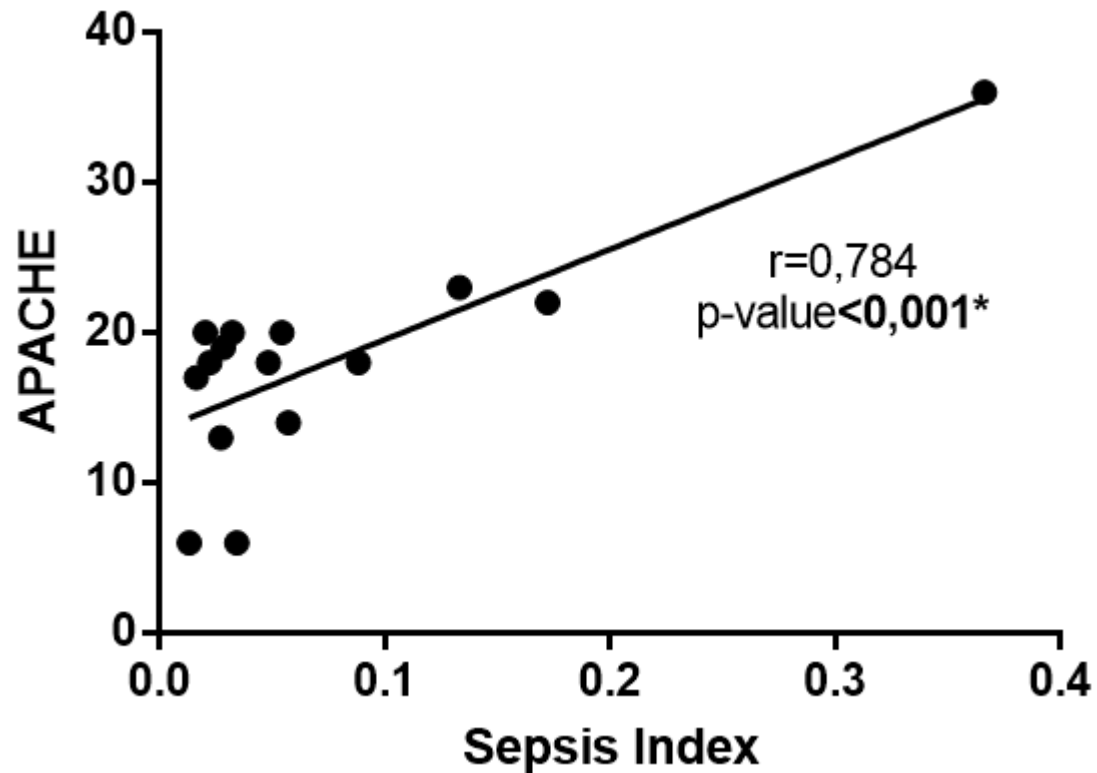


Figure. Correlation between the sepsis index and APACHE score in the first 24 hours of admission to the ICU (n=15)

Correlation Sepsis Index vs. SOFA

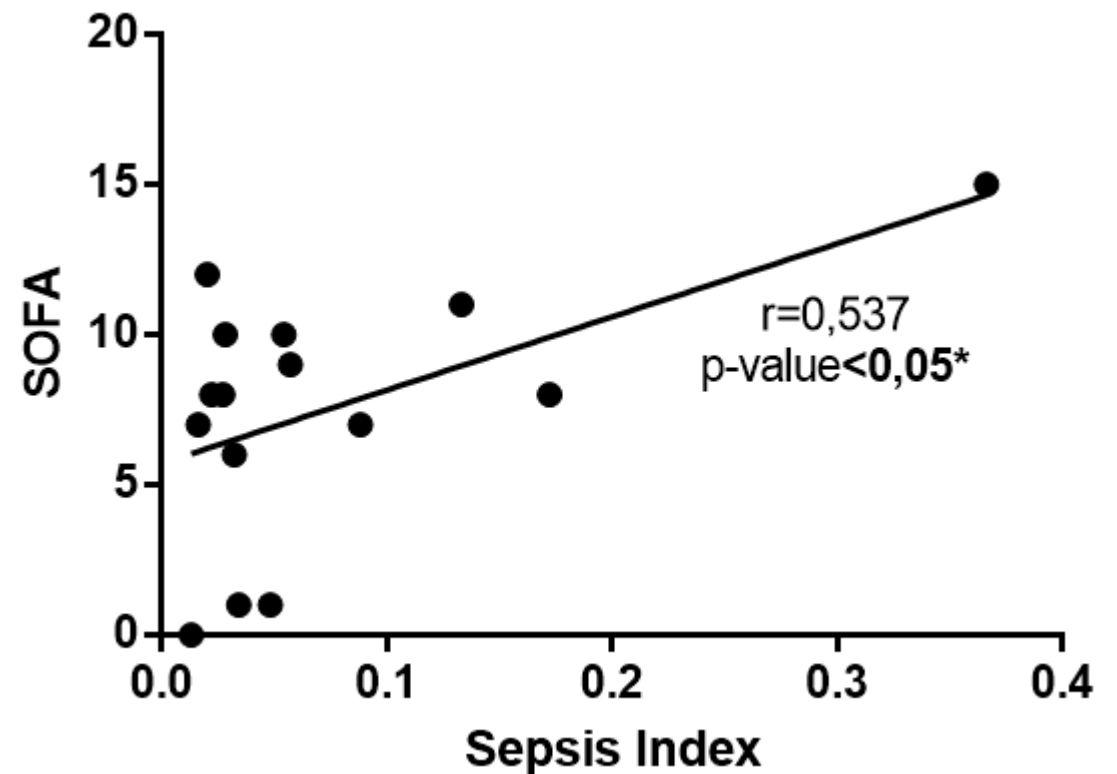


Figure. Correlation between the sepsis index and SOFA score in the first 24 hours of admission to the ICU (n=15)



7. Conclusions

Preventive

Monitoring of the percentage of **mHLA-DR** and HLA-DR Index



Preventive marker



7. Conclusions

Preventive

Monitoring of the percentage of **mHLA-DR** and HLA-DR Index



Preventive marker

Diagnostic

The expression levels of **nCD64** and the Sepsis Index



High sensibility and specificity for the early detection of infection

Diagnostic marker



7. Conclusions

Preventive

Monitoring of the percentage of **mHLA-DR** and HLA-DR Index



Preventive marker

Diagnostic

The expression levels of **nCD64** and the Sepsis Index



High sensibility and specificity for the early detection of infection

Diagnostic marker

Prognostic

The **Sepsis Index** has a positive correlation with APACHE and SOFA scores



Prognosis marker



Germans Trias i Pujol
Hospital



UAB
Universitat Autònoma
de Barcelona

Thank you

Team

Intensive Care Unit

Fernando Arméstar Rodríguez
Oriol Plans Galvan

Immunology

Bibiana Quirant Sánchez
Eva M^a Martínez- Cáceres