JOURNAL OF
CONTEMPORARY MEDICINE

DOI: 10.16899/jcm.823844
J Contemp Med 2021;11(4):500-505

Orjinal Araştırma / Original Article


# Role of NLR and MLR in Differentiating Childhood Tuberculosis From Community Acquired Pneumonia

## Çocukluk Çağı Tüberkülozunu Toplum Kaynaklı Pnömoniden Ayırmada Yeni Parametreler Arayışı - Mümkün mü?

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## Abstract

**Background:** The neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) are useful biomarkers of inflammation used in many diseases to evaluate bacteremia, disease activity, recurrence rate, surveillance and prognosis.

**Objective:** Aim of this study was to evaluate NLR and MLR in the differential diagnosis of children with pulmonary tuberculosis disease from community acquired pneumonia (CAP).

**Material and Method:** I reviewed hospital-records of 50 children with pulmonary tuberculosis disease in the Pediatric Infectious Disease Ward between June 2016 and December 2018, and compared; NLR and MLR with 50 CAP and 50 healthy children. Also; erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were compared between the tuberculosis and CAP group.

**Results:** When 3 groups were compared there was significant difference among NLR and MLR values between 3 groups. In pairwise-comparisons, there was significant difference among NLR and MLR values between tuberculosis versus healthy controls, and CAP versus healthy controls. However, there was no significant difference among NLR, MLR values between tuberculosis versus CAP groups.

**Conclusion:** This study is unique that evluates NLR and MLR in tuberculosis differentiation. Although NLR and MLR values are useful biomarkers of inflammation in both pulmonary tuberculosis and CAP seperately, they're not as useful as expected in differentiating tuberculosis from CAP in children.

**Keywords:** Tuberculosis, community acquired, pneumonia, child, neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio

## Öz

**Giriş:** Nötrofil-lenfosit oranı (NLO) ve monosit-lenfosit oranı (MLO), bakteriyemi, hastalık aktivitesi, nüks oranı, sürveyans ve prognozu değerlendirmek için birçok hastalıkta kullanılan yararlı inflamasyon biyobelirteçleridir.

**Amaç:** Bu çalışmanın amacı akciğer tüberkülozu olan çocukların TKP'den ayırıcı tanısında NLO ve MLO' nı değerlendirmektir.

**Gereç ve Yöntem:** Haziran 2016 ile Aralık 2018 tarihleri arasında Çocuk Enfeksiyon Hastalıkları Servisi'nde akciğer tüberkülozu olan 50 çocuğun hastane kayıtlarını incelenerek NLO ve MLO değerleri 50 TKP ve 50 sağlıklı çocuk ile karşılaştırıldı. Ayrıca; tüberküloz ve TKP grubu arasında eritrosit sedimantasyon hızı (ESR) ve C-reaktif protein değerleri (CRP) karşılaştırıldı.

**Bulgular:** 3 grup karşılaştırıldığında, 3 grup arasında NLO ve MLO değerleri arasında anlamlı fark vardı. İkili karşılaştırmalarda, sağlıklı kontrollere karşı tüberküloz ve TKP ile sağlıklı kontroller arasında NLO ve MLO değerleri arasında anlamlı fark vardı. Ancak tüberküloz ve TKP grupları arasında NLO, MLO değerleri arasında anlamlı bir fark yoktu.

**Sonuç:** Bu çalışma, çocukluk çağı tüberküloz ayırıcı tanısında NLO ve MLO'nı değerlendiren ilk çalışmadır. NLO ve MLO değerleri, hem akciğer tüberkülozu hem de TKP'de ayrı ayrı iyi birer inflamasyon biyobelirteci olmasına rağmen, çocuklarda tüberkülozu TKP'den ayırmada beklendiği kadar yararlı değildir.

**Anahtar Kelimeler:** Tüberküloz, toplum kaynaklı pnömoni, çocuk, notrofil lenfosit oranı, monosit lenfosit oranı

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**Received *(Geliş Tarihi)*:** 10.11.2020 **Accepted *(Kabul Tarihi)*:** 26.04.2021

## INTRODUCTION

Diagnosis of tuberculosis disease in children is still a very difficult problem for pediatricians all over the world. Children with pulmonary tuberculosis present various clinical symptoms; such as prolonged cough, fever, fatigue, sweating and anorexia but none of these symptoms are specific to tuberculosis. The gold standard test for the diagnosis of tuberculosis is culture, however the bacteriological confirmation rate is <30% for all pediatric tuberculosis cases.[1] Currently, tuberculosis disease diagnosis relies on clinical and radiological features, history of household exposure to Mycobacterium tuberculosis and the tuberculin skin testing (TST) in children. Interferon Gamma Release Assays (IGRAs) were evaluated for diagnosing tuberculosis disease; however their usage was expensive. The results were sometimes confusing; especially in children <5 years. Also like the TST, IGRAs did not differentiate TB disease from infection and had poor sensitivity among immunocompromised children with severe tuberculosis disease. Recently, mycobacteria specific antigen-induced and unstimulated cytokines IP10, IL5, IL13, IFN–γ, IL18 are evaluated as biomarkers to discriminate between tuberculosis disease and tuberculosis infection. These studies need funding and a long time through to be proven useful.[2,3]

Most of all childhood pulmonary tuberculosis cases are hospitalized as pneumonia at first and some of them are given pneumonia treatment during the diagnostic stage. Delays in the diagnosis can both lead to the worsening in the patient's clinical and nosocomial transmission of the bacilli to other patients and healthcare workers.[4]

While searching for a new, inexpensive and easily accessible marker contributing to the differential diagnosis of childhood pulmonary tuberculosis from CAP, we decided to evaluate the neutrophil to lymphocyte ratio (NLR), and monocyte to lymphocyte ratio (MLR) in tuberculosis patients and CAP groups. There are many studies investigating the hematological parameters NLR and MLR as markers of inflammation in several rheumatologic, cancer and/or infectious diseases.[5-8] While many studies supported the usefulness of these parameters, some studies did not.[9-12] In this study, we compared the NLR and MLR values of our pulmonary tuberculosis patients with CAP patients and healthy children to determine their usability in the differential diagnosis of childhood pulmonary tuberculosis on admission. Also, the well known inflammation markers ESR and CRP were compared between the tuberculosis and CAP groups. Healthy controls did not have any ESR or CRP values studied, so they weren't included in the comparison of ESR and CRP.

## MATERIAL AND METHOD

The medical records of patients who were diagnosed and treated for pulmonary tuberculosis disease and community acquired pneumonia in the pediatric infection ward between June 2017 and December 2019 were evaluated. A total of 50 children with pulmonary tuberculosis; group T and 50 children with community acquired pneumonia; group P and 50 age- and gender-matched healthy control children; group C were enrolled in the study.

The diagnosis of tuberculosis disease was established according to the first 3 diagnostic categories of NIH criteria.[13] The first category included confirmed tuberculosis cases with positive smear of sputum or early morning gastric aspirate and/ or positive culture for M.tuberculosis. The second category included highly probable cases having clinical symptoms and radiological signs of tuberculosis disease with an active or recently treated family member with tuberculosis disease. The third category included possible cases with positive TST or IGRAs and not responding to standard pneumonia treatment, with/or without an active or recently treated family member with tuberculosis disease. Of the tuberculosis group 17 (34%) patients were in category 1, 31 (62 %) patients were in category 2, 2 (4%) patients were in category 3. All children in the third category fully recovered with antituberculosis treatment.

The community acquired pneumonia diagnosis was established according to the physical examination, laboratory findings, and chest X-ray findings of children.[14,15] Children admitted with cough, fever and/or localized chest pain, having moderate to severe respiratory distress, focal auscultatory findings, elevated acute phase reactants and radigraphic features of alveolar infiltrates, segmental/ lobar consolidation, with/without pleural effusion/empyema were diagnosed as pneumonia.[14-16] CAP group consisted of these children whose hospital records were available.

Healthy children were selected through children who applied to hospital for routine check-up, or vaccination status screening or for preoperative evaluation of minor elective surgery (for example: hernia repair). Children with any sign of infection or systemic illness were excluded from the control group.

Hematological parameters including white blood cell (WBC) count, hemoglobin (Hb), neutrophil count, lymphocyte count, platelet count (PLT), monocyte count and mean platelet volume (MPV) were recorded for all groups. NLR, MLR and platelet to lymphocyte ratio (PLR) were calculated as the ratio of neutrophils to lymphocytes, monocytes to lymphocytes and platelets to lymphocytes, respectively. C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) of all tuberculosis and CAP patients were recorded if available. Comparison between the three groups were performed with regards to WBC, neutrophil count, lymphocyte count, monocyte count, platelet count, MPV, NLR and PLR. White blood cell, Hb, neutrophil count, lymphocyte count, PLT, MPV, NLR, MLR and PLR values. CRP and ESR were compared between the tuberculosis and CAP groups.

The blood cell counts were performed in the Sysmex XN-350 and C-reactive protein measures were determined on the BN Prospec (Dade Behring, Siemens) Nephelometer.

The Non-Interventional Clinical Ethics Committee of Yüksek İhtisas Education and Research Hospital approved the article with number 2019/01-26.

### Statistical Analysis

The normality of data distribution was determined using the Kolmogorov-Smirnov test. Normally distributed numerical variables were expressed in mean plus/minus standard deviation. Normally distributed numerical variables were compared using the Student's t-test or One-way ANOVA test. Tukey test was used for Post Hoc Tests. Data corresponding to an abnormal distribution were expressed in median (minimum-maximum). Abnormally distrubuted numerical data were compared using the non-parametric Mann–Whitney U-test or Kruskal-Wallis test. The Chi-square test was used to compare categorical variables between the groups. P-values of less than 0.05 were considered statistically significant. The data were analyzed using Statistical Package for Social Sciences (SPSS) version 22.0 program for Windows.

## RESULTS

The median age of the tuberculosis group was 132 months (15-202 months) and 56% (n=28) were male. The median age of the CAP group was 87.5 months (3-201 months) and 58% (n=29) were male. The median age of the control group was 89 months (16-194 months) and 60% (n=30) were male. There were no significant difference among the median ages (p=0.061) and gender distribution (p=0.686) between the three groups (**Table 1**).

Table 1. Demographic features of tuberculosis, CAP and healthy control group

| Demographic features | Tuberculosis Group | CAP Group | Healthy Control Group | p value |
|---|---|---|---|---|
| Age (months) Median (min-max) | 123 (15-202) | 87,5 (3-201) | 89 ( 16-194) | 0.061 |
| Gender (Male/Female) N (%) | 28/22 (56 /44) | 29/21 (58/42) | 30/20 (60/40) | 0.686 |

The most common symptoms in tuberculosis group at admission were cough (92%), persistent cough (88% with cough longer than 3 weeks, 72% with sputum), night sweating (72%), anorexia (72%), weakness (64%), fever (52%), hemoptysis (26%) and chest pain (8%). The CAP group was admitted with cough (92%, 24% with sputum), fever (92%), chest pain (24%) anorexia (20%), and weakness (18%). Only 4 (8%) of CAP patients had prolonged cough longer than 3 weeks and all of them were diagnosed with empyema. There was significant difference among the frequencies of persistent cough, cough with sputum, night sweating, anorexia, weakness, fever, and chest pain between the tuberculosis and CAP groups (all were p<0.001) (**Table 2**). Peripheral lymphadenitis was found in 14%, hepatomegaly and/or splenomegaly in 10%, abdominal pain in 6% and erythema nodosum in 4% in the tuberculosis group. Abdominal pain was found in 6%, hepatomegaly and/or splenomegaly in 4% in the CAP group. There was no significant difference among the frequencies of abdominal pain (p=0.42) and hepatomegaly and/or splenomegaly (p=0.26).

Tuberculin skin test (TST) of ≥15mm was found in 60% (BCG vaccination is a part of routine childhood vaccination program applied at age 2 months in Turkey), ≥10 mm was found in 66% while the anergy rate was 20% in the tuberculosis group. TST was applied to 12 (24%) of the CAP patients and none of them had positive tuberculin skin test ≥15 mm (**Table 2**). Four of these cases were diagnosed with empyema and 8 other cases had mild to moderate parapneumonic effusion fully recovering with pneumonia treatment.

Table 2. Symptoms, clinical signs and TST results of tuberculosis and CAP patients

| Symptoms and clinical signs | Tuberculosis Group (n=50; %) | CAP Group (n=50; %) | p value |
|---|---|---|---|
| Cough | 45; 96% | 46; 92% | 1 |
| Persistent Cough* | 44; 88% | 4; 8% | <0.001 |
| (cough with sputum) | 36; 72% | 12; 24% | <0.001 |
| Night sweating | 36; 72% | 2; 4% | <0.001 |
| Anorexia | 36; 72% | 10; 20% | <0.001 |
| Weakness | 32; 64% | 9; 18% | <0.001 |
| Fever | 26; 52% | 46; 92% | <0.001 |
| Hemoptysis | 13; 26% | - | |
| Peripheral lymphadenitis | 7; 14% | - | |
| Chest pain | 4; 8% | 12; 24% | 0.055 |
| Abdominal pain | 5; 10% | 3; 6% | 0.425 |
| Hepatomegaly±Splenomegaly | 5; 10% | 2; 4% | 0.264 |
| Erythema nodosum | 2; 4% | - | |
| **TST result** | **(n; %)** | **(n; %)** | |
| 0 mm | 10; 20% | 3; 6% | |
| <10 mm | 7; 14% | 7; 14% | |
| 10-14 mm | 3; 6% | 2; 4% | |
| ≥15 mm | 30; 60% | - | |

*Cough longer than 3 weeks

Of the tuberculosis patients 17 (34%) had microbiological diagnosis [M. tuberculosis recovered from either sputum or early morning gastric aspirate (GA) or another body fluid (pleural fluid)], 3 (6%) patients had also histopathological diagnosis simultaneously with microbiological diagnosis; 33 (66%) patients had clinical and radiological diagnosis.

There was statistically significant difference among WBC, hemoglobin, neutrophil count, lymphocyte count, monocyte count, NLR, MLR and PLR values between the three groups (p<0.05). There was no statistically significant difference among platelet count and MPV between the three groups (p>0.05) (**Table 3**). In pairwise-comparisons, there was significant difference among WBC, hemoglobin, neutrophil count, lymphocyte count, monocyte count, NLR, MLR and PLR values between tuberculosis group versus healthy controls, and also CAP group versus healthy controls. However, although there was significant difference among WBC, neutrophil count and monocyte count between tuberculosis group and CAP groups, there was no difference among NLR, MLR and PLR values between tuberculosis and CAP groups (**Table 3**).

There was no significant difference among ESR values between the tuberculosis and CAP group (p<0.589), while median CRP value of CAP group significantly higher than tuberculosis group (p<0.017) (**Table 3**).

Table 3. Total comparison and pairwise-comparison of the laboratory findings of tuberculosis (T), CAP (P) and healthy control (C) groups

| Parameter | Tuberculosis group (T) | CAP group (P) | Healthy Control group (C) | p1 | p2 | p3 | p4 |
|---|---|---|---|---|---|---|---|
| WBC (µL) Median (min-max) | 8055 (4100-26920) | 11460 (3060-41140) | 6665 (4000-11820) | <0.001 | 0.006 | 0.002 | <0.001 |
| Hemoglobin (g/dL) Mean ± SD | 12.3±1.89 | 12.2±1.73 | 13.2±1.18 | <0.05 | 0.963 | 0.017 | 0.008 |
| Neutrophil count (µL) Median (min-max) | 5120 (1900-25120) | 6985 (970-37120) | 3060 (890-6600) | <0.001 | 0.018 | <0.001 | <0.001 |
| Monocyte count (µL) Median (min-max) | 570 (270-1420) | 695 (220-2420) | 435 (260-1150) | <0.001 | 0.005 | <0.001 | <0.001 |
| NLR Median (min-max) | 2.09 (0.43-30.43) | 3.3 (0.14-25.34) | 0.93 (0.28-2.75) | <0.001 | 0.479 | 0.001 | <0.001 |
| MLR Median (min-max) | 0.25 (0.09-1.91) | 0.35 (0.04-2.2) | 0.14 (0.03-0.32) | <0.001 | 0.345 | <0.001 | <0.001 |
| PLR Median (min-max) | 158.3 (53.7-647.1) | 141.9 (26.2-365.8) | 105.8 (57-203) | <0.001 | 0.329 | <0.001 | 0.002 |
| ESR (mm/h) Median (min-max) | 19 (2-101) | 26 (3-100) | | | 0.589 | | |
| CRP (mg/dL) Median (min-max) | 3.36 (0.10-202) | 26.3 (1.60-294) | | | 0.017 | | |

WBC: white blood cell; NLR: neutrophil/ lymphocyte ratio; MLR: monocyte/ lymphocyte ratio; PLR: platelet/ lymphocyte ratio; CRP: C reactive protein, ESR: erythrocyte sedimentation rate; p1: comparison of T&P&C; p2:comparison of T&P; p3: comparison of T&C; p4: comparison of P&C

## DISCUSSION

Differentiating children with pulmonary tuberculosis from CAP based only on history, physical examination, and radiological findings is difficult, since they mostly develop paucibacillary disease and cannot easily generate sputum.

In this study, I found that the frequency of persistent cough with sputum (cough longer than 3 weeks), anorexia, night sweating, weakness and hemoptizis were higher in the tuberculosis group. There was statistically significant difference in all these symptoms (p>0.001) .On the other hand, fever and chest pain frequency were higher in the CAP group. There was statistically significant difference in fever frequency (p<0.001) despite chest pain (p=0.055). In the study by Yoon et al.[17] adult tuberculosis cases were compared with CAP cases. In the study cough (p=0.030), night sweating (p=0.021), weight loss (p<0.001), symptom duration >2 weeks (p<0.001) and hemoptizis (p=0.024) were higher in tuberculosis group than CAP cases. Also, similar to this study, fever was statistically significantly higher in CAP group than tuberculosis group (p<0.001).

Many children with pulmonary tuberculosis are hospitalized with the initial diagnosis of pneumonia and some of them are given antibiotic treatment during the diagnostic stage. In some tuberculosis cases treatment failure or relapsing after standard pneumonia treatment gives us clues about tuberculosis especially when the families do not give appropriate information. Delay in the isolation and early treatment with anti-TB agents can cause worsening in the patient's clinical, higher mortality and morbidity and nosocomial transmission of the bacilli to other patients and healthcare workers.[4,18] Therefore, a rapid and readily available test to distinguish pulmonary TB from CAP is becoming essential.

White blood cell populations play an important role in the systemic inflammatory response to infection.[19,20] In some studies the value of NLR in infectious lung diseases is evaluated. In a study by Abakay et al.[21] NLR was reported to be significantly higher in patients with advanced pulmonary TB as opposed to patients with mild to moderate pulmonary TB. In the study by Yoon et al.[17] they stated that NLR could be used for the discrimination of tuberculosis and community acquired pneumonia in the adults. Myeloid-specific cells have been known to serve as host cells for M. tuberculosis growth and lymphoid cells are thought to be the major effector cells in TB immunity. Given the central role of monocytes and lymphocytes in the induction of immune responses, their levels in peripheral blood might be expected to reflect the state of an individual's immunity to tuberculosis. In a recent clinical analysis from a cohort of South African infants the relative ratio of monocytes to lymphocytes at the start of monitoring was shown to predict risk of developing tuberculosis disease during follow-up.[22] In a study by Ozdemir et al.[23] NLR and PLR were found not useful in differentiating tuberculous lymphadenitis from sarcoidosis in adults. In this study, I evaluated NLR and MLR values of children with pulmonary tuberculosis, CAP and compared with healthy children. I found NLR and MLR values were elevated in both groups of children either with tuberculosis or CAP. The results showed that NLR and MLR are useful inflammatory indicators of either tuberculosis or CAP in children when compared to healthy children. However, when these parameters are compared for differential diagnosis of TB from CAP, NLR and MLR are not as useful as expected. To describe all, NLR and MLR are not promising parameters for differential diagnosis of childhood pulmonary tuberculosis from CAP. Our results differed from the studies of adult studies above mentioned. I did not classify TB patients having moderate or advanced radiological disease in the study. Moreover, I did not perform statistical comparisons between subgroups of TB patients according to NIH categories and CAP patients. The pneumonia patients were also not classified as moderate or complicated pneumonia (with parapneumonic effusion or amphyema). It can be argued, however the number of study participants are in small numbers.

CRP is a well known inflammation marker, levels of which is related to tuberculosis disease severity.[24,25] I n a study by Schleicher et al.[26] levels of CRP were found to be higher in patients with HIV-positive CAP than in those with pulmonary TB disease. In a study by Kang et al.[27] CRP was found helpful in discriminating pulmonary tuberculosis from CAP ($p<0.001$). In the study CRP levels of CAP patients were found higher than pulmonary TB patients. Similar to these studies, CRP was high in 44% of tuberculosis group and 86% of CAP group. CRP levels of CAP patients in this study were higher than TB patients and the results were helpful in making differential diagnosis ($p=0.017$).

The retrospective nature of this study is the major limiting factor. Also, the study population is consisted of limited number of patients. However, as far as I know, there is no other study evaluating the NLR and MLR in childhood tuberculosis. As well, all the patients in the CAP were hospitalized patients with severe symptoms and complication of pneumonia. Some of them were also investigated thoroughly for tuberculosis exclusion. I speculate that the number of study population should be increased to reach a clearer conclusion about the diagnostic value of NLR and MLR in differential diagnosis of tuberculosis and CAP in children. Further prospective studies are needed to compare the results and make a final decision.

## CONCLUSION

This study shows that tuberculosis diagnosis still depends on clear evaluation of signs and symptoms, history of contact to an adult with tuberculosis disease, radiologic evidence and PPD test results. CRP can be a useful marker in differentiating pulmonary TB from CAP. However, NLR and MLR values are not as useful as expected..

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The Non-Interventional Clinical Ethics Committee of Yüksek İhtisas Education and Research Hospital approved the article with number 2019/01-26.

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

**Acknowledgment:** I have many thanks to Dr. Hümeyra Aslaner for her precious statistical analysis in this article.

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