

# The White Blood Cell Count to Hemoglobin Level Ratio is Correlated with the Presence of Cortical Defects on DMSA Renal Scans in Children with Febrile Urinary Tract Infection

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Received: 16 July 2018  
Revised: 20 September 2018  
Accepted: 28 September 2018

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Pediatric Nephrology

**Purpose:** We investigated whether the white blood cell (WBC) count to hemoglobin (Hgb) level ratio is correlated with the presence of cortical defects on dimer-captosuccinic acid (DMSA) renal scan in children with febrile urinary tract infection (UTI).

**Methods:** We examined 95 children who were consecutively admitted to our hospital with their first episode of febrile UTI. Blood tests (C-reactive protein [CRP], WBC, Hgb) were performed. All enrolled children underwent DMSA scanning during admission. Data were compared between children with positive and negative DMSA results. The correlations between WBC to Hgb ratio and the presence of cortical defects on DMSA scan, and between WBC to Hgb ratio and CRP level were analyzed using the Pearson chi-squared test. Multiple logistic regression analysis was used to evaluate whether WBC to Hgb ratio could predict the cortical defects on DMSA scan in children with febrile UTI.

**Results:** The WBC to Hgb ratio was significantly higher in children with positive DMSA results than in those with negative DMSA results; positively correlated with the presence of cortical defects on DMSA scan and CRP; and was a significant factor for predicting the presence of cortical defects on DMSA scan.

**Conclusion:** The WBC to Hgb ratio may predict the presence of cortical defects on acute DMSA scans in children with febrile UTI.

**Key words:** Hemoglobin, Pyelonephritis, Urinary tract infection, White blood cell count

## Introduction

Febrile urinary tract infection (UTI) is common in children, especially those under two years old who are immunocompromised hosts or have severe congenital urinary tract anomalies. Febrile UTI is considered as upper UTI or pyelonephritis. However, according to data from acute dimer-captosuccinic acid (DMSA) scans routinely performed in children with febrile UTI regardless of how urine samples were collected before the year of 2011, only less than 30% of them had positive DMSA renal scan results<sup>1)</sup>.

Children with febrile UTI but with negative DMSA results have pyelitis or lower UTI with other fever focus and manifesting only fever initially. Only pyelonephritis can produce acquired renal scarring, and only recurrent pyelonephritis can lead to chronic renal insufficiency. Therefore, among children

with febrile UTI, determining the presence of pyelonephritis is very important. However, positive urine culture results, which is currently the gold standard in the diagnosis of acute pyelonephritis, cannot predict the presence of cortical defects on DMSA scan in children with febrile UTI, although urine sampling was appropriately collected. Furthermore, urine culture results cannot contribute to making treatment decisions during clinical visits. Nevertheless, performing DMSA renal scans in all children with febrile UTI is not acceptable because of its invasiveness.

Due to these reasons, trying to find simple, cheap, prompt, and more accurate diagnostic methods than serum C-reactive protein (CRP), white blood cell (WBC) count, or urine culture for determining the presence of pyelonephritis among children with febrile UTI is challenging to pediatricians.

Authors previously reported that mean hemoglobin (Hgb) level was significantly lowered in children with positive DMSA results than in those with negative DMSA results<sup>2)</sup>.

In the present study, we investigated whether WBC to Hgb ratio could be helpful for determining the presence of cortical defects on DMSA scan in children with febrile UTI.

## Materials and methods

Among 124 consecutive children admitted to our hospital with their first episode of febrile UTI from July 2013 to June 2015, 95 children with completed data sheets were included in this study. Twenty-two children who did not undergo a DMSA renal scan at the time of acute infection and seven children with missing data were excluded. Febrile UTI was defined as follows: high fever  $\geq 38^{\circ}\text{C}$ , abnormal urinalysis (pyuria [ $>5$  WBC counts/high-power field] and positive leukocyte esterase results), positive CRP results ( $>0.3$  mg/dL), and lack of other fever focus. Urine was sampled by collecting a midstream urine specimen in toddlers or in older children and using the clean catch bag method in non-toilet trained children. Significant bacteriuria (BU) was defined as the presence of  $\geq 10^5$  colony-forming units/high-power field of a single-strain isolate. All the enrolled children with febrile UTI underwent a DMSA renal scan upon admission. In addition, blood (C-reactive protein [CRP], white blood cell [WBC] count, he-

moglobin [Hgb]) tests were performed at their admission.

DMSA scans were performed using the planar technique with a dual-headed Symbia E gamma camera (Siemens, Erlangen, Germany) equipped with low-energy high-resolution collimator (140 KeV, 20% symmetric window) and were interpreted by two nuclear medicine consultants. A positive DMSA result (indicative of cortical defects) was defined as reduced or absent tracer localization and indistinct margins that did not deform the renal contour.

Written informed consent was obtained from the parents of all febrile UTI children prior to DMSA scans. The CHA University Institutional Review Board approved this study, including the consent procedure (CHA IRB No.2018-06-057).

All data were collected retrospectively and were compared between the children with the positive and negative DMSA results. The correlation was analyzed between WBC to Hgb ratio and the presence of cortical defects on DMSA scan and between WBC to Hgb ratio and CRP.

### 1. Statistical analysis

All variables are presented as mean $\pm$ standard deviation, and continuous variables were analyzed using the Student's t-test. Qualitative variables and correlations were analyzed using the Pearson chi-squared test and Pearson correlation coefficient (two-tailed probability), respectively. Non-parametric variables were analyzed using Spearman's rank correlation coefficient. Using multiple logistic regression analysis (MLRA), the ability of WBC to Hgb ratio to predict the presence of cortical defects on DMSA scan was investigated. The areas under the receiver operating characteristic (ROC) curves of relevant factors and the associated levels of significance were evaluated when the value of the state variable was 1. Statistical analysis was performed using SPSS statistics 22 (SPSS Inc, Chicago, IL). Statistical significance was defined as  $P \leq 0.05$ .

## Results

### 1. Demographic and laboratory findings of the study population

Nine children (20%) with positive DMSA results were diagnosed with culture-negative pyelonephritis. There were

no differences in congenital anomalies, including hydro-nephrosis, on renal sonogram between children with positive and negative DMSA results. Congenital hypoplastic kidney (relative renal uptake of less than 35%) was not detected on DMSA scan in this study. Voiding cystourethrogram was not performed at the first episode of acute pyelonephritis.

The study group included children aged 0 to 109 months, with a mean age of 10.8 months. There was no difference in the age and sex ratio between the two groups. CRP, WBC count, WBC/Hgb ratio were significantly higher in children with positive DMSA results than in those with negative DMSA results ( $7.4\pm 4.1$  vs.  $2.7\pm 2.7$ ,  $P<0.001$ ;  $18,771\pm 5,817$  vs.  $13,033\pm 6,241$ ,  $P<0.001$ ;  $1,721\pm 579$  vs.  $1,138\pm 456$ ,  $P<0.001$ , respectively). Hgb levels were significantly lower in children with positive DMSA results than in those with negative DMSA results ( $10.6\pm 0.69$  vs.  $11.4\pm 0.89$ ,  $P=0.005$ ) (Table 1).

## 2. Significant correlations between parameters in the study population

The presence of cortical defects on acute DMSA scan correlated positively with CRP, WBC, and WBC/Hgb ratio and negatively with Hgb ( $r=0.55436$ ,  $P<0.001$ ;  $r=0.49031$ ,  $P<0.001$ ;  $r=0.49031$ ,  $P<0.001$ ;  $r=-0.26319$ ,  $P=0.01$ , respectively). CRP correlated positively with WBC and WBC/Hgb ratio and negatively with Hgb ( $r=0.40457$ ,  $P<0.001$ ;  $r=0.37390$ ,  $P<0.001$ ;  $r=-0.30751$ ,  $P=0.002$ , respectively). WBC count was not correlated with Hgb ( $r=-0.16374$ ,  $P=0.11$ ).

**Table 1. Comparison of the Mean Laboratory Data for Children with Positive and Negative DMSA Results**

	DMSA (+)	DMSA (-)	P value
N	45	50	
Age (months)	10.1±16.5	11.5±13.8	0.57
M:F	29:16	34:16	
CRP (mg/dL)	7.4±4.1	2.7±2.7	<0.001*
WBC (/mm <sup>3</sup> )	18,771±5,817	13,033±6,241	<0.001*
Hemoglobin (Hgb, g/dL)	10.6±0.69	11.4±0.89	0.005*
WBC/Hgb ratio	1,721±579	1,138±456	<0.001*

The laboratory examination results are expressed as mean±standard deviation.

Abbreviations: DMSA, Technetium 99m-dimercaptosuccinic acid; N, number of patients; M, male; F, female; CRP, C-reactive protein; WBC, white blood cell count.

\* $P<0.05$ .

## 3. MLRA of WBC/Hgb ratio to predict the presence of cortical defects on acute DMSA scan

Using MLRA, Table 2 demonstrates that WBC/Hgb ratio was a significant factor for predicting the presence of cortical defects in acute DMSA scan similar to CRP (Table 2).

## 4. ROC curves and 95% confidence interval (CI) of CRP, WBC, WBC/Hgb ratio and Hgb to predict the presence of cortical defects on acute DMSA scan

The areas of the ROC curves and 95% CI of CRP, WBC, WBC/Hgb ratio and Hgb to predict the presence of cortical defects on acute DMSA scan were significant (Table 3).

## Discussion

There are many possible advantages if the exact prediction of cortical defects through acute DMSA scans in children with febrile UTI. First, admission is not necessary in children with pyelitis or lower UTI with other fever foci even if they are less than 12 months old. Second, performing imaging studies according to UTI guidelines is not necessary if UTI is not recurrent. To some extent, the possibility of recurrent febrile UTI or developing acquired renal scars in the future can be individually predicted. Total medical expenses at the national level can be reduced.

There are disadvantages in urine culture results being considered as a gold standard for a diagnosis of pyelonephritis: if all children with positive urine culture results among children with febrile UTI might have cortical defects on acute DMSA scans, which might result in false po-

**Table 2. Results of Multiple Logistic Regression Analyses for C-reactive Protein and White Blood Cell to Hemoglobin Ratio to Predict the Presence of Cortical Defects on Acute DMSA Scanning [DMSA (+)].**

DMSA (+)	P-value	OR	95% CI
CRP	<0.000*	1.368	1.164–1.607
WBC	0.045*	1.009	1.000–1.018
Hgb	0.529	0.836	0.479–1.460
DMSA (+)	P-value	OR	95% CI
CRP	<0.001*	1.360	1.153–1.604
WBC/Hgb	0.004*	1.002	1.001–1.003

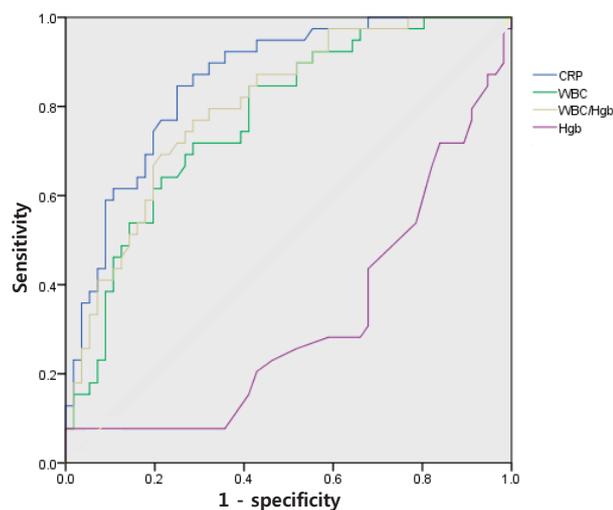
Abbreviations: DMSA, 99m-dimercaptosuccinic acid; OR, odds ratio; CI, 95% confidence interval; CRP, C-reactive protein; WBC, white blood cell count; Hgb, hemoglobin; WBC/Hgb, WBC to Hgb ratio.

\* $P<0.05$ .

sitive findings of urine culture are high (71%) even though urine sampling is appropriately collected<sup>3</sup>. Most of them include children with pyelitis or lower UTI associated with other fever foci. False negative results (15%) of urine culture are not low even though urine sampling is appropriately collected<sup>4</sup>. The discrimination of children with pyelonephritis from children with lower UTI and other fever foci accompanying asymptomatic bacteriuria is impossible. Urine culture is not helpful when a prompt diagnosis of pyelonephritis is needed at clinics.

Therefore, many clinicians depend on other helpful parameters correlated with pyelonephritis, such as serum CRP, WBC or procalcitonin etc. when pyelonephritis is considered as a diagnosis in children with abnormal urinalysis. Serum WBC level is a known factor helpful for predicting the presence of cortical defects on acute DMSA scans<sup>4,5</sup>. Authors reported that Hgb level was significantly lower in children with positive DMSA results than in those with negative DMSA results<sup>2</sup>. Thus, authors hypothesized

**Table 3. Area Under the Receiver Operating Characteristic (ROC) Curves of Relevant Factors to Predict the Presence of Cortical defects on DMSA Scanning and their associated Levels of Significance**



APN	AUC	P-value	95% CI
CRP	0.857	<0.001*	0.783–0.931
WBC	0.773	<0.001*	0.679–0.866
Hgb	0.318	0.003*	0.207–0.429
WBC/Hgb	0.802	<0.001*	0.714–0.889

Abbreviations: AUC, areas under the ROC curve; CI, 95% confidence interval; CRP, C-reactive protein; WBC, white blood cell count; Hgb, hemoglobin; WBC/Hgb, WBC to Hgb ratio.

\* $P < 0.05$ .

that the combination of these two factors could be more helpful for predicting positive DMSA results in children with febrile UTI. If the cut-off value of WBC count would be 14,000/mm<sup>3</sup>, sensitivity, specificity, positive predictive value, and negative predictive value of WBC count for predicting positive DMSA results would be 80.9% [95% CI (confidence interval), 66.7–90.9%], 56.1% (95% CI, 43.3–68.3%), 56.7% (95% CI, 49.1–64.0%) and 80.4% (95% CI, 68.8–88.5%). If the cut-off value of WBC/Hgb ratio be 1200, sensitivity, specificity, positive predictive value, and negative predictive value of WBC/Hgb ratio for predicting positive DMSA results would be 84.6% [95% CI, 69.5–94.1%], 57.1% (95% CI, 43.2–70.3%), 57.79% (95% CI, 49.7–65.7%) and 84.2% (95% CI, 71.2–92.0%). The sensitivity and negative predictive value of WBC/Hgb ratio is slightly increased compared to that of WBC count alone. Although the predicting power of WBC/Hgb ratio is not comparable to that of serum CRP, it can be used as a complementary tool for evaluation.

The reason why Hgb level decreases in children with positive DMSA results is unknown. However, authors thought that their decreased Hgb level could be due to dilutional effect resulting from the activation of intrarenal renin-angiotensin-aldosterone system in the pathogenesis of acute pyelonephritis<sup>2</sup>.

The limitations of this study are as follows: WBC/Hgb ratio is not better compared to other factors by a large margin. Other factors influencing Hgb levels like nutrition, nutritional supplements, socioeconomic status, or previous Hgb levels were not considered. The reason for decreased Hgb level in children with the positive DMSA results is currently unclear. Follow-up of their Hgb levels is needed.

In conclusion, WBC/Hgb ratio may help predict the presence of cortical defects on acute DMSA scans in children with febrile UTI.

## Patient consent

This study was approved by the institutional review board (IRB), and the consent was waived due to the nature of the retrospective study [CHA IRB No.2018-06-057].

## Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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