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MIP-1α Is More Sensitive than MCP-1, and CXCL10 Immune Markers in Diagnosis of Pediatric Sepsis

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Abstract

Background: Pediatric sepsis is a leading cause of mortality among children both in Iraq and globally. The underlying causes of pediatric sepsis are diverse, encompassing a broad range of pathogenic mechanisms and varying responses to these triggers. However, a common characteristic of pediatric sepsis is the secretion of cytokines and chemokines.

Objectives: To evaluate the sensitivity and specificity of macrophage inflammatory protein-1 alpha (MIP-1α) in a comparison with monocyte chemotactic protein-1 (MCP-1) and C-X-C motif chemokine ligand 10 (CXCL10) immune markers in the pediatric sepsis and effort an evidence-based linking between the three biomarker and the laboratory value of neutrophil, lymphocyte and CRP.

Patients and Methods: This case control study includes 100 participants (50 patients and 50 control). Sandwich ELISA test used to evaluate the MIP-1α, MCP-1, and CXCL10 immune markers in pediatric sepsis and control groups.

Results: Present study shows high level of the neutrophil (62.45%), lymphocyte (47.90%) and CRP (50.52 mg / L) in the cases of pediatric sepsis compared with the normal range. Furthermore, this study shows that MIP-1α is more sensitive (82%) than MCP-1, and CXCL10 (56% and 54% respectively).

Conclusions: At the end, this study suggests that MIP-1α has the highest diagnostic sensitivity value, so it could be concerned as essential immunodiagnostic marker for pediatric sepsis.

MIP-1α اكثر حساسية من العلامات المناعية MCP-1 و CXCL10 في تشخيص الانتان عند الأطفال

سمر عطاالله سهيل، علي جليل علي الياسري , عبير ظاهر ناجي الحسناوي

الخلاصة

المقدمة: يعتبر الانتان أحد الأسباب الرئيسية للوفاة لدى الأطفال في العراق والعالم أجمع. الأسباب الكامنة وراء الانتان لدى الأطفال متنوعة وتشمل مجموعة واسعة من الآليات المرضية واستجابات مختلفة لهذه المحفزات. ومع ذلك، فإن السمة المشتركة للانتان لدى الأطفال هي إفراز السيتوكينات والكيموكينات

الهدف: تقييم حساسية وخصوصية البروتين الالتهابي البلاعم 1 ألفا **(MIP-1α)** مقارنة مع البروتين الكيميائي احادي الخلية 1 **(MCP-1)** ورابط الكيموكين من نوع **CXC 10 (CXCL10)** كعلامات مناعية في الانتان لدى الأطفال، والسعي لإيجاد علاقة بين هذه العلامات الحيوية الثلاثة والقيم المخبرية لعدد العدلات والخلايا اللمفاوية و بروتين سي التفاعلي.

الطرق والعينات: تتضمن دراسة الحالات والسيطرة 100 مشارك (50 مريض و 50 مجموعة سيطرة). تم استخدام اختبار الإليزا الساندويتش لتقييم علامات**MIP-1α** ، **MCP-1**، و **CXCL10** المناعية في حالات الانتان ومجموعة الاشخاص الاصحاء

النتائج: أظهرت الدراسة الحالية ارتفاعًا في مستوى العدلات (62.45%) والخلايا اللمفية (47.90%) وبروتين سي التفاعلي (50.52 ملغم/لتر) في حالات الانتان مقارنة بالمعدل الطبيعي. علاوة على ذلك، أظهرت هذه الدراسة أن **MIP-1α** أكثر حساسية (82%) من **MCP-1 (56%) , CXCL10** (54 %)على التوالي .

الاستنتاجات: في النهاية، تشير هذه الدراسة إلى أن **MIP-1α** لديه أعلى قيمة حساسية تشخيصية، لذلك يمكن اعتباره علامة مناعية تشخيصية أساسية للإنتان لدى الأطفال.

1. Introduction

Sever paediatric sepsis is defined as two or more systemic inflammatory response syndrome criteria, confirmed or suspected invasive infection, and cardiovascular dysfunction, acute respiratory distress syndrome, or two or more organ dysfunctions (Andrea T. Cruz et al., 2020) . The prevalence of pediatric sepsis in Iraq was reported to be (8.9%)

which may stand in a bit lower than other country ware prevalence stands at (39%) in New Delhi and (45.9%) in Egypt (Weiss et al., 2015)

Common etiologies in pediatrics sepsis were urinary tract infection (UTI) and meningitis especially in the ages below 6 month and above 10 years. Meanwhile, pneumonia were the main etiologies in the period from 6 month and until 5 years (Pawar et al., 2016) Innate immune response in pediatric sepsis starts with the recognition on the pathogens by the host immune system pattern recognition receptors (PRRs) on innate immune cells monocytes and neutrophils and somatic tissues (Mithal et al., 2022). Adaptive immune response also plays various crucial roles. It is essential in controlling inflammation and preventing tissue damage following an infection, as well as restoring the overall balance of the host's immune system through multiple mechanisms, and these processes and functions are disturbed or become unregulated in sepsis, resulting in inadequate protection against infections and/or immune suppression (Brady et al., 2020). One of the main macrophage inflammatory protein 1 alpha (MIP-1) is MIP-1α/CCL3 which are secreted by variant of cells including monocytes, T and B lymphocytes, neutrophils, dendritic cell (Dc) and natural killer (NK). It plays a critical role in the T Lymphocyte Recruitment whereas MIP-1β/CCL4 tends selectively toward the activation of CD4+ T cells, while, MIP-1α/CCL3 is directed towards the selectively activation of CD8+ T cell (Bhavsar et al., 2015). The recent researches demonstrate that the influx of granulocytes and macrophages into the peritoneal cavity during polymicrobial sepsis is temporally associated with increases in peritoneal CXCL10 concentrations. Blockade of CXCL10 significantly reduces the influx and phagocytic activity of peritoneal granulocytes during polymicrobial sepsis and worsens survival, in addition to providing evidence that CXCL10 is critical for the effective recruitment of innate immune effector cells during neonatal sepsis, it was demonstrated that exogenous CXCL10 can directly stimulate granulocyte and macrophage phagocytic function in vitro (Cuenca et al., 2011). Furthermore, numerous studies have shown that MCP-1 is linked to polarized Th2 responses which boost the secretion of IL-4 by T cells. Moreover, a growing body of evidence suggests that MCP-1 plays a crucial role in the pathogenic processes that lead to sepsis, also controls the advancement of inflammation and the generation of pro-inflammatory cytokines, and other Multiple studies have revealed that MCP-1 levels are significantly elevated in sepsis and contribute to systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). (Wang et al., 2018)

For all of the above, this study aims to identify the relationship between the most important and most related laboratory values (neutrophil and lymphocyte values in addition to C-reactive protein) with these three biomarkers (Monocyte chemotactic Protein 1, Macrophage inflammatory protein 1 alpha and CXC motif chemokine Ligand 10) in addition to identifying the quality and sensitivity of these biomarkers and showing the most important differences between them.

2. Materials and Methods

Blood sample were collected from 100 participants which includes 50 cases of sepsis and 50 as healthy control group at age ranged from > 1-14 years old attending to Children's Teaching Hospital in Karbala /Iraq during the period extended from October to April (2024). The blood specimen collected on EDTA tube and shaken up then was examined as soon as possible in automated hematology analysers (Swelab Alfa, Sweden) to count white blood cells. Immunological markers examined and estimated by Sandwich ELISA technique.

2.1. Statistical Analysis

Measures of central tendency for demographic data and laboratory values were defined by using frequencies expressing the sample size and arithmetic means. Furthermore, Statistical dispersion was estimated using Standard deviation (SD) for both the demographic parameters of the sample and the laboratory values. Person's correlation test was used in order to identify the association between Serum biomarkers and laboratory values of neutrophils, lymphocytes and CRP, (0.05 and 0.01 probability) using SPSS software (Version 26.0). ROC Curve analysis was used to estimate the sensitivity and selectivity of the biomarker using MedCalc software (Version 22).

3. Results:

3.1. Demographical and Clinical Characteristics of The Study Patients

This study recruited a total of 100 individuals comprising of 50 pediatric sepsis patients at the Children Teaching Hospital in kerbala . The patients were aged-matched with 50 healthy control group with matched demographic features as the pediatric sepsis patients. The mean age of the pediatric sepsis patients was 5.46 ±3.5 years, comprising of 32 females, aged 4.97±3.9 years with a weight of 17.45±9.1 kg and temperature at 38.66±0.8, as well as 18 males, aged 6.31±2.7 years with a weight of 19.64±8.6 kg and temperature at 38.60±0.5. The control group had the mean age of 6.96±3.4 years, comprising of 29 females, aged 6.65±3.9 years with a weight of 17.10±7.3kg, as well as 21 males, aged 7.38±2.5 years with a weight of 18.19±5.3 kg. The age, gender, weight and temperature of the study subjects were highly significant results, as present in Table1.

Table1: Age, Gender, Weight and Temperature of the Study Subjects

Groups	Gender	n	Age (mean±SD) (years)	p value	Weight (mean± SD)/Kg	p value	Mean Temp (± SD) (C°)	p value
Pediatric sepsis	**Female**	32	4.97±3.9	0.000*	17.45±9.1	0.028*	38.66±0.8	0.000*
	Male	18	6.31±2.7		19.64±8.6		38.60±0.5	
	Total	50	5.46±3.5		18.24±8.9		38.64±0.71	
Control	**Female**	29	6.65±3.9		17.10±7.3			
	Male	21	7.38±2.5		18.19±5.3			
	Total	50	6.96±3.4		17.56±6.5			
* Significant *p value* < 0.05, SD (standard deviation)								

3.2.Laboratory Data of Patients Group

Regarding Laboratory data Table2, the Neutrophil mean of the pediatric sepsis patients was 62.45±24.6 cell (range, 10 – 97 cell), lymphocyte mean 47.90±33.4 cell (range, 6 – 103cell) and the mean of CRP was 50.52±44.1mg/L (range, 0.88 – 221mg/L).

Table2: Laboratory Data of Pediatric Sepsis Patient

Laboratory data	Mean	SD	Min	Max
Neutrophil	62.45	24.6	10	97
Lymphocyte	47.90	33.4	6	103
CRP mg/L	50.52	44.1	0.88	221
CRP: C-Reactive Protein				

3.3. Analysis of Serum Biomarker and Laboratory Data

Table3 shows Pearson's correlation matrix indication the association between the Serum biomarkers (MCP-1, MIP-1α and CXCL10) and the laboratory data (Neutrophils, Lymphocyte and CRP) of the pediatric sepsis studied subjects. Weak negative correlation was observed between Lymphocyte and the three biomarkers (r = -0.060, r = -0.099, r = -0.015 for MCP-1, MIP-1α and CXCL10 respectively). While a weak positive correlation was observed between MCP-1 and the Neutrophils, CRP (r = 0.093, and r = 0.020 respectively), and between CXCL10 and the Neutrophils, CRP (r = 0.092, and r = 0.202 respectively).

Table3: Pearson's Correlation Matrix for The Serum Biomarkers (MCP-1, MIP-1α And CXCL10) And the Lab Data (Neutrophils, Lymphocyte And CRP) For the Study Subjects

Parameters	Neutrophils	Lymphocyte	CRP
MCP-1	0.093	-0.060	0.020
MIP-1α	0.084	-0.099	0.068
CXCL10	0.092	-0.015	0.202
MCP-1: monocyte chemotactic protein-1, MIP-1α: macrophage inflammatory protein-1 alpha, CXCL10: C-X-C motif chemokine ligand 10			

3.4. ROC Analysis of MCP-1, MIP-1α And CXCL10 Serum Biomarker and Gender

The ROC curves Fig.1 data showed that all of the three-biomarker had significant results ($p < 0.001$) with efficiency very good AUC curve with specificity of 100% for MCP-1 and 52%, 96%for MIP-1α and CXCL10 respectively, and with the sensitivity of 82% for MIP-1α, and 56%, 54%for MCP-1 and CXCL10 respectively Table4.

Table4: ROC Curve Data for the Measured MCP-1, MIP-1α and CXCL10

Parameters	MCP-1	MIP-1α	CXCL10
AUC	0.770	0.696	0.758
p-value	<0.0001	<0.001	<0.0001
Best Cut-off	>981.17	>109	>142
Sensitivity (%)	56	82	54
Specificity (%)	100	52	96
AUC: Area Under Curve			

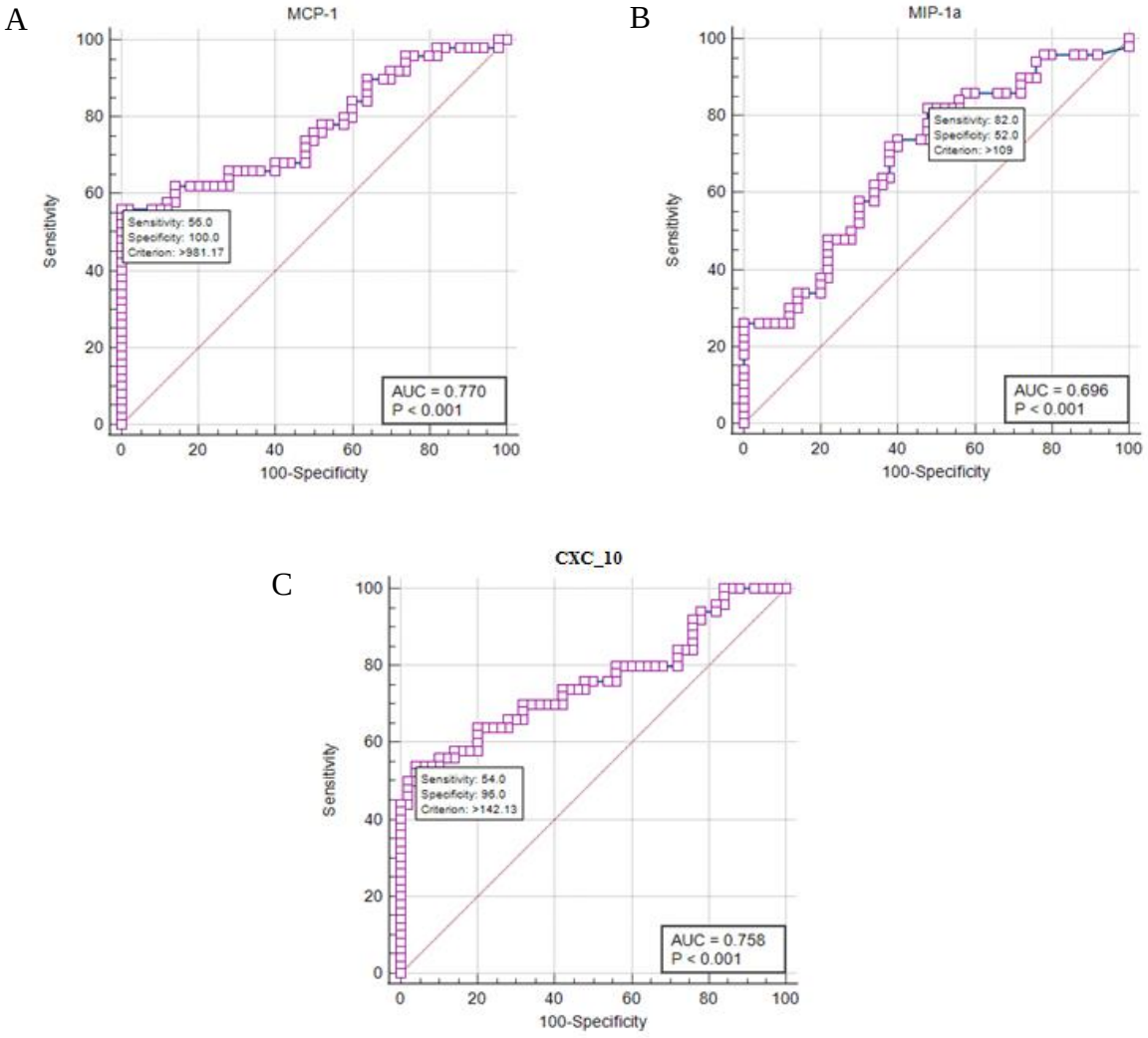

Figure1: Represents ROC Curve for The Measured of:
A) MCP-1, **B**) MIP-1α and **C**) CXCL10

4. Discussion

Differential diagnosis is considered very difficult in the case of pediatric sepsis due to the presence of many possible diagnoses that must be differentiated between them, especially congenital heart disease and metabolic disease in newborns, which are very common and can be confused with the features of pediatric sepsis shock (Hilarius et al., 2020). In addition, Age and underlying cardiovascular condition associated with the increasing in the odds ratio of the prevalence of pediatric sepsis with were estimated by 1.4 time for each variable in the United states (US) hospitalized pediatric patient between 2004 to 2012. Factors mentioned above were considered significant prognostic and risk factors side by side even with the organ dysfunction (Ruth et al., 2014). The current study showed a range of age results among male and female children with sepsis as shown in Table1, where the average age for females was (4.97 ± 3.9). (Charlson et al., 2018; Li et al., 2023) found that most cases of sepsis infection occur in children under the age of 10 years, Miura *et al* noted

in a study conducted in Japan using a national patient database where the study included children under the age of 20, and among 761 affected children, the age mean was (3), while, (McMullan et al., 2016) conducted a study on children under the age of about 18 years of age and they found that among the children with data, 1,873 children were infected, and the age mean was 57 months. Also, (Watson et al., 2003) found in a study conducted by the American Journal that the incidence of sepsis among males were (15) times higher than among females, this result was disagreeing with result of present study and this difference may be due to the sex-related differences in immunity and infection-related outcome that which have been found previously in animal and adult studies (40–47) suggesting that sex-related differences may be hormonal in origin. Najman *et al*., 2020 noted in a study of a group of children with fever between the ages of 1 month and 16 years, who had ≥ 1 warning sign for sepsis and their body temperature with a mean of 38.5(38.0-39.0). This result was consistent with current study result. Rapid diagnosis is considered one of the most important factors affecting the severity of pediatric sepsis. In order to achieve a rapid and effective diagnosis, there are several methodologies proposed (Andrea T Cruz et al., 2020), dysfunction of neutrophils which its leads to serious dangerous consequence that include TLR signaling deficits and altered apoptosis signaling pathways leading to immune dysfunction (Delano and Ward, 2016) . This immune system responds at a slower pace, but has the ability to identify specific antigens and use immunological memory to boost the immune response upon subsequent encounters with the same antigens, and it can depend on a smaller variety of cell types for its functions, which are lymphocytes, specifically T cells and B cells. In turn, B cells play a crucial role in producing antibodies and plasma cells essential for long-term immune defense, while T cells can be further categorized into various subclasses, each with distinct roles, such as CD4+, CD8+, gamma delta (γδ), and regulatory T cells (Tregs). (Brady et al., 2020). A study accomplished by (Ng et al., 2002)who found the neutrophil count in children with sepsis was 4.89(3.02-8.33). Also, another study who stated about children with mild sepsis, the neutrophil mean was 4.47(3.01-6.95) (da Silva et al., 2020; Sumitro et al., 2021). While in children with severe sepsis, the neutrophil mean was 5.52 (3.05-9.37). Also, there were increased in laboratory values, as the CRP mean was (50.5±44.1). A study conducted by the library International Medical Center on pediatric patients with a mean age of (6-169) months, where the CRP mean was (10.2±119.51), $p = 0.006$. In another study conducted on children, many children were found to have fever, as a high temperature is a warning sign of sepsis. This study included 291 children whose CRP value was 24 ml/l (Nijman et al., 2020). The present study showed that the Pearson correlation matrix indicated a set of associations between serum biomarkers (MCP-1, MIP-1α, and CXCL10) with laboratory data including neutrophils, lymphocytes, and CRP, for a pediatric sepsis subject Table3. (Inaba et al., 1997) reported the serum levels in children with meningitis showed that MIP-1α levels were strongly correlated with the number of neutrophils within the cerebrospinal fluid., $r = 0.750$ with $p < 0.001$, and there were significant correlations between MIP-1α levels and total lymphocyte count or neutrophil count ($r = 0.682$, $r = 0.478$) with ($p < 0.001$, $p < 0.001$) respectively. The present study showed that all three biomarkers had significant results ($p < 0.001$) with very good AUC curve efficiency with specificity of 100 for MCP-1 and 52, 96 for MIP-1α and CXCL10 respectively with sensitivity of 82 for MIP-1α, 56 and 54 for MCP. -1 and CXCL10, respectively Table4. A study

conducted by Li et *al* (2021b) showed that the levels of CXCL-10 in the serum of the sepsis children were high. It was also possible to measure serum levels using an area under the curve (AUC) of (0.885), a sensitivity of 81, and a specificity of 83.3. Also, (Song and Zheng, 2024) explained the value of the MCP-1. In the sepsis children, where the data of 82 children suffering from acute inflammatory conditions were analyzed according to the diagnostic criteria for sepsis, and their effectiveness, and the levels of use of this serum were analyzed using the area under the curve (AUC). The results were MCP-1 = 452.32 ± 2.97 pg/ Ml. AUC = 0.9406 with $p < 0.001$, as the results were significantly higher than those in the control group. In addition, (Gilholm et al., 2023) screened 3473 children for sepsis, and 523 children (15.1%) were found to have sepsis. The area under the receiver operating characteristic curve were (0.80, 95 CI 0.78 to 0.82) to reach a sensitivity of 90% the final model achieved a specificity of 51% confirmed by sensitivity analyzes using sepsis-related organ dysfunction scores and shock.

5. Conclusion

Our study suggests that MIP-1α have the highest sensitivity, so this marker seems to be exemplified an additional marker for immunodiagnostic of pediatric sepsis.

6. Ethical approval

The study protocol will be sent to the relevant ethical committee in the health directorate. Also, verbal approval will be taken from each participant before taking the sample. During samples collection, health measures and safety will be taken.

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