

ORIGINAL RESEARCH

## Correlation Of Interleukin-6 And C-Reactive Protein In Children With Fever

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### ABSTRACT

**Introduction:** Fever is the most frequent reason for hospital visit by the children. Paediatricians need markers, especially which increases early, to identify children at risk of severe bacterial infection. CRP and Interleukin-6 are such markers. Interleukin-6 is reported to rise earlier than CRP in children with fever.

**Objective:** To study the level and correlation of Interleukin-6 and C-reactive protein in children presenting with febrile illness

**Study Design:** Cross Sectional and descriptive study.

**Methods:** 45 children with history of fever within last 72 hours were enrolled. Immuno-compromised patient were excluded from the study. Serum levels of CRP and IL-6 were analyzed along with haematological parameters. Microsoft SPSS version 20 was used for data analysis. P- value less than 0.05 was considered as significant.

**Results:** Mean CRP value was  $4.2 \pm 0.9$  mg/dl. Mean interleukin-6 was  $60.5 \pm 10.9$  pg/ml. Interleukin-6 was found to be positively correlated with CRP ( $r=0.644$ ). This correlation was found to be statistically significant.

**Key words:** CRP, fever, IL-6

### INTRODUCTION

Fever is an important clinical signs of an infection in children <sup>(1)</sup>. It is a leading cause of morbidity and mortality in children worldwide. It encompasses a wide clinical spectrum including severe infection, septic shock, and multi-organ failure <sup>(2)</sup>. Global data on sepsis in children are incomplete, but it is estimated that infection accounts for most deaths (almost 60%) in children age under 5 years. The World Health Organization (WHO) has stated that the major cause of death in children worldwide are infectious diseases <sup>(2)</sup>. CRP is an acute phase protein whose synthesis increases within 4 to 6 hours after the onset of inflammation, doubling every 8 hours thereafter, and peaking at 36 to 50 hours <sup>(3)</sup>. Interleukin-6 (IL-6) is another important pro-inflammatory cytokine which rises in the early phase of inflammation, caused by

infection, surgery and trauma <sup>(4)</sup>. The present study was therefore undertaken with an aim to evaluate the level of IL-6 and CRP in children with febrile illness, and to evaluate their correlation.

## MATERIAL AND METHODS

This cross sectional and descriptive study was conducted in tertiary care Hospital after receiving permission from the Institutional Ethics Committee. Children of age group 1-10 year admitted in paediatric ward with fever (temp>38.0<sup>0</sup>C) in last 72 hours were enrolled. Children having immunodeficiency disorder or on prolonged high dose of steroid, antibiotic use within 72 hours before admission to the hospital, vaccination during the previous 3 days, fever of unknown origin, systemic fungal Infection and history of chronic illness were excluded from the study. Detailed clinical assessment was done. Serum levels of IL-6 and CRP were analysed by ELISA method (IL-6 Kit-Diclone Kit) and nephrometry method respectively along with other haematological parameters. Interpretation and analysis of obtained results has been carried out by using Microsoft Excel & statistical package for social sciences version 20. Qualitative data was expressed in the form of frequencies and percentages. Quantitative data was expressed in terms of mean  $\pm$  standard deviation (SD). Pearson's correlation test was used for statistical analysis. P < 0.05 was taken as significant.

## RESULTS

In the present study 45 children of age 1-10 years were enrolled. Female to male ratio was 1:1.6. 26 children were having fever at the time of blood sampling. Ratio of rural to urban population was 1:0.8. Base line characteristics have been shown in table 1.

**Table 1: Base line characteristics of subjects (n=45)**

<b>Mean age(SD<sup>#</sup>)</b>	6.08(3.56)
<b>Gender- Female : Male</b>	1:1.6
<b>Immunization Status- Complete: Incomplete</b>	0.6 1: 1.6
<b>Children having fever at the time of blood sampling (%)</b>	26 (57.78)
<b>Habitat- Rural : Urban</b>	1:0.8
<b>Food habit- Vegetarian : Non vegetarian</b>	1:0.32

### # SD: STANDARD DEVIATION

In six cases (13.33%) blood culture was positive; C-reactive protein was raised (>1mg/dl) in 25 cases (55.56%). Mean value of CRP and IL-6 was 4.23 $\pm$ 5.88 mg/dl

and  $60.45 \pm 73.43$  pg/ml respectively. The values of IL-6 and CRP were found to be positively correlated ( $r = 0.644$ ) and statistically significant ( $p < 0.001$ ).

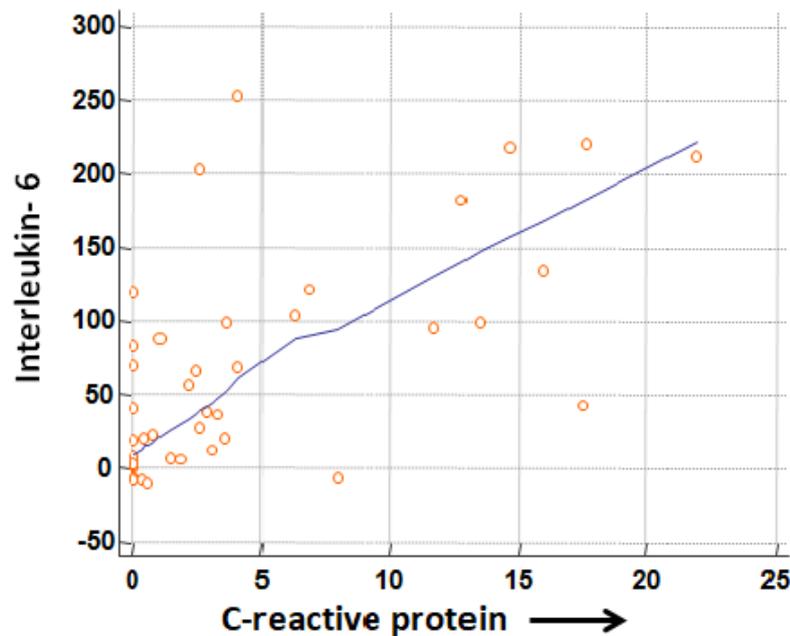
**Table 2: Statistical correlations between the variables of systemic inflammatory markers**

Pairs	Number of cases (N)	Correlation coefficient (r)	Significance (p value)**	95% CI*
IL-6 v/s TLC <sup>#</sup>	45	0.112	0.461	-0.1871 to 0.3932
IL-6 v/s Degree of temp <sup>β</sup>	45	-0.171	0.259	0.4428 to 0.1285
CRP v/s TLC	45	0.105	0.492	-0.1944 to 0.3867

\*CI = Confidence Interval; \*\* $P < 0.05$  is considered to be statically significant; # Total leucocyte count;  $\beta$  = temperature at the time of blood sampling

It was also observed that IL-6 and CRP had positive correlation with TLC count. However correlation was not statistically significant. Also, IL-6 was found to be negatively correlated with degree of body temperature at the time of sampling.

**Figure1: Correlation of Interleukin-6 and C-reactive protein.**



Number of cases: 45; Confidence Interval (CI): 0.432 - 0.788;  $P < 0.05$ ; Correlation coefficient ( $r$ ) = 0.644

## DISCUSSION

C-reactive protein is an acute phase protein, whose serum concentration is remarkably increased right after the occurrence of aggression to the body <sup>(5)</sup>. IL-6 is an important cytokine of the host's early response to infection. After exposure to bacterial product, concentration of IL-6 increases sharply and leads to the increase of CRP <sup>(6)</sup>.

In present study, it was observed that the mean value of IL-6 and CRP were  $60.45 \pm 73.43$  pg/ml and  $4.23 \pm 5.88$  mg/dl respectively. Interleukin-6 (IL-6) was positively correlated with C-reactive protein ( $r = 0.644$ ) and this correlation was found to be statistically significant ( $p < 0.05$ ). This was in accordance to the study by Marjaneh Zarkesh et al who had reported significant rise of both CRP and Serum IL-6 values in patients with serious bacterial infection <sup>(7)</sup>.

XiuliLv et al in a study on children with pneumonia had also reported a strong positive correlation between serum CRP level and serum IL-6 level in children with streptococcal pneumonia ( $R = 0.893$ ,  $p = 0.003$ ) <sup>(8)</sup>. Ghada El-Nady et al, in a study of IL-6 in paediatric patients admitted to intensive care unit (PICU), had reported that at the time of admission the children who had sepsis and progressed to develop septic shock, had mean Interleukin-6 (IL-6) value to be 215.4 pg/ml which was significantly higher ( $p = 0.017$ ) than the children who at the time of admission had only sepsis (but did not progress to septic shock); and the children with sepsis had mean IL-6 value of 65.3 pg/ml.

Thus we successfully documented a positive correlation between IL-6 and sepsis severity. Interleukin-6 can thus be a useful marker in initial evaluation of severity of illness in children <sup>(9)</sup>. Interleukin-6 can be used as an adjuvant to CRP in managing children presenting with febrile illness. As rise of IL-6 is known to be earlier than CRP<sup>(6)</sup>, so IL-6 can be used as an earlier predictor of severity of infection in children presenting with febrile illness, however further research is required to establish this fact. Also there is need for further studies to determine the cut off limit of IL-6 in differentiating the children with or without risk of severe bacterial infection.

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## COMPETING INTEREST

None

## CONTRIBUTORS

Conception & design of study: RM,AG; Generation of Data: RM, AG, VK; Drafting of Manuscript: RM, AG, VK, AK; intellectual input: RM, AG, VK, AK ; All authors have approved the final manuscript.

## REFERENCES

1. Salameh Khalil, GJ Awean, N Alkume, AK Shah Abdussalam. The outcome of blood cultures in febrile children presenting at the emergency department. Journal of Neonatal and Pediatric Medicine 2: 117. Doi:10.4172/2572-4983.1000117.
2. Plunkett A. Sepsis in children. BMJ. 2015; 350: 30-37.

3. Isaacman DJ, Burke BL. Utility of the serum C-reactive protein for detection of occult bacterial infection in children. *Arch Pediatr Adolesc Med.* 2002; 156(9): 905-9.
4. Zarkesh M, Sedaghat F, Heidarzadeh A, Tabrizi M, Bolooki-Moghadam K, Ghesmati S. Diagnostic value of IL-6, CRP, WBC, and absolute neutrophil count to predict serious bacterial infection in febrile infants. *Acta Med Iran.* 2015;53(7):408-11.
5. Sim JE, March CD, Cosman D. cDNA expression cloning of the IL-1 receptor, a member of the immunoglobulin super-family. *Science.* 1988;241:585-9.
6. Celik IH, Demirel G, Uras N, Oguz ES, Erdeve O, Dilmen U. The role of serum interleukin-6 and C-reactive protein levels for differentiating aetiology of neonatal sepsis. *Arch Argent Pediatr.* 2015;113(6):534-7.
7. Zarkesh M, Sedaghat F, Heidarzadeh A, Tabrizi M, Bolooki-Moghadam K, Ghesmati S. Diagnostic value of IL-6, CRP, WBC, and absolute neutrophil count to predict serious bacterial infection in febrile infants. *Acta Med Iran.* 2015;53(7):408-11.
8. XiuliLv, Le Kang, Yi Wang, Yan Shi, Jun Xin, Xiaodong Yang. Diagnostic and clinical value of C-reactive protein and interleukin-6 serum levels in children with *Streptococcus pneumoniae*. *Int J ClinExpPathol.* 2016;9(2):1474-80.
9. Nady G, Bayoumi M, Abdelkader A. Serum Interleukin-6 levels in children with sepsis and septic shock. *Egyptian Journal of Medical Microbiology.* 2008;17(3):411-12.