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Original Article

High sensitivity C-reactive protein level in various manifestations of tuberculosis in children

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Abstract

Background Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. Of all TB patients, 40-50% are children. C-reactive protein (CRP) is produced during the inflammation process and is an indicator of active TB disease. High sensitivity CRP (hs-CRP) test has higher accuracy and sensitivity to detect CRP at lower levels.

Objective To compare hs-CRP in children with TB infection, pulmonary TB, and extra-pulmonary TB.

Methods This cross-sectional study of children with tuberculosis was conducted at Dr. Kariadi Hospital and the Semarang Community Health Center, Semarang, Central Java, from January 2020 - February 2021. Inclusion criteria were patients aged 1-18 years with suspected TB (contact with adult TB patient or clinically suspected to have TB).

Results From 95 study subjects, 19 had TB infection, 51 had pulmonary TB, and 25 had extra-pulmonary TB. There was a significant increase in hs-CRP level based on prolonged fever (P<0.001), enlarged lymph glands (P=0.004), joint swelling (P=0.006), low WHZ or BMI for age (P=0.048), positive bacteriological evidence (P<0.001), and negative/not done tuberculin skin test (P=0.001). There was a significant difference of hs-CRP level based on TB status, with the highest hs-CRP level in extra-pulmonary TB [14.3 (0.16-321.5) mg/L], followed by pulmonary TB [0.8 (0.3-129.1) mg/L], and TB infection [0.7 mg/l (0.3-20.2)]. The highest hs-CRP level for extra-pulmonary TB was found in abdominal TB [84.5 (0.6-321.5) mg/L].

Conclusion Children with extra-pulmonary TB have significantly higher hs-CRP than children with TB infection or pulmonary TB.

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Keywords: *high sensitivity C-reactive protein; tuberculosis; children*

Tuberculosis (TB) is a global health problem. According to the *World Health Organization* (WHO), the highest number of TB cases in 2016 resided in the Southeast Asia region (45%), and Indonesia is one of the top 5 countries with the highest number of TB cases in the world. Worldwide, children comprise 40-50% of the total patient population, and about 500,000 children suffer from TB every year.[1,2] The proportion of pediatric TB cases in Indonesia from 2007 to 2013 was 7.9% to 12%. In 2017, Indonesia ranked third in the world with 8% of TB cases, after India (27%) and China (9%). The WHO estimated a total of 842,000 TB cases in Indonesia in 2017, with 49 thousands cases aged ≤ 14 years, and 792,000 cases aged > 14 years.[3]

The condition of persistent immune response to Mycobacterium tuberculosis antigen but a lack of active TB clinical manifestations, is known as TB infection or latent TB infection (LTBI).[4] Only 5 to 10% of children over 3 years of age with LTBI progress to TB disease, mostly occurring within 1 to 2 years of

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initial infection. The most common site of infection are the lungs (80%). The risk of extra-pulmonary TB is highest in immunocompromised children, infants, and adolescents, such as those with human immunodeficiency virus (HIV) and malnourishment.[5]

C-reactive protein (CRP) is an acute phase marker, and its levels increase in response to IL-6-mediated pyogenic infection, such as in active TB.[6] The CRP has a high sensitivity to TB,[6] as CRP rises during the immune response. It has a relatively short half-life (about 19 hours), therefore, serum CRP levels reflect production and can, therefore, act as a biomarker of disease activity.[7] High-sensitivity CRP (hs-CRP) is a more accurate measurement of CRP, as it can detect low levels and is more sensitive. Increased hs-CRP levels indicate active processes of tuberculosis. The level of hs-CRP is useful as a biochemical parameter to assess for active TB disease, because smear culture takes a longer time to get results.[8] We aimed to compare hs-CRP in children with TB infection, pulmonary TB, and extra-pulmonary TB.

Methods

This analytic observational study with a cross-sectional design was conducted at Dr. Kariadi Hospital, Semarang and the Semarang Community Health Center, Semarang, Central Java, in January 2020 - February 2021. Subjects were children who met the inclusion criteria: aged 1-18 years, with suspected TB (contacts of adult TB patients or clinically suspected to have TB), and willing to participate in this study. Exclusion criteria were patients with overweight or obese nutritional status, chronic disease such as HIV, cardiovascular disease, malignancies, chronic kidney disease, diabetes mellitus, or other comorbidities. Patients with such conditions were excluded based on history, physical examination, and laboratory investigation, in addition to patients with trauma such as burns or fractures. Sampling was carried out consecutively. The minimum required sample size was determined using an unpaired numerical analysis formula, and calculated to be 20 subjects for each category.

Subjects were classified into three TB status categories: TB infection, pulmonary TB, and extra-pulmonary TB. The diagnosis of TB infection was confirmed by positive tuberculin skin test, no clinical symptoms of TB, negative bacteriological evidence if done, and normal X-ray results for LTBI or suggestive TB (subclinical TB). The diagnosis of pulmonary TB was confirmed by positive TB infection, clinical symptoms of TB, X-ray suggestive of TB, and may be accompanied by positive bacteriological examination results. Tuberculous disease that affects organs other than the lungs, such as the central nervous system (CNS), head and neck, musculoskeletal tissue, abdomen, heart, skin, eyes, and urogenital tract, was categorized in the extra-pulmonary TB category.

Subjects' data were taken from the medical records of pediatric patients at Dr. Kariadi Hospital, Semarang, Central Java, from January 2020 – January 2021. Subjects had been diagnosed with tuberculosis and undergone hs-CRP examination (*Nanopia*® CRP reagent produced by *Sekisui Medical Co.*, LTD Japan, in mg/dL, then converted to mg/l by multiplying it by 10). At the Semarang Community Health Center, Semarang, Central Java, subjects' parents provided informed consent; subjects underwent blood sampling and data collection from February 2020 - February 2021. Their hs-CRP was measured using hs-CRP ELISA reagent produced by Calbiotech, Inc, California, in mg/dL.

The data analysis was done by comparative test using *SPSS 16* software. For nominal variables, Chi-square test was performed. If the Chi-square test requirements were not met, Fisher's exact test, Mann-Whitney test, or Kruskal-Wallis test was performed. For numerical variables with normal data distribution, one-way ANOVA test was used. For non-normal data distribution, a non-parametric analysis was performed by either Mann-Whitney or Kruskal-Wallis test, accordingly. Results were considered significant if P values were < 0.05. This study was approved by the Health Research Ethics Committee at Dr. Kariadi Hospital, Semarang.

Results

Of 116 TB patients, 21 were excluded due to co-morbidities or overweight. In total, 95 subjects were analyzed, as shown in **Figure 1**.

Table 1 shows the characteristics of subjects. There was significant relationship between older age with extra-pulmonary TB, low weight-for-length/height

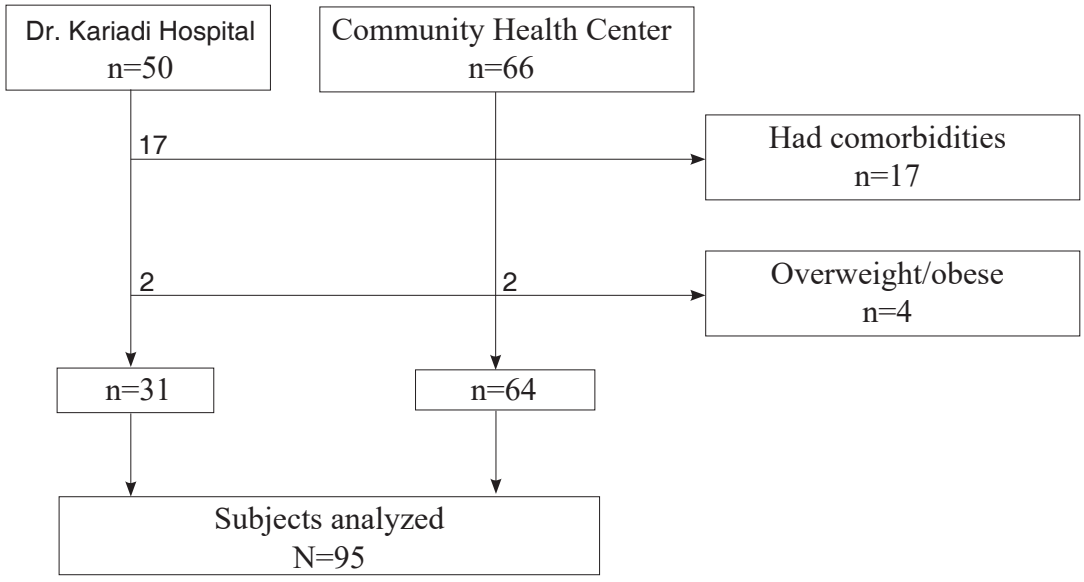


Figure 1. Flow diagram of subject inclusion

Table 1. Subjects' characteristics

Characteristics	TB infection (n=19)	TB disease		P value
		Pulmonary TB (n=51)	Extra-pulmonary TB (n=25)	
Gender, n				0.300[a]
Male	9	28	9	
Female	10	23	16	
Median age, months (range)	72 (12-177)	72 (12-203)	158 (29-312)	0.001[b]
Age, n				0.013[a]
<5 years	8	21	5	
5-10 years	7	19	5	
>10 years	4	11	15	
Median weight (range), kg	18 (7.74-55)	16.5 (4,5-45.35)	29.4 (9.3-58)	
Median height (range), cm	109.5 (69-161)	112 (61.5-160)	146 (83-174.2)	
Median HAZ (range)	-1.01 (-3.72 – 0.18)	-1.24 (-3.45 – 3.13)	-1.23 (-4.57 – 0.95)	0.855[b]
Mean WHZ or BMI for age (SD)	-0.38 (0.84)	-1.28 (1.19)	-1.23 (1.67)	0.008[c]
Tuberculin skin test, n				1.000[b]
Positive	19	51	13	
Negative	0	0	6	
Not done	0	0	6	
TB contact, n				<0.001[b]
No contact	8	19	22	
AFB -/not cler	8	20	2	
AFB +	3	21	1	
Chest X-ray, n				0.047[b]
Suggestive TB	18	51	14	
Not suggestive TB	1	0	8	
Not done	0	0	3	
Bacteriology, n				<0.001[b]
Positive	0	2	5	
Negative	1	6	15	
Not done	18	43	5	

Significant (P<0.05); [a]Chi-square; [b]One-way ANOVA; [c]Kruskal-Wallis; HAZ=height-for-age; WHZ=weight-for-length/height z-score; BMI=body mass index; SD=standard deviation; AFB=acid-fast bacillus

z-score (WHZ) or body mass index (BMI) for age with, pulmonary/extra-pulmonary TB, no history of TB contact, with extra-pulmonary TB, suggestive chest x-ray , with pulmonary TB, and positive bacteriologyical with extra-pulmonary TB.

Patients in the TB infection group had no clinical symptoms. The clinical profiles comparisons of the pulmonary TB and extra-pulmonary TB groups are shown in **Figure 2**. There were significant relationships between TB status and clinical history of prolonged fever and joint swelling. Prolonged fever was more commonly found in extra-pulmonary TB, and joint swelling was only found in extra-pulmonary TB.

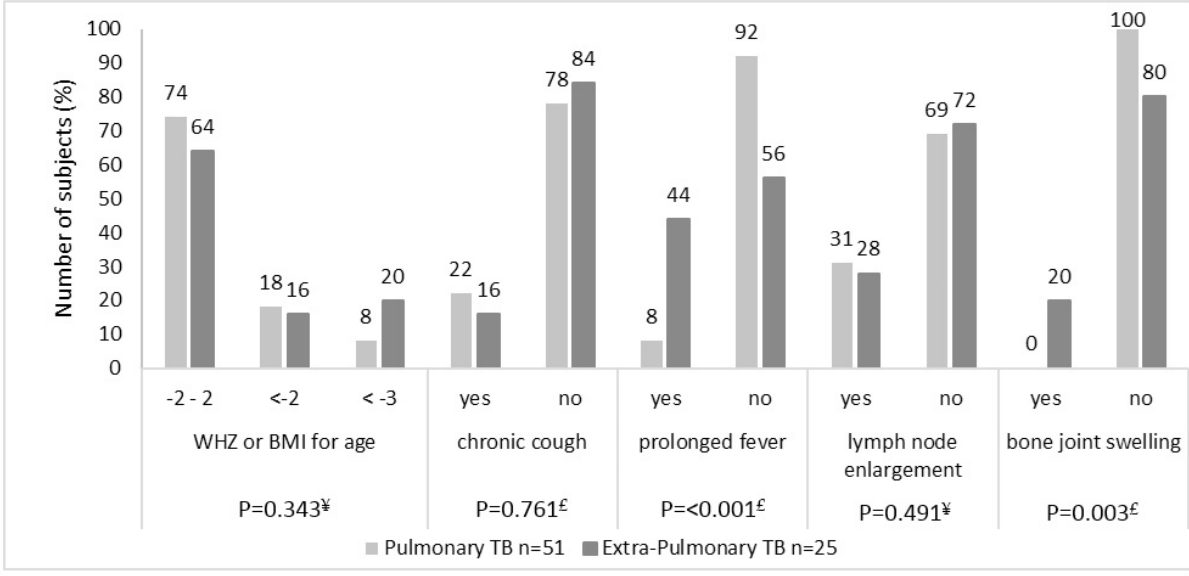
Table 2 shows hs-CRP levels based on characteristics of subjects. The Hs-CRP was significantly higher in the < -3 SD WHZ group than the < -2 SD and -2 – 2SD groups, as well as in the prolonged fever, enlarged lymph node, joint swelling, negative/not done TST, positive bacteriology, and extra-pulmonary TB groups.

Table 3 shows hs-CRP levels according to the location of the extra-pulmonary TB. The highest levels of hs-CRP were in abdominal TB, followed by arthritis TB. The lowest level of hs-CRP was found in ocular TB.

Discussion

Slightly more of our TB patients were girls (49; 51.6%) than boys (46; 48.4%), in contrast to the global situation, in which TB affects more males. A study in South India noted a male to female ratio of 2 to 1 in TB patients.[9] However, a study in Semarang, Central Java, found that most pediatric TB cases were female (55.2%).[10] We also found no significant difference in hs-CRP levels between genders.

There was a significant relationship between patient age and TB status. TB infection and pulmonary TB were mostly from the <5 years age group, whereas 60% of those with extrapulmonary TB were >10 years of age. A previous study reported that the highest risk of pulmonary tuberculosis after primary infection was in the young-age groups, <2 years old (10-20%) and infancy (30-40%), due to immature immunity.[11] However, extra-pulmonary TB patients had a median age of 158 (29-312) months, who were mostly in the > 10 years age group. In contrast, a previous study described a high risk of disseminated TB in the <2 years of age group (2-5%), especially for infants (10-20%), while the >10 years of age group had the lowest risk (<0.5%).[12] Primary infection before 2 years of age often progresses to serious illness within the first 12



Significant (P<0.05); ¥Chi-square; £Fisher's exact test

Figure 2. Differences in clinical profiles of patients with pulmonary TB and extra-pulmonary TB

Table 2. Subjects' characteristics and hs-CRP levels (N=95)

Characteristics	n (%)	Median hs-CRP (range), mg/L	P value
Gender			0.453[a]
Male	46 (48.4)	0.95 (0.04-13.47)	
Female	49 (51.6)	0.6 (0.05-32.15)	
Age			0.061[b]
<5 years	34 (35.8)	0.6 (0.04-20.2)	
5-10 years	31 (32.6)	1.0 (0.05-16.76)	
>10 years	30 (31.6)	0.95 (0.06-32.15)	
WHZ or BMI for age, n (%)			0.048[b]
-2 - 2 SD	73 (76.8)	0.8 (0.16-321.5)	
< -2 SD	13 (13.7)	2.5 (0.4-129.1)	
< -3 SD	9 (9.5)	8.3 (0.4-167.6)	
Chronic cough, n (%)			0.553a
Yes	15 (15.8)	0.6 (0.16-167.6)	
No	80 (84.2)	0.9 (0.3-321.5)	
Prolonged fever, n (%)			<0.001[a]
Yes	15 (15.8)	38.4 (0.16-167.6)	
No	80 (84.2)	0.85 (0.3-321.5)	
Lymph node enlargement, n (%)			0.004[a]
Yes	23 (24.2)	3.4 (0.3-167.6)	
No	72 (75.8)	0.8 (0.16-321.5)	
Bone joint swelling, n (%)			0.006[a]
Yes	5 (5.3)	20.5 (4.3-125.2)	
No	90 (94.7)	0.9 (0.16-321.5)	
Tuberculin skin test, n (%)			0.001[b]
Positive	83 (87.4)	0.8 (0.16-134.7)	
Negative	6 (6.3)	34.85 (0.9-167.6)	
Not done	6 (6.3)	46.4 (0.8-321.5)	
TB contact, n (%)			0.729[b]
No contact	49 (51.6)	0.9 (0.16-321.5)	
AFB–/not clear	30 (31.6)	0.95 (0.3-20.2)	
AFB +	16 (16.8)	0.75 (0.3-84.5)	
Chest X-ray, n (%)			0.099[b]
Suggestive TB	83 (87.4)	0.9 (0.16-321.5)	
Not suggestive TB	9 (9.5)	20.5 (0.4-125.2)	
Not done	3 (3.1)	1.7 (0.6-8.3)	
Bacteriology, n (%)			<0.001[b]
Positive	7 (7.4)	49.2 (0.6-129.1)	
Negative	22 (23.1)	9.1 (0.16-321.5)	
Not done	66 (69.5)	0.7 (0.3-134.7)	
TB status, n (%)			<0.001[b]
TB infection	19 (20)	0.7 (0.3-20.2)	
Pulmonary TB	51 (53.7)	0.8 (0.3-129.1)	
Extra-pulmonary TB	25 (26.3)	14.3 (0.16-321.5)	

Significant (P<0.05); [a]Mann-Whitney; [b]Kruskal-Wallis; AFB=acid-fast bacillus

months without significant symptoms.[12] There were no significant differences in hs-CRP levels according to patient age.

There was a significant relationship between WHZ/BMI for age and TB status. In the pulmonary and extra-pulmonary TB groups, normal nutritional status (WHZ or BMI for age -2SD to 2SD) was predominant, followed by wasted (WHZ or BMI for age <-2SD), whereas 100% of those in the TB infection group were normal nutritional status. This finding was consistent with a study in Semarang, in which most pediatric TB cases had normal and wasted nutritional status. In our study, patients with malnourished nutritional status (WHZ or BMI for age <-3SD) had the highest

Table 3. hs-CRP levels by location of extra-pulmonary TB (n=25)

Location	n	Median hs-CRP (range), mg/L
Abdomen	9	84.5 (0.6-321.5)
Meningitis	6	20.2 (0.8-117.8)
Spondylitis	4	31.3 (4.3-125.2)
Arthritis	2	51.75 (20.5-83)
Ocular	1	0.5
Pericarditis	1	1.6
Scrofuloderma	1	43.6
Tuberculoma	1	10.7

median hs-CRP level [8.3 (range 0.4-167.6) mg/L], followed by wasted [2.5 (range 0.4-129.1) mg/L], and normal [0.8 (range 0.16-321.5) mg/L]; (P=0.048). Malnutrition is a predictor of TB disease and is associated with poor outcome.[13]

The pulmonary TB group had more patients with chronic cough (11 patients) and lymph node enlargement (16 patients) than the extra-pulmonary group. This finding was consistent with previous studies which noted that cough was the most common symptom of pulmonary TB compared to extra-pulmonary TB.[14,15] There were significant relationships between TB status and prolonged fever (P<0.001) and joint swelling (P=0.003). Complaints of prolonged fever were mostly in the extra-pulmonary TB group (11 patients), and joint swelling was only in the extra-pulmonary TB group (5 patients). The hs-CRP levels were significantly higher in patients with prolonged fever (P<0.001), lymph node enlargement (P=0.004), and joint swelling (P=0.006). High sensitivity-CRP increases in response to inflammatory stimuli. This observation was consistent with a study that noted an increase in CRP levels in TB patients with fever.[16]

With regards to tuberculin skin test status, median hs-CRP levels were significantly higher in the groups that did not undergo tuberculin skin test [46.4 (range 0.8-321.5) mg/L] and that were negative [34.85 (range 0.9-167.6) mg/L], than in the positive tuberculin skin test group [0.8 (range 0.16-134.7) mg/L] (P=0.001). The most likely reason for this finding was that the TST negative/not done subjects had extra-pulmonary TB. There was no significant difference in hs-CRP levels based on whether they had a history of TB contact. Most of the patients did not have a history of TB contact.

Tuberculosis status and radiological status had a significant relationship (P=0.047). In our study, 94.7% of the TB infection group had chest X-ray suggestive of TB. The classification of intra-thoracic TB in children is divided into exposed TB, latent TB infection, subclinical TB, non-severe TB, and severe TB.[17] However, in our study, latent TB infection and subclinical TB were included in the TB infection category. The kappa test was not carried out between the chest X-ray results from Kariadi Hospital and Community Health Center. There was no significant relationship between hs-CRP levels and radiological evidence status.

We found a significant relationship between TB status and bacteriological evidence. Positive bacteriological evidence was noted in 5 extra-pulmonary TB patients and 2 pulmonary TB patients. Only 29 patients (30.5%) underwent bacteriological examination. Patients with positive bacteriological evidence had significantly higher levels of median hs-CRP [49.2 (range 0.6-129.1) mg/L] than those with negative bacteriological evidence [9.1 (range 0.16-321.5) mg/L] and those who did not undergo bacteriology examination [0.7 (range 0.3-134.7) mg/L] (P<0.001). A previous study also noted higher CRP levels in positive cultures.[7]

There was a significant difference in hs-CRP levels based on TB status. The highest median hs-CRP level was in the extra-pulmonary TB group [14.3 (range 0.16-321.5) mg/L], followed by pulmonary TB [0.8 (range 0.3-129.1) mg/L], and TB infection [0.7 (range 0.3-20.2) mg/L] (P<0.001). This observation was consistent with several previous studies in which serum hs-CRP levels were significantly increased in TB patients compared to healthy groups.15,18,19 In addition, CRP levels are higher in pulmonary TB and disseminated TB patients.[7]

In the extra-pulmonary TB group, the highest levels of hs-CRP were in abdominal TB [84.5 (range 0.6-321.5) mg/L], followed by arthritis TB [51.75 (range 20.5-83) mg/L]. The lowest level of hs-CRP was in ocular TB [0.5 mg/L]. A study noted that locations with high bacterial levels such as pulmonary TB or disseminated TB, have significantly higher levels of CRP than that of skin, glands, or CNS.[7] Another study found that disseminated TB patients had significantly higher CRP, followed by pulmonary TB and extra-pulmonary TB.[20] Our study had only three

TB status categories: TB infection, pulmonary TB, and extra-pulmonary TB; patients with disseminated TB were included in the extra-pulmonary TB category.

There were several limitations in our study: (1) We included subclinical TB in the category of TB infection, and disseminated TB in the category of extra-pulmonary TB. As such, we were unable to describe hs-CRP levels according to TB category in more detail; (2) Not all patients underwent bacteriological examination; (3) The number of subjects was not evenly distributed among TB categories; (4) A Kappa test was not carried out to assess the consistency of chest x-ray interpretation by different radiologists.

In conclusion, hs-CRP levels were significantly higher in extra-pulmonary TB, followed by pulmonary TB, and TB infection. Pediatric TB patients had significantly higher hs-CRP levels in the following: clinical evidence (low WHZ or BMI for age, clinically prolonged fever, enlarged glands, and joint swelling); evidence of infection (negative/note done tuberculin skin test), and positive bacteriological evidence. However, hs-CRP levels in pediatric TB patients were not significantly different according to sex, age, and radiological evidence. In extra-pulmonary TB patients, the highest hs-CRP level was found in abdominal TB, followed by TB arthritis; the lowest hs-CRP level was found in ocular TB.

Conflict of interest

None declared.

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