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Macrophage Migration Inhibitory Factor in Early and Late Neonatal Sepsis

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Abstract

Background: Neonatal Sepsis (NS) is a major health risk for newborns, particularly those bornpreterm, and is a primary contributor to morbidity. Research has identified Macrophage Migration Inhibitory Factor (MIF) as a key player in the development of sepsis and other immunerelated diseases.

Aim of Study: The current research aimed to quantify MIF-concentrations in neonates with early and late-onset sepsis and correlate its levels with other key clinical and laboratory indicators in comparison to non-septic neonates.

Patients and Methods: Thiscross-sectional research was conducted from March to September 2023 and involved 32 neonates with Early-Onset (EONS, n=16) and Late-Onset (LONS, n=16) neonatal sepsis, confirmed by positive blood cultures, compared to another 32 non-septic neonates (controls), matched for age and gender. All neonates underwent basic laboratory tests, and MIF levels were assessed using ELISA.

Results: The mean levels of MIF were significantly higher in both early-onset (169.11±51.88ng/ml) and late-onset (150.6±57.43ng/ml) neonatal sepsis groups, in comparison with the non-septic group (41.97±17.5ng/ml, *p*-value=0.000). The two groups with sepsisexhibited comparable MIF values. A cutoffvalue >66.7ng/ml for MIF levels was determined to discriminate between septic and non-septic neonates with (100% sensitivity; 96.87% specificity; positive predictive value: 97%; negative predictive value: 100%; AUC: 0.997). Furthermore, MIF levels were negatively correlated with absolute lymphocytic count, PH level in early-onset and random blood glucose in late-onset neonatal sepsis groups.

Conclusion: MIF could be an excellent and early diagnostic marker for NS even in preterm neonates. Further studies are needed to correlate MIF levels with severity of neonatal sepsis and compare the diagnostic and prognostic utility of Macrophage Migration Inhibitory Factor with other inflammatory biomarkers, like procalcitonin and C-Reactive Protein (CRP).

Key Words: *Macrophage migration inhibitory factor – Early-onsetneonatal sepsis – Late-onset neonatal sepsis.*

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Introduction

NEONATAL sepsis has been described as a systemic inflammatory response syndrome to a suspected or confirmed infection happening within the initial twenty-eight days of life. This condition is often categorized into two groups: Early (during the first three days of life) and late (from the fourth day upto twenty-eight days following delivery) **[1]**. Newborn sepsis is the leading cause of death among newborns, accounting for thirty-five percent of deaths. The elevated susceptibility to infection in neonates has been related to their restricted ability to mount effective innate immune responses **[2]**.

Macrophage Migration Inhibitory Factor has been illustrated to activate macrophages and to promote the release of Tumor Necrosis Factor α (TNF-α), Interleukins (ILs) 1,8, Nitric Oxide (NO), and Prostaglandin E2 (PGE2) through the induction of Cyclooxygenase-2 (COX-2). In addition, MIFhas been implicated in devolvement of various diseases, such as autoimmune and allergic conditions as well as infections caused by parasites, helminths, bacteria and viruses. In septic adult patients, elevated MIF levels were associated with increased expression of proinflammatory markers, disrupted adrenal and pituitary functions, higher severity scores, and poorer result **[2]**. Consequently, this research aimed to examine MIF level in neonates with early-onset and late-onset sepsis and to examine the correlations between MIF levels and various vital and laboratory parameters, compared to non-septic neonates.

Patients and Methods

Study type and setting: A cross-sectional research was used with data collection taking place in the Neonatal Intensive Care Unit (NICU), Children's Hospital, Ain Shams University, from March 2023 to September 2023.

Inclusion criteria:

Full-term (gestational age thirty-seven weeks or more) and preterm (from 32 up to 36 0/6 weeks of gestation) newborns fulfilling the criteria of neonatal sepsis with regard to the report on the expert meeting on pediatric and neonatal sepsis of European Medicines Agency (EMA) [3], as well as non-septic neonates, matched for age and gender.

Exclusion criteria:

Neonates with severe illness by Score for Neonatal Acute Physiology with Perinatal Extension (SNAPPE IIScore) (>40) [4], hypoxic ischemic encephalopathy, inborn errors of metabolism, inborn errors of immunity,congenital anomalies, syndromic features and birth weight ≤1500 grams were excluded from the study.

Study tools:

A- Cases and controls were enrolled sequentially after their hospitalization and completed a comprehensive perinatal and family history assessment, clinical examination, and standard newborn care protocols. Monitoring and recording were performed on the clinical condition of each newborn, as well as vital data and the length of their hospital stay.

B- Gestational age was confirmed by new Ballard score [5].

C- Birth weight was assessed according to Centers for Disease Control and Prevention (CDC) z-scores [6].

D- APGAR score at one minute and five minutes [7].

E- The severity of disease was classified using the SNAPPE II score into three categories: Mild (1-20), moderate (21-40), and severe (> 40) [4].

F- Hematologic Scoring System (HSS) of Rod well for the expectation of neonatal sepsis: A score above two suggests a heightened probability of sepsis, whereas a score of two or fewer indicates a near certainty of the absence of the newborn sepsis [8].

Laboratory investigations:

Laboratory analyses were performed on admission and then every 3 days according to NICU protocol of Ain Shams University and including:

A- Complete Blood Count (CBC) was done through urtilizing Cell Dyne-Ruby automated cell counter (Abbott Diagnostics-Santa Clara-Ca-USA) and the manual differential count was done using Leishman's stain.

B- C-Reactive Protein (CRP) was performed by using Beckman Coulter AU 480-CA-USA for quantitative turbidimetric detection of CRP, Cat No. OSR6147.

C- Venous Blood Gases (VBG) was analysed by using Radiometer ABL 800 basics, SN: 1902-754R2714N0019 for recording pH, partial pressure of carbon dioxide (PCO_2) and bicarbonate level (HCO_3).

D- Blood Chemistry including liver and kidney functions tests by using the automated chemistry analyzer pentra e400 (HORIBA ABX SAS, France).

E- Blood Cultures were collected on admission, or in cases of suspected sepsis, blood samples were collected under complete aseptic conditions to be inoculated on BD BACTECTM Peds PlusTM media, using BD-Bactec FX40, SN: FF6009.

F- Measurement of serum Macrophage Migration Inhibitory Factor level: 1mL was withdrawn, centrifuged and serum was separated and kept in the –80°C freezer until the samples have been examined utilizing enzyme-linked immunosorbent assay (ELISA) technique based on human MIF ELISA kit (Elabscience ELISA kits. Houston, Texas, USA). Catalog No: E-EL-H1530. All steps were performed in accordance with the manufacturer's specifications.

Ethical consideration:

Written consent was obtained from the parents of all participants following an explanation of the research's objectives and tools. They had the right to withdraw from the research at any time. Permission has been obtained from the Ain Shams University Ethical Committee (FMASU MS 125/2023). All authors contributed, revised the final manuscript, and permitted the publication.

Sample sizecalculation:

The sample size was determined utilizing the G power program, with a power of eighty percent and an alpha error of five percent, as calculated by [9]. The required sample size comprised a minimum of thirty-two newborns in both the non-septic and septic groups, with the septic group further separated into early-onset sepsis (number--sixteen) and late-onset sepsis (number--sixteen).

Statistical analysis:

The data were utilized the Statistical Package for Social Science (IBM SPSS) version 27. Normally distributed numerical variables were reported as mean ± SD. Quantitative non-parametric data were determined by median and interquartile ranges.

Qualitative data were described by frequency and percentages. To compare many groups about quantitative and parametric distribution, a One-Way

ANOVA test accompanied by post-hoc analysis has been utilized. The Kruskal-Wallis test, followed by post-hoc analysis, has been utilized to compare quantitative and non-parametric variables among the three groups. The comparison of groups with qualitative data has been conducted utilizing the Chi-square test. Spearman correlation coefficients have been utilized to evaluate the association between two quantitative variables within the same group. Receiver Operating Characteristic (ROC) curve analysis has been utilized for determining the best cutoff point and the diagnostic efficacy of each test. The Area Under the Curve (AUC) has been computed for each plot. A *p*-value less than 0.05 has been deemed as the cutoff value for significance in all analyses.

Results

Regarding maternal and neonatal characteristics among the examined groups; both mean gestational age and median birth weight Z scores were comparable between EONS and LONS groups, while both groups had a significantly reduced mean gestational age and birth weight Z scores, compared to non-septic control group (*p*-value=0.000 for all). The septic groups had a higher incidence of preterm birth, compared to the non-septic group. Additionally, both septic groups had longer hospital stays than the non-septic group, with more prolonged hospitalization days in the late-onset group, in comparison with the early-onset group. The frequency of PROM was higher in the septic groups, in comparison with the non-septic group, as illustrated in Table (1).

Table (1): Maternal and neonatal characteristics of the examined groups.

Variables	Control group Number = 32	EONS group Number = 16	LONS group Number = 16	Test value	*p*-value
GA (weeks):					
Mean ± SD	37.41±1.27	33.63±1.63	34.19±2.07	39.343•	0.000
Range	34 – 39	32 – 37	32 – 38		
Birthwight (kg):					
Median (IQR)	0.94 (0.77 – 1.05)	-0.73 (-0.99 – -0.39)	-1.07 (-1.36 – -0.73)	47.322#	0.000
Range	0.34 – 1.38	-1.74 – 0.34	-1.74 – 0.34		
Term, n (%):					
Preterm (<37 weeks)	9 (28.1%)	15 (93.8%)	14 (87.5%)	26.040*	0.000
Full term (≥37 weeks)	23 (71.9%)	1 (6.2%)	2 (12.5%)		
Sex, n (%):					
Male	15 (46.9%)	7 (43.8%)	12 (75.0%)	4.141*	0.126
DM, n (%)	5 (15.6%)	4 (25.0%)	4 (25.0%)	0.869*	0.648
PROM, n (%)	3 (9.4%)	7 (43.8%)	6 (37.5%)	8.500*	0.014
Chorioamnionitis, n (%)	2 (6.3%)	4 (25.0%)	3 (18.8%)	3.491*	0.175
UTI, n (%)	2 (6.3%)	5 (31.3%)	4 (25.0%)	5.599*	0.061
Mode of delivery, n (%):					
Cesarean	15 (46.9%)	10 (62.5%)	8 (50.0%)	1.064*	0.588
Apgar at 1 (min):					
Median (IQR)	8 (7– 9)	8 (7– 9)	8 (7– 9)	0.198#	0.906
Range	5 – 10	5 – 10	5 – 10		
Apgar at 5 (mins):					
Median (IQR)	8 (8 – 9)	9 (8 – 9)	9 (7 – 9)	0.384#	0.825
Range	7 – 10	6 – 10	6 – 10		
Days of hospitalization:					
Median (IQR)	6 (5 – 8)	11 (9-13)	10 (9 – 13)	31.946#	0.000
Range	3 – 10	5 – 15	8 – 15		

Post hoc analysis: Parameters	Control vs EONS	Control vs LONS	EONS vs LONS
GA (weeks)	0.000	0.000	0.320
Term, n (%)	0.000	0.001	0.548
Days of hospitalization	0.000	0.000	0.005
Weight (kg)	0.000	0.000	0.125
PROM, n (%)	0.009	0.018	0.365

p-value above 0.05: Non-significant.
p-value less than 0.05: Significant.
p-value less than 0.01: Highly significant.
*: Chi-square test.
•: One Way ANOVA test.
#: Kruskal-Wallis test.

GA: Gestestional Age.
UTI: Urinary Tract Infection.
DM: Diabetes Mellitus.
PROM: Premature Rupture of Membrane.
LONS: Late-Onset Neonatal Sepsis.

EONS: Early-Onset Neonatal Sepsis.
IQR: Interquartile Range.
SD: Standard Deviation.
Kg: Kilogram.

In the view of laboratory investigations, Table (2) shows a statistically significant difference, where platelet counts and PH levels were lower in septic groups, compared to the non-septic one (*p*-value= 0.010, 0.003 respectively), CRP titers were significantly higher among EONS and LONS groups than the control group (*p*-value=0.000).

Compared to the control group, significantly higher mean MIF levels were observed in both EONS (169.11±51.88ng/ml) and LONS group (150.6±57.43ng/ml) with *p*-value=0.000. Notably, an insignificant variance in MIF levels was detected between the EONS and LONS groups, as shown in Table (3).

Table (2): Laboratory parameters of the studied groups on admission.

Variables	Control group Number = 32	EONS group Number = 16	LONS group Number = 16	Test value	*p*-value
Hb (g/l):					
Mean ± SD	15.71 ± 2.6	14.19 ± 3.18	14.59 ± 3.22	1.722•	0.187
Range	11 – 20	10 – 19	10 – 19		
WBCs (10^9/L):					
Mean ± SD	14.25 ± 3.75	12.53 ± 6.49	13.36 ± 6.85	0.566•	0.571
Range	8 – 20	3.5 – 22	3.1 – 23		
ANC (10^9/L):					
Mean ± SD	5.59 ± 0.85	5.36 ± 1.02	5.2 ± 0.83	1.096•	0.341
Range	4.29 – 6.95	4.06 – 6.93	4.2 – 6.82		
ALC (10^9/L):					
Mean ± SD	2.42 ± 0.84	2.44 ± 0.96	2.47 ± 0.83	0.019•	0.981
Range	1.03 – 3.89	1.03 – 3.68	1.15 – 3.94		
PLTs (10^9/L):					
Mean ± SD	235.09 ± 76.8	175.44 ± 80.95	173.25 ± 74.11	4.957•	0.010
Range	110 – 365	80 – 332	90 – 350		
CRP (mg/l):					
Median (IQR)	1 (1 – 4)	78 (54 – 85)	82 (58 – 96)	109.709	0.000
Range	0 – 6	45 – 96	45 – 120		
PH:					
Mean ± SD	7.4 ± 0.04	7.29 ± 0.15	7.32 ± 0.15	6.444•	0.003
Range	7.35 – 7.45	7 – 7.5	7 – 7.5		
PCO_2 (mmHg):					
Mean ± SD	39.69 ± 3.35	40.5 ± 6.76	40.06 ± 5.74	0.143•	0.867
Range	35 – 45	30 – 50	30 – 48		
HCO_3 (mmol/l):					
Mean ± SD	23.88 ± 1.41	23.94 ± 1.39	24 ± 1.32	0.045•	0.956
Range	22 – 26	22 – 26	22 – 26		
Blood Cultures	0 (0.0%)	16 (100.0%)	16 (100.0%)	64.000*	0.000
Causative Organisms:					
Klepseilla pneumonae	–	13 (81.25%)	15 (93.75%)	1.143*	0.285
Staphylococcus aureus	–	3 (18.75%)	1 (6.25%)		

Post hoc analysis

Parameters	Control vs EONS	Control vs LONS	EONS vs LONS
PLTs (10^9/L)	0.014	0.011	0.936
CRP	0.000	0.000	0.073
PH	0.001	0.025	0.361

Hb : Hemoglobin.
ANC : Absolute Neutrophil Count.
WBCs : White Blood Cells.
ALC : Absolute Lymphocytic count.
CRP : C-Reactive Protein.
PLTs : Platelets.
PCO_2: Partial Pressure of Carbon Dioxide.
HCO_3: Bicarbonate.
LONS: Late-OnsetNeonatal Sepsis.
EONS: Early-Onset Neonatal Sepsis.
IQR: Interquartile Range.
SD : Standard Deviation.

Table (3): MIF levels in (ng/ml) among the studied groups.

	Control group Number = 32	EONS group Number = 16	LONS group Number = 16	Test value	*p*-value
MIF (ng/ ml):					
Mean ± SD	41.97±17.5	169.11±51.88	150.6±57.43	69.113•	0.000
Range	11 – 82.2	81.3 – 247.8	70.5 – 264.6		
			Post hoc analysis		
Parameters	Control vs EONS		Control vs LONS	EONS vs LONS	
MIF (ng/ml)	0.000		0.000	0.199	

•: One Way ANOVA test
MIF : Macrophage Migration Inhibitory Factor.
LONS: Late-Onset Neonatal Sepsis.
EONS: Early-Onset Neonatal Sepsis.
SD : Standard Deviation.

As illustrated in Fig. (1), MIF demonstrates the ability to distinguish between septic and non-septic neonates, with a cutoff value >66.7 (ng/ml) yielding 100% sensitivity, 96.9% specificity and an AUC 0.997 using ROC curve.

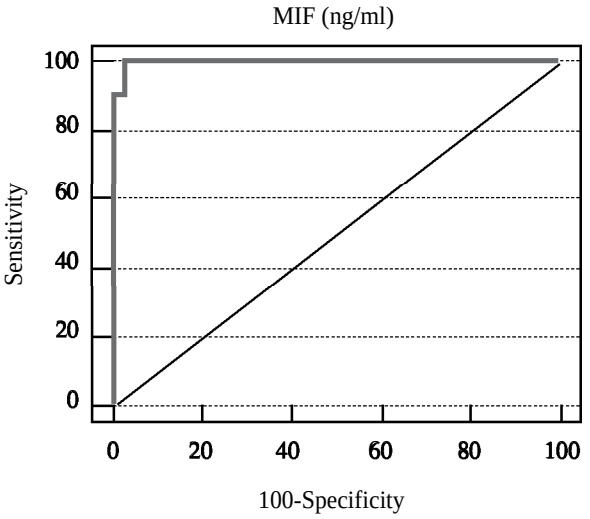

Fig. (1): Receiver operating characteristic curve (ROC) for MIF (ng/ml) level to differentiate between septic and non-septic neonates.

Both Tables (4,5) show a significant negative correlation between absolute lymphocytic count, PH level and MIF level in the EONS group (*p*-value=0.039, 0.031 correspondingly). While neonates withLONS illustrated a notable inverse correlation among MIF level and random blood glucose with *p*-value=0.015.

Table (4): Correlation between MIF level (ng/ml) and the others studied parameters in EONSgroups.

EONS group	MIF (ng/ml)	
	r	*p*-value
GA (weeks)	–0.003	0.991
Apgar at 1 (min)	–0.11	0.686
Apgar at 5 (mins)	–0.052	0.848
Birth Weight (kg)	–0.18	0.504
Systolic BP (mmHg)	0.155	0.566
Diastolic BP (mmHg)	0.043	0.875
Pulse (beat/min)	–0.349	0.186
Respiratory rate (rate/min)	–0.043	0.874
Random blood glucose (mg/dl)	–0.131	0.629
Urine output (ml/kg/hr)	–0.216	0.421
Hb (g/l)	0.43	0.096
WBCs	–0.029	0.914
ANC (10^9/L)	0.065	0.812
ALC (10^9/L)	–.521*	0.039
PLTs (10^9/L)	–0.018	0.948
PH	–.541*	0.031
PCO_2 (mmHg)	0.126	0.643
HCO_3 (mmol/l)	0.307	0.248
Days of hospitalization	–0.108	0.691

GA : Gestational Age.
Hb : Hemoglobin.
ANC : Absolute Neutrophil Count.
WBCs : White Blood Cells.
ALC : Absolute Lymphocytic Count.
PLTs : Platelets.
CRP : C-Reactive Protein.
BP : Blood Pressure.
PCO2 : Partial Pressure of Carbon Dioxide.
HCO3 : Bicarbonate.
EONS : Early-Onset Neonatal Sepsis.

Table (5): Correlation between MIF (ng/ml) and the others studied parameters in LONS group.

EONS group	MIF (ng/ml)	
	r	*p*-value
GA (weeks)	–0.233	0.386
Apgar at 1 (min)	0.072	0.792
Apgar at 5 (mins)	0.142	0.601
Birth Weight (kg)	–0.142	0.6
Systolic BP (mmHg)	0.343	0.194
Diastolic BP (mmHg)	–0.328	0.215
Pulse (beat/min)	0.221	0.411
Respiratory rate (rate/min)	–0.105	0.698
Random blood glucose (mg/dl)	–.596*	0.015
Urine output (ml/kg/hr)	0.262	0.328
Hb (g/l)	0.164	0.543
WBCs	0.037	0.892
ANC (10^9/L)	0.021	0.94
ALC (10^9/L)	–0.091	0.737
PLTs (10^9/L)	–0.087	0.747
PH	0.145	0.592
PCO_2 (mmHg)	0.467	0.068
HCO_3 (mmol/l)	0.201	0.455
Days of hospitalization	0.294	0.269

GA : Gestational Age.
Hb : Hemoglobin.
ANC : Absolute Neutrophil Count.
WBCs : White Blood Cells.
ALC : Absolute Lymphocytic Count.
PLTs : Platelets.
BP : Blood Pressure.
PCO2 : Partial Pressure of Carbon Dioxide.
HCO3 : Bicarbonate.
LONS : Late-Onset Neonatal Sepsis.
Kg : Kilogram.

Discussion

Macrophage Migration Inhibitory Factor is a proinflammatory cytokine that has a crucial role in regulating immune responses. Despite multiple research studies on MIF's role in neonatal health, its clinical implications are not yet fully understood **[10].** The current study aimed to assess MIF levels in newborns late with and early-onset sepsis and correlate its levels with other vital and laboratory parameters in comparison to non-septic neonates.

The results illustrated a significant reduction in mean platelet counts among septic cases in comparison with controls. Microbial products can trigger platelets clumping and activation, resulting in increased platelets clearance and destructions **[11].**

C-Reactive Protein is an acute-phase reactant that elevates throughout sepsis. The delayed synthesis throughout the inflammatory response contributes to its reduced sensitivity in the early stages of the illness **[12].**

In the current study, positive blood cultures were instrumental in confirming the diagnosis of neonatal sepsis, reaffirming their status as the gold standard diagnostic tool, similar to the findings reported by **[13].**

The outcomes of current research indicated that MIF concentration was a significantly higher among neonates with EONS and LONS than non-septic ones (*p*-value=0.000). The study observed similar MIF levels in neonates with EONS and LONS, supporting the previous findings by Chen, et al. **[14]** that endorse the critical role of MIF levels in immune regulation during neonatal sepsis.

Also, the exact mechanisms by which MIF modulates neonatal immune responses to sepsis require further elucidation. During sepsis, MIF levels are elevated and were found to correlate with increased loads of proinflammatory cytokines, dysregulated adrenal and pituitary functions, severity scores of sepsis and prognosis **[15].**

The MIF cutoff level for distinguishing between septic and non-septic neonates was >66.7ng/ml with 100 % sensitivity, 96.87% specificity and an AUC 0.997. MIF level served as a reliable discriminator between septic and non-septic neonates, consistent with the findings reported by Toldi, et al. **[16].**

The current research demonstrates that in the LONS group, a significant negative association was observed between MIF and random blood glucose. MIF negatively impact insulin action by triggering on inflammatory cascade and disrupting the responsiveness of target cells to insulin **[17].**

In conclusion: Being comparable in EONS and LONS, and considering the most septic neonates were premature, MIF level could be an excellent and early diagnostic marker for neonatal sepsis. Further research is warranted to directly compare the diagnostic and prognostic utility of MIF with other inflammatory biomarkers, like C-reactive protein and procalcitonin.

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عامل تثبيط هجرة الخلايا البلعمية لدى حديثى الولادة المصابين بالإنتان المبكر والمتأخر

يعد الإنتان لدى حديثى الولادة مشكلة صحية كبرى ومسبب أساسى للمراضة وخاصة لدى المبتسرين منهم. أثبتت الأبحاث أن عامل هجرة الخلايا البلعمية يلعب دوراً محورياً فى حدوث الإنتان والأمراض المتعلقة بالمناعة.

هَدفت هذه الدراسة الي قياس نسبة عامل تثبيط هجرة الخلايا البلعمية فى حالات الإنتان المبكر والمتأخر لدى حديثى الولادة مع ربط مستوياته بالعلامات السريرية و الفحوصات المعملية مقارنةً بالأصحاء منهم . كانت هذه الدراسة مقطعية أُجريت من مارس ٢٠٢٣ وحتى سبتمبر ٢٠٢٣ وإشتملت على ٣٢ من حديثى الولادة تم تقسيمهم إلى ١٦ حالة حديثى ولادة مصابة بالإنتان المبكر و١٦ حالة أخرى مصابة بالإنتان المتأخر وتم تأكيد تشخيص الإصابة بالإنتان بتحليل مزرعة الدم مع مقارنتهم ب٣٢ من حديثى الولادة غير المصابين بالإنتان ومتوافقين بالعمر الرحمى والجنس مع عمل الفحوصات المعملية الأولية وعامل تثبيط هجرة الخلايا البلعمية لجميع المشاركين فى الدراسة.

أَظهرت الدراسة إرتفاع نسبة عامل تثبيط هجرة الخلايا البلعمية فى جميع حديثى الولادة المصابين بالإنتان المبكر والمتأخر عن أقرانهم الأصحاء بينما كانت النسب متقاربة بدون إختلافات إحصائية فى مجموعتى الإنتان المبكر والمتأخر وكان الحد الفاصل التمييزى لحديثى الولادة المصابين بالإنتان عن غير المصابين بينهم هو أعلى من ٦٦,٧ نانوغرام لكل مل وقد وجُدت علاقة عكسية بين عدد الخلايا الليمفاوية المطلق ودرجة حموضة الدم وعامل تثبيط هجرة الخلايا البلعمية فى مجموعة الإنتان المبكر مع وجود علاقة عكسية أخرى بين نفس العامل ونسبة السكر فى الدم فى مجموعة الإنتان المتأخر.

نستخلص من هذه الدراسة إلى حساسية عامل تثبيط هجرة الخلايا البلعمية كمؤشر تشخيصى ممتاز ومبكر للإنتان لدى حديثى الولادة والمبتسرين منهم مع الحاجة الى إيجاد علاقة بين نسبة هذا العامل مع درجة خطورة الإنتان ومقارنته أيضا مع عوامل تشخيص الإنتان الشائعة الأخرى كبروتين سى التفاعلى والبروكالسيتونين فى دراسات مستقبلية.