

# **Diagnostic Performance of CD64, CD11b, CD14 and Presepsin in Neonatal Sepsis**

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بسم الله الرحمن الرحيم

" إِنَّ الَّذِينَ آمَنُوا وَعَمِلُوا الصَّالِحَاتِ كَانَتْ لَهُمْ جَنَّاتُ الْفِرْدَوْسِ نُزُلًا ( 107 ) خَالِدِينَ فِيهَا لَا يَتَغَوَّنَ عَنْهَا حَوْلًا ( 108 )  
قُلْ لَوْ كَانَ الْبَحْرُ مِدَادًا لِكَلِمَاتِ رَبِّي لَنَفَذَ الْبَحْرُ قَبْلَ أَنْ تَنْفَدَ كَلِمَاتُ رَبِّي وَلَوْ جِئْنَا بِمِثْلِهِ مَدَدًا ( 109 )  
قُلْ إِنَّمَا أَنَا بَشَرٌ مِثْلُكُمْ يُوحَى إِلَيَّ أَنَّمَا إِلَهُكُمُ إِلَهٌ وَاحِدٌ  
فَمَنْ كَانَ يَرْجُوا لِقَاءَ رَبِّهِ فَلْيَعْمَلْ عَمَلًا صَالِحًا وَلَا يُشْرِكْ بِعِبَادَةِ رَبِّهِ أَحَدًا ( 110 )"

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This work is dedicated to ...

**My parents** for always being for me and to whom I owe everything I ever did in my life and will achieve.

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# List of Abbreviations

<b><i>Abbreviations</i></b>	<b><i>Full term</i></b>
<b>AAP</b>	American Academy of Pediatric
<b>ADC</b>	Analogue-to-Digital Conversion
<b>ADCC</b>	Antibody Dependent Cellular Cytotoxicity
<b>ALC</b>	Absolute lymphocyte Count
<b>AMC</b>	Absolute Monocyte Count
<b>ANC</b>	Absolute Neutrophil Count
<b>AUC</b>	Area Under the Curve
<b>CBC</b>	Complete Blood Count
<b>CD</b>	Cluster of Differentiation
<b>CoNS</b>	Coagulase-Negative <i>Staphylococci</i>
<b>CRP</b>	C-Reactive Protein
<b>CSF</b>	Cerebrospinal Fluid
<b>CSFs</b>	Colony Stimulating Factors
<b>CVP</b>	Central Venous Pressure
<b>dC</b>	Delta Change
<b>DNA</b>	Deoxyribonucleic Acid
<b>DOH</b>	Duration of Hospitalization
<b>E. coli</b>	<i>Escherichia coli</i>
<b>ELISA</b>	Enzyme-Linked Immuno-Sorbant Assay
<b>EDTA</b>	Ethyl- Enediamine Tetraacetic Acid
<b>EFF.</b>	Efficacy
<b>EOS</b>	Early Onset Sepsis
<b>ETT</b>	Endotracheal Tube
<b>FcγRI</b>	Fc-Gamma Receptor 1
<b>FITC</b>	Fluorescein Isothio-Cyanate
<b>FN</b>	False Negative
<b>FP</b>	False Positive
<b>FSC</b>	Forward Side Scatter
<b>GA</b>	Gestational Age
<b>GBS</b>	Group B <i>Streptococcus</i>
<b>GC-MS</b>	Gas Chromatography–Mass Spectrometry
<b>G-CSF</b>	Granulocyte Colony Stimulating Factor
<b>Hb</b>	Hemoglobin

<b>HDL</b>	High Density Lipoprotein
<b>hs-CRP</b>	Highly Sensitive C-Reactive Protein
<b>HSS</b>	Hematological Scoring System
<b>I/T Ratio</b>	Immature: Total Neutrophil Ratio
<b>ICAM-1</b>	Circulating Intracellular Adhesion Molecule-1
<b>IL-1</b>	Interlukin-1
<b>IL-3</b>	Interlukin-3
<b>IL-6</b>	Interleukin-6
<b>IL-8</b>	Interleukin-8
<b>ILO</b>	International Labor Organization
<b>LBW</b>	Low Birth Weight
<b>LDL</b>	Low Density Lipoprotein
<b>LOS</b>	Late Onset Sepsis
<b>LPS</b>	Lipopolysaccharide
<b>mCD14</b>	Monocyte CD14
<b>MFI</b>	Mean Fluorescent Intensity
<b>nCD11b</b>	Neutrophil CD11b
<b>nCD64</b>	Neutrophil CD64
<b>nCD64 MFI</b>	nCD64% Mean Fluorescent Intensity
<b>nCD64%</b>	nCD64 Percent
<b>NICU</b>	Neonatal Intensive Care Unit
<b>NPV</b>	Negative Predictive Value
<b>P Value</b>	Probability Value
<b>PBS</b>	Phosphate Buffered Saline
<b>PCR</b>	Polymerase Chain Reaction
<b>PCT</b>	Procalcitonin
<b>PLT</b>	Platelet Count
<b>PMNL</b>	Total Polymorph Nuclear Leukocyte
<b>POC</b>	Point of Care
<b>PPV</b>	Positive Predictive Value
<b>PROM</b>	Premature Rupture of Membrane
<b>P-SEP</b>	Presepsin
<b>ROC</b>	Receiver of Curve
<b>sCD14-ST</b>	Soluble CD14 Sub-Type
<b>SIRS</b>	Systemic Inflammatory Response Syndrome.
<b>Spp.</b>	Species
<b>SPS</b>	Sodium-Polyanetholesulphonate
<b>SSC</b>	Side Scatter
<b>sTREM-1</b>	Soluble Triggering Receptor Expressed on Myeloid Cells-1



<b>TAT</b>	Turnaround Time
<b>TC</b>	Total Cholesterol
<b>TG</b>	Triglycerides
<b>TLC</b>	Total Leukocyte Count
<b>TN</b>	True Negative
<b>TNF-<math>\alpha</math></b>	Tumor Necrosis Factor- $\alpha$
<b>TP</b>	True Positive
<b>UN</b>	United Nations
<b>UNICEF</b>	United Nations International Children's Emergency Fund
<b>USA</b>	United States of America
<b>UTI</b>	Urinary Tract Infection
<b>VLBW</b>	Very Low Birth Weight
<b>WBC</b>	White Blood Cells
<b>WHO</b>	World Health Organization

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## **Introduction**

Neonatal sepsis is a very critical medical situation. Despite the extensive researches for understanding and managing neonatal septicemia, it is still a major source of the morbidities and mortalities specially among the developing countries (***Cohen et al., 2015***).

Neonatal septicemia passes into various clinical stages; systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, septic shock and multi-organ failure ending by death (***Mearelli et al., 2015***).

The minimal initial non-specific symptoms and signs of the disease besides to many obstacles encountered in the diagnostic modalities, makes the early diagnosis is very challenging for the clinicians. Furthermore, the clinical course can be fulminate and fatal if the proper management couldn't initiated at the proper time and with the proper dosage (***Zambon et al., 2008 & Umlauf et al., 2013***).

The traditional sepsis diagnostic modalities still suffer from many disadvantages; the blood culture remains the gold standard for the diagnosis despite the fact that its results are usually delayed for more than 48 hours besides to the many false positives due to the impossibility of excluding contamination and many false negatives encountered in case of prior antibiotic administration and with special consideration in the neonatal setting where the withdrawn blood volume may be insufficient in some circumstances (***Shozushima et al., 2011 & Camacho-Gonzalez et al., 2013***).

As a result, during the last decades, many studies were directed toward a new diagnostic and prognostic modality not only for early accurate diagnosis; but also, for the rational antibiotic use (*Laxminarayan et al., 2013 & Mahmoud et al., 2014*).

Those Effective biomarkers included; cell surface markers [e.g; cluster of differentiation 64 (CD64), Soluble CD14 subtype (sCD14-ST), CD14, CD163, CD11b], bacterial surface antigens, genetic biomarkers, protein biomarkers [e.g procalcitonin (PCT), Neopterin], cytokines and chemokines (*Chauhan et al., 2017*).

Regarding the C-Reactive Protein (CRP) which is the most extensively studied sepsis marker, it represents the preferred index in many neonatal intensive care units (NICUs) despite the ongoing rise and fall of the new infection biomarkers (*Hofer et al., 2013*).

The sensitivities and specificities of CRP widely differ between the studies, ranging from 29% to 100% and from 6% to 100%, respectively. In addition, the sensitivity of CRP is well known to be the lowest during the initial stages of the infection (*Hofer et al., 2013*).

Among the new sepsis markers, neutrophil CD64 (nCD64) represents a one of the most researchable and valuable early diagnostic biomarker (*Mahmoud et al., 2014 & Mearelli et al., 2015*).

Neutrophil CD64 is a membrane glycoprotein that mediates endocytosis, phagocytosis, antibody dependent cellular cytotoxicity (ADCC), cytokine release, and superoxide generation.

It is constitutively expressed on monocytes and the macrophages **(Delanghe and Speeckaert, 2015)**.

It is well known that nCD64 is expressed at low concentration on the surface of the non-activated neutrophils but can be markedly up-regulated at the onset of the sepsis process **(Ten Oever et al., 2016)**.

Neutrophil CD11b (nCD11b) is another sepsis biomarker. It acts as Fc-receptor which expressed in huge quantities on the surface of the activated inflammatory cells upon encountering bacteria or their cellular products by the same mechanism as CD64 acts. nCD11b appears to be promising for neonatal sepsis diagnosis **(Hofer et al., 2012)**.

Monocyte CD14(mCD14) has also been investigated as a valuable sepsis diagnostic tool, it represents a specific high-affinity receptor for the complexes of lipopolysaccharide (LPS) and LPS binding protein (LBP) which activates a specific proinflammatory signaling cascade, and thereby starting the inflammatory reaction of the host against the different infectious agents **(Mussap et al., 2013)**.

The soluble CD14 subtype (sCD14-ST) has been extensively researched as another biomarker which named (Presepsin), it originates from the cleavage of CD14 on the cell membrane by the cathepsin and the other lysosomal enzymes **(Mussap et al., 2012)**.

Several studies suggest a promising role for Presepsin as an early diagnostic and prognostic sepsis marker **(Ulla et al., 2012, Ali et al., 2016, Jacobs and Wong., 2016 & Tabl and Abed., 2016)**.