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# Tumor Necrosis Factor Alpha Levels As A Predictor Of Intussuception In Children: A Cross-Sectional Study

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## ABSTRACT

**Introduction:** Intussusception (IS) is a medical emergency characterized by intestinal obstruction, which can be fatal if not promptly treated. In addition, several studies have identified infectious diseases, both viral and bacterial, as common predisposing factors for IS, often leading to elevated serum levels of Tumor Necrosis Factor alpha (TNF-α). Inflammatory mediators, such as TNF-α can significantly influence gastrointestinal motility, and the resulting alterations may contribute to the development of intussusception. Hence, this study determines the relationship between TNF-α levels and intussusception in children.

**Methods:** This cross-sectional study was performed applying simple random sampling, which examined ELISA results on the blood of intussusception patients before exploratory laparotomy milking, resection, or enterostomy at an institution from January to December 2023.

**Results:** The sample population was 10 patients (6 males and 4 females) who underwent exploratory laparotomy milking (3) and resection/enterostomy (7). Based on the results, the TNF-α mean level was higher at 357.4032 in patients who underwent resection than 83.6314 in those who did not undergo the procedure. In addition, TNF-α levels in patients with resection/enterostomy were higher compared to those without resection with a p-value of $< \alpha$ ($0.000 < 0.05$).

**Conclusion:** The findings showed a significant association on TNF-α levels and the incidence of intussusception. TNF-α levels in intussusception patients who underwent resection/enterostomy were higher compared to those without resection. However, further studies using larger sample sizes were still needed to assess the relationship between TNF-α levels and other diseases, with healthy children as controls.

***Keywords:*** *Intussusception, Emergency treatment, Laparotomy, Tumor Necrosis Factor-alpha.*

## 1. INTRODUCTION

The IS (incidence of intussusception) typically ranges 1.5-4 cases for every 1000 live births.[1] This incidence decreases with age, only 30% of all cases in children aged older than 2 years. Several studies have shown that intussusception is a medical emergency associated with intestinal obstruction and can have fatal consequences if not treated immediately.[2] Although this condition etiology remains unclear, various factors and mechanisms suspected as potential causes. Among these, certain pathogens, particularly adenoviruses, are correlated with the onset of acute intussusception in children. Infectious etiology leading to mesenteric lymphadenopathy is another general pediatric intussusception cause. Hypertrophy of the Peyer patches in viral illnesses including adenovirus and rotavirus can also lead to the condition. In addition, several analysis have obtained a correlation between infection with viral and bacterial agents as well as intussusception, including adenovirus, Yersinia

enterocolitica, rotavirus, and Campylobacter jejuni. Intussusception is rarely correlated with generations of rotavirus vaccine administration in some settings.[3]

According to previous studies, the intussusception etiology was unclear but various pathogens, specifically adenovirus, have been found to be correlated with acute cases in children. In addition, viral and bacterial infectious diseases can raise serum Interleukin (IL)-6 and TNF-α (Tumor Necrosis Factor alpha) of affected patients. These cytokines can affect gastrointestinal motility, promoting intussusception development. Despite the association, no comprehensive cytokines profiling of patients with natural intussusception has been obtained to date.[4]

Several studies have shown that rotavirus infection is related to increased levels of TNF-$\alpha$ in vitro.[5,6] Inflammatory mediators, such as TNF-α, can also significantly influence gastrointestinal motility, [7] and alterations in motility induced by these agents may increase the intussusception development.[8] Children who underwent surgical reduction exhibited significantly higher IL-6, TNF-$\alpha$, and CRP (C-reactive protein) than those who were subjected to pneumatic reduction. [4] Hence, this analysis investigates the correlation between TNF-α levels as a predictor of intussusception in children.

## 2. METHODS

This observational cross-sectional study with simple random sampling was conducted among pediatric patients (<18 years old) who had a diagnosis of bowel intussusception. In addition, the procedures were carried out at Hasanuddin University Hospital, Network Hospital, Dr. Wahidin Sudirohusodo Hospital, and the network hospitals from September 2021 to October 2023. The inclusion criteria were intussusception patients aged <18 years, while the exclusion criteria were intussusception patients who underwent hydrostatic or pneumatic reduction and infectious comorbidities, such as bronchopneumonia and pneumonia. Diagnosis was carried out with sonography/plain abdominal radiographs or by contrast (including air) enema examinations of the colon.

*Clinical data and sample collection*

Clinical and demographic data were taken from patient medical records, and was diagnosed with intussusception who met the criteria (inclusion and exclusion) and provided informed consent were sampled.

*ELISA examination*

The TNF-$\alpha$ levels were quantified applying the human TNF-$\alpha$ ELISA kit manufactured by BT Lab (Shanghai Korain Biotech, Shanghai, China, catalog number E0082Hu-48T). TNF-$\alpha$ concentration was quantified in pg/mL (units of picograms per milliliter).

*Statistical analysis*

The data was examined with SPSS IBM version 25 (IBM Corp., Armonk, NY, USA), and the methodology applied to develop statistical tests and descriptive approaches. Descriptive methods were designed to identify the general characteristics of the study sample. Additionally, TNF-$\alpha$ levels of each patient were quantified using the conventional method of calculating the mean and standard deviation (SD). The statistical analysis employed the Chi-Square Test, and the results were deemed statistically significant when the p-value <0.05.

## 3. RESULTS

The demographic characteristics collected from the subjects were gender and age of patients, and when seen based on sex, most participants were male 6 (60%). The age group with the highest participants was the age group > 9 months (8 participants, 80%) (Table 1 and Figure 1).

**Table 1. Intussusception Patient Characteristics**

| Characteristics | n (%) |
|---|---|
| Birth weight (g) (mean±SD) | 2,850 ± 227.30 |
| **Sex** | |
| Male | 6 (60.0) |
| Female | 4 (40.0) |
| **Age** | |
| 0 - 9 month(s) | 2 (20.0) |
| > 9 months - 18 years | 8 (80.0) |

| Characteristics | n (%) |
|---|---|
| **Procedure** | |
| Milking Procedure | 3 (30.0) |
| Resection/enterostomy | 7 (70.0) |
| **History of Complimentary Feeding (weaning food)** | |
| No. | 4 (40.0) |
| Yes | 6 (60.0) |
| **History of Pregnancy** | |
| Aterm | 10 (100.0) |
| Preterm | 0 (0) |
| **History of Delivery** | |
| Normal | 5 (50.0) |
| Sectio Caesarea | 5 (50.0) |
| **History of Diarrhea** | |
| No. | 10 (100.0) |
| Yes | 0 (0.0) |
| **History of URTI** | |
| No. | 7 (70.0) |
| Yes | 3 (30.0) |
| **History of GI Tract Infection** | |
| No. | 10 (100.0) |
| Yes | 0 (0.0) |

Note: URTI, upper respiratory tract infection; GI, Gastrointestinal; SD, standard deviation.

In this study, it was found that 7 subjects (70.0%) underwent a Resection Anastomosis type of procedure, and the majority of participants including 6 subjects (60.0%), were infants with a mean birth weight (2,850 ± 227.30 gr). All samples had a history of a term birth and no history of diarrhea and gastrointestinal infections. However, 7 subjects (70.0%) were patients with a history of acute respiratory infections. In this study, it was found that the level of TNF-α in intussusception patients who did not undergo intestinal resection or milking was 83.63 ± 8.15, while intussusception patients who underwent intestinal resection and enterostomy had mean levels of 357.40 ± 39.85.

**Table 2. Relationship between TNF-α Levels with Intussusception**

| Variable | Procedure | | OR | p-value |
|---|---|---|---|---|
| | Milking Procedure | Resection/ Enterostomy | | |
| **Sex** | | | | |
| Male | 2 (33.3) | 4 (66.7) | 1.500 (0.08-25.39) | 0.77 |
| Female | 1(25.0) | 3 (75.0) | | |
| **Age (month)** | | | | |

| Variable | Procedure | | OR | p-value |
|---|---|---|---|---|
| | Milking Procedure | Resection/ Enterostomy | | |
| 0 - 9 | 1 (50.0) | 1 (50.0) | 0.30 (0.12-73.64) | 0.49 |
| >9 | 2 (25.0) | 6 (75.0) | | |
| **History of Complimentary Feeding (weaning food)** | | | | |
| Yes | 1 (25.0) | 3(75.0) | 0.66 (0.39-11.28) | 0.77 |
| No | 2 (33.3) | 4 (66.7) | | |
| **History of Pregnancy** | | | | |
| Normal | 1 (20.0) | 4 (80.0) | 0.37 (0.02-6.34) | 0.49 |
| Sectio caesaria | 2 (40.0) | 3490 (60.0) | | |
| **History of URTI** | | | | |
| Yes | 2 (28.6) | 5 (71.4) | 0.37 (0.02-6.34) | 0.88 |
| No | 1 (33.3) | 2 (66.7) | | |
| **TNF-a** | | | | |
| Low | 3 (75.0) | 1 (25.0) | 0.250 (0.04-1.36) | 0.01 |
| High | 0 (0.0) | 6 (100.0) | | |

Note: Chi-Square Test; significant if p-value <0.05; URTI, upper respiratory tract infection.

In Table 2, the 5 demographic variables assessed in this study were found to have no association with the occurrence of intussusception, where the p-value for sex was 0.77 and for age was 0.49. The complementary feeding (weaning food) history was 0.778, the history of childbirth was 0.490, and the history of URTI was 0.880. There was a significant association between the TNF- $\alpha$ level and the intussusception occurrence with 0.011 p-value (p-value <0.05).

## 4. DISCUSSION

This analysis showed most participants were male, with the highest number in the age group > 9 months. The majority underwent Resection Anastomosis procedures and were infants with normal birth weight. All had a history of a term birth and some had a history of acute respiratory infections. Based on the results, patients who underwent intestinal resection had significantly higher TNF-α. The variables assessed showed no association with intussusception except for TNF-α levels, which had a significant association. Li et al. reported that the recurrent intussusception incidence was 18.41%, and TH2/Th1 cytokine synchrony was closely correlated with the recurrence. Children aged under 2 years account for 80% of intussusception cases, with the incidence rate decreasing from year to year, and cases were very rare in those aged over 5 years.[9] Marsicovetere et al. also obtained a higher incidence of intussusception in males than females, with the usual age of 6 to 18 months.[10]

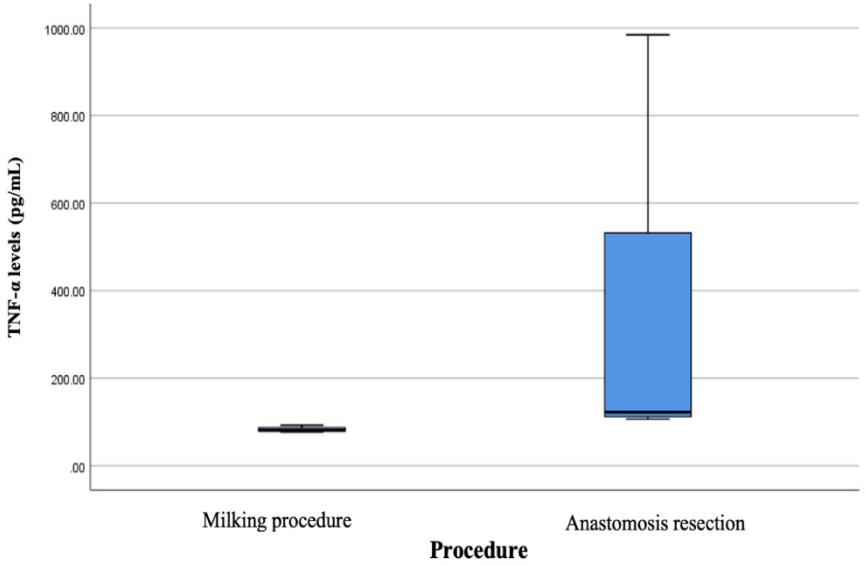


**Figure 1. TNF- α Levels in milking procedure and resection/enterostomy**

The analysis of intussusception incidence rate was 21/100,000 children aged<15 years. Additionally, previous analysis, the intussusception incidence was 31.61/100,000 in children aged < 5 years, and it was more common in boys.[10,11] The most common age group diagnosed with intussusception in this analysis was 1-3 years. Meanwhile, in the previous analysis, the common age group impacted was 6-11 months. This is appropriate to this study results, where the most common age for intussusception was above or equal to 9 months, there were more men than women.[12] The etiology of intussusception in children was unknown, but several studies had shown that intestinal invagination was caused by lymphoid hyperplasia in the gastrointestinal tract after an infection. [4,13] The digestive tract, as the largest surface exposed to environmental factors, was lined by a single epithelial cells layer which served as a barrier between the tissue and the contents of the intestinal lumen. This lumen contained a diverse microflora of viruses, fungi, and bacteria, along with water, nutrients, and environmental toxins. Maintaining a balance between cell growth at the crypt base and cell death at the villi tips was essential for intestinal homeostasis. Disruption in this balance, with excessive proliferation, could lead to tumor formation, while excessive cell death often affected the integrity of the epithelial barrier.[11,14-16]

The TNF-α was primarily characterized as a proinflammatory cytokine that is crucial in balancing intestinal integrity. Paradoxically, it was also implicated in the intestinal inflammation pathogenesis.[5] In the intestine, TNF-α was produced by immune cells and by intestinal epithelial cells, specifically Paneth cells. Studies in mice had demonstrated constitutive TNF-α production by Paneth cells, and during inflammation, patients with chronic inflammatory conditions also exhibited increased TNF-α production by these cells. Furthermore, individuals experiencing chronic intestinal inflammation demonstrated a raising TNF-α levels because of a raising TNF-α-secreting cells in the intestinal tissue.[17] Based on this study, most patients, specifically 6 subjects (60.0%), were infants introduced to complementary feeding with a mean birth weight of 2,85 ± 227.30 (mean ± SD). All samples had a history of full-term births and no reported instances of diarrhea or gastrointestinal infections. However, 3 subjects (30.0%) had a history of URTI, and in most intussusception cases in children, the cause was not obtained. Intussusception seemed to occur more often in the fall and winter. This is due to children with the signs also had flu-like symptoms, and some suspected a virus could affect the condition.

Viruses also played a role in gastrointestinal diseases caused by bacteria. For example, Rotavirus is widely known to be the causal agent of gastroenteritis, particularly among children aged < 5 years. In addition, its infection is related to increased levels of TNF- α in vitro.[5] When exogenous TNF- α was applied to Rotavirus-infected intestinal epithelial cells, a significant reduction in total viral RNA levels was observed. The TNFR1 gene in these cells counteracted the TNF- α -mediated antiviral effects, indicating that TNF- α signaling played a protective role.[5,14,17,18]

Recent studies had shown that intestinal inflammation induced by TNF- α in TNF $^{deltaARE}$ mice depended entirely on the microbiota. In germ-free TNF $^{deltaARE}$ mice, intestinal inflammation was absent. These results had implications for understanding the relationship between TNF- α signaling, inflammation, and microbial composition. Furthermore, these studies suggested that during bacterial infection, increased TNF- α signaling could exert deleterious effects on intestinal epithelial cells.[19-23]

Bessey *et al,* obtained that children with intussusception exhibited raised pro-inflammatory cytokines, including IFN-γ, TNF-α, MIP-1β, IL-1β, IL-2, IL-6, IL-7, IL-8, and IL-17, as well as anti-inflammatory cytokines such as IL-1RA, IL-4, IL-5, and IL-13 than those treated for surgical conditions or symptoms of gastroenteritis.[4] These cytokines served as markers for intussusception. Infectious diseases due to bacteria and viruses could lead to a raise in IL-6 and TNF-α levels in a patient's serum. Both cytokines were known to influence gastrointestinal motility, potentially impacting or promoting the development of intussusception.[16,20-23] Another study, conducted for post-licensure monitoring of intussusception in South Africa following the Rotarix vaccine introduction into the immunization program nationally in 2009, found no association between intussusception and rotavirus vaccination in infants.[10,24]

Serum analysis revealed a significant development in various pro-inflammatory and anti-inflammatory cytokines in intussusception cases than those with GEA controls. The most notable raise in pro-inflammatory cytokines was observed in IL-1β, IL-6, and IL-8 when compared with both surgical controls and GEA patients. Furthermore, proinflammatory cytokines including IFN-γ, TNF-α, MIP-1β, IL-2, PDGF-BB, IL-7, and IL-17 were also significantly upregulated in intussusception cases. Previous associations were observed between a raising level in IFN-γ, IL-6, TNF-α, and CRP and the severity of intussusception in children and experimental animal models. Children undergoing surgical reduction exhibited a significant development in IL-6 and TNF-α, as well as CRP, compared with those undergoing pneumatic reduction.[14,17,18] Badriyyah *et al,* reported a raising level in serum TNF-α levels related to LPS, but it was not blocked by rofecoxib pretreatment. However, no association between serum TNF-α and the intussusception development. The findings indicated that intussusception could be significantly reduced by pretreatment with a selective COX-2 inhibitor.[16] Sönmez *et al*, reported in a mouse study that a raising TNF-α and IL-6 levels induced by LPS associated well with intussusception [8]. Moreover, reducing these levels through COX inhibition by indomethacin prevented the occurrence of intussusception in an experimental model.[22,23]

The primary treatment for intussusception includes pneumatic/surgical reduction, with bowel resection being necessary when reduction fails. Another analysis compared these reduction technique and reported that children undergoing surgical intussusception reduction experienced a raising level in IL-6, TNF-α, and CRP than others with non-operative procedures (pneumatic reduction). The increased CRP correlated positively with the severity of the disease. A study by Bessey et al also observed a raising level in IL-6, TNF-α, and CRP in patients requiring surgical intervention compared to those undergoing pneumatic reduction.[4] In addition, GM-CSF (granulocyte-macrophage colony-stimulating factor) and G-CSF (granulocyte-colony stimulating factor) were found to be elevated in intussusception patients. This could be due to the upregulation of IL-1β, TNF-α, or IL-12, which were known to induce the cytokines production.[20-22]

The response of the body to surgery is associated with the tissue damage degree and the intestinal tract being particularly vulnerable to surgical stress. According to Tabuchi et al., the blood granulocyte-to-lymphocyte ratio served as a clinically significant marker for assessing perioperative stress in patients with colorectal surgery.[25] In addition, toll-like receptors, α-defensins, high-sensitivity CRP, and IL-6 had been employed as early indicators to measure the inflammatory response after colorectal resection.

The results of the study demonstrated elevated levels of TNF-α in intussusception patients who underwent resection compared to those in intussusception patients without resection. A significant correlation between TNF-α levels and intussusception was observed, with 0.011 p-value (p-value < 0.05). The assessment of high levels of TNF-α before surgery could serve as an indicator predicting that the intestine experiencing intussusception could have undergone necrosis.[16,22,23] During bacterial and viral infections, the regulation of various cytokines fluctuated based on the type of pathogen. Associated with infection, the host could activate a programmed cell death pathway to prevent the pathogen's spread. However, many pathogens had developed mechanisms to inhibit this process by producing apoptosis inhibitors. `Several studies showed that when apoptosis was blocked by viral proteins, it could trigger necroptotic cell death, a form of cell death independent of caspases.[16,23] In contrast to Nissan *et al*, intussusception induction by LPS occurs through a parallel pathway including cytokines, prostaglandins, and NO.[26] Their analysis reported LPS did not induce any changes that could be a starting point for intussusception by altering intestinal motility.[5,14,18]. Further study was needed with a larger sample size to evaluate the correlation between TNF-α levels in intussusception and other diseases, using healthy children as controls.

## 5. CONCLUSION

In conclusion, a significant association existed between TNF-α levels and the incidence of intussusception. TNF-α levels in intussusception patients who underwent resection/enterostomy were higher compared to intussusception patients without resection.

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