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Research Article

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USE OF CRP/ALBUMIN RATIO IN THE DIFFERENTIATION OF UPPER URINARY SYSTEM INFECTION IN CHILDREN WITH A URINARY SYSTEM INFECTION

ÜRİNER SİSTEM ENFEKSİYONU OLAN ÇOCUKLARDA ÜST ÜRİNER SİSTEM ENFEKSİYONUNUN AYIRT EDİLMESİNDE CRP/ALBÜMİN ORANININ KULLANILMASI

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Öz

Amaç: İdrar yolu enfeksiyonları (İYE) çocukluk çağında sık görülen enfeksiyonlardır. Enfeksiyonun seyri ve klinik takibi lokalizasyonuna göre (alt ve üst) değişir. C-reaktif protein (CRP) albümin oranı (CAO), son yıllarda kullanılan enflamatuar belirteçlerden biridir. Çalışmamızın amacı CAO kullanarak bu ayrımı araştırmaktır.
Materyal ve Metot: Bu çalışma, İYE tanısı almış 95 çocuğun hasta dosyaları taranarak gerçekleştirildi. Hastalar enfeksiyon bölgesine göre üst İYE (Ü-İYE) ve alt İYE (A-İYE) olarak iki gruba ayrıldı. Hastaların laboratuvar ve demografik özellikleri hastane kayıtlarından elde edilmiş ve gruplar arasında karşılaştırılmıştır.
Bulgular: CAR, Ü-İYE grubunda anlamlı olarak daha yüksekti (p <0,001). Alıcının çalışma karakteristik eğrisine göre, Ü-İYE tahmini için CAO'nın optimal kesme değeri>% 97 özgüllüğü ve% 53 duyarlılığı olan> 12,65 idi (AUC = 0,864; % 95 güven aralığı CI: 0,792– 0,9363, LR: 24,40; p <0,001). Univaryant analizde anlamlı bulunan ve Ü-İYE ile korele olan değişkenlerin de alınarak yapıldığı çok değişkenli lojistik regresyon analizinde CAO (OR = 0,897,% 95 CI: 0,838-0,960, p = 0,002) ve mutlak nötrofil sayısının (OR = 0,182,% 95 CI: 0,039-0,841, p = 0,029) halen anlamlı olduğu bulundu.
Sonuç: CAO, İYE'de Ü-İYE ile bağımsız olarak ilişkilidir ve Ü-İYE'yi tahmin etmek için yararlı olabilir.
Anahtar Kelimeler: Albümin, C-reaktif protein, çocuk, piyelonefrit, idrar yolu enfeksiyonu.

Abstract

Objectives: Urinary tract infections (UTI) are common infections in childhood. The course of infection and its clinical follow-up vary according to its localization (lower vs. upper). C-reactive protein (CRP) albumin ratio (CAR) is one of the inflammatory markers that have been used in recent years. The purpose of our study is to investigate this distinction by using CAR.
Materials and Methods: This study was conducted by scanning the patient files of 95 children diagnosed with UTI. The patients were divided into two groups according to the infection site as upper UTI (UUTI) and lower UTI (LUTI). Laboratory and demographic features of the patients were obtained from the hospital records and compared between the groups.
Results: CAR was significantly greater in the UUTI group (p<0.001). According to receiver operating characteristic curve, the optimal cut-off value of CAR for prediction of UUTI was >12.65, which had a specificity of 97% and sensitivity of 53% (AUC = 0.864; 95% confidence interval CI: 0.792–0.9363, LR: 24.40; p < 0.001). In the multivariate logistic regression analysis, in which variables found to be significant in univariate analysis and correlated with UUTI were also taken, CAR (OR = 0.897, 95% CI: 0.838-0.960, p = 0.002) and absolute neutrophil count (OR = 0.182, 95% CI: 0.039 -0.841, p = 0.029) was still found to be significant.
Conclusion: CAR is independently related to UUTI in UTI and may be useful to predict UUTI.
Keywords: Albumin, C-reactive protein, children, pyelonephritis, urinary tract infection.

Introduction

Urinary system infections (UTI) are common infections in childhood.[1] The infections are classified as acute pyelonephritis (APN) or upper urinary tract infection (UUTI) and lower urinary tract infections (LUTI) involving the lower urinary tract, primarily cystitis.[2] There is a relationship between the localization of the infection and disease severity and additional diseases that may occur.[1] Particularly, APN should be considered important because it causes scar formation in the kidneys and consequently high blood pressure and end-stage kidney failure due to renal parenchymal involvement.[2] Therefore, it is important to determine the localization of the infection. However, at this point, some difficulties waiting for clinicians. Although some symptoms such as high fever, vomiting, anorexia, diarrhea, abdominal pain, and flank pain have indicated APN, they are weak in clarifying the diagnosis because they are non-specific in children under 2 years of age.[3-5] Therefore, some tests were needed to make this distinction. 99mTc-Dimercaptosuccinic Acid (DMSA) scintigraphy is the gold standard test used for both renal scar imaging and APN diagnosis.[1-3] However, the routine use of this method in children is not very reasonable in terms of both radiation damage and cost-effectiveness, and its power in distinguishing old damage from acute pyelonephritis in those with frequent recurrent infections.[6] Frequently used laboratory parameters such as leukocyte and neutrophil count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin, and new markers like interleukin (IL)-6 and IL-8 have low sensitivity in differentiating APN in children with UTI.[3, 7, 8]

According to a review that examined the studies performed on CRP distinguishing between APN and LUTI, overall sensitivity and specificity were 94% and 39% at a cutoff value of 2 mg/dl.[9] However, low specificity has shown that it is insufficient to make this distinction alone. Serum albumin is a negative acute-phase reactant. In critical care, hypoalbuminemia grade is correlated to that of infection-triggered inflammation. Similarly, CRP albumin ratio (CAR) has also been shown to correlate with infection severity.[10] In recent years this ratio was correlated with mortality in premature infants and other patient groups in addition to sepsis.[11-13] The combination of these parameters may be more sensitive and useful to predict APN in UTI. We aimed to investigate the relationship between CAR and LUTI and UUTI, and its possible predictive role in the differential diagnosis of these two UTI types.

Materials and Methods

This retrospective cross-sectional study included 95 children diagnosed with urinary system infection who applied to our clinic between October 2017- October 2018. We included individuals with a pediatric patient population aged between 1 month and 18 years. UTI was defined according to the UTI guidelines of the American Academy of Pediatrics, as the presence of pyuria (≥5 WBCs / high power field) and positive urine culture (bacterial growth forming more than 10^5 colonies) accompanied by fever (body temperature ≥ 38 °

C).[14] Urine samples for culture were taken from catheterization or suprapubic aspiration in children without toilet training, and from clean voided midstream in those who received toilet training. UUTI and LUTI differentiation was made according to DMSA results and patients were divided into two groups accordingly.[15] Patients with renal calculi, chronic renal failure, other bacterial infection, obstructive uropathy, neurogenic bladder, congenital anomaly of the urinary system except vesicoureteral reflux were excluded from the study. Those missing information in their files were also excluded from the study. Demographic information such as age, gender, and, other laboratory values including CRP/albumin and renal ultrasonography results were recorded by scanning patient files at the time of the first encounter.

This study was approved by the ethics committee of Kahramanmaraş Sütçü İmam University under protocol number 419, on October 24, 2018, and has been performed by the 1964 Declaration of Helsinki and its later amendments.

Statistical analysis

SPSS v. 17 (SPSS Inc., Chicago, IL) statistical software was used for all analyses. A two-sided P-value ≤ 0.05 was considered statistically significant. Continuous data were expressed as mean ± standard deviation or median (minimum-maximum), and categorical data as number and percentage. An independent sample t-test was used to compare normally distributed quantitative data while the Mann-Whitney U test was used for non-normally distributed variables. Categorical data were compared using the Chi-square test. Spearman correlation test was used to assess correlation. An optimal cut-off point for CRP/albumin ratio, as indicated by the sum of the highest sensitivity and specificity-1, as well as an area under the curve (AUC) with 95% confidence interval (CI) were calculated for the prediction of UUTI using a receiver operator characteristic (ROC) curve with the MedCalc (v12.7.8) software package. Univariate analysis was used to determine variables correlated with UUTI. Those that were statistically significant in the univariate analysis were entered into a multivariate logistic regression model with the backward stepwise method for the prediction of UUTI.

Results

Pediatric patients with 95 UTIs included in the study were divided into two groups according to infection localization. There were 46 (24 male / 22 female) patients in the LUTI group and 49 (17 male / 32 female) patients in the UUTI group. There was no age or gender difference between the groups (p=0.669 and p=0.085, respectively). The demographic and laboratory characteristics of the study groups were given in Table 1. CAR, white blood cell counts (WBC), absolute neutrophil counts (ANC), and CRP levels were significantly greater in UUTI (p<0.001, both).

In the correlation analysis CAR was correlated with WBC and ANC ($p<0.001$, $r=0.430$ and $p<0.001$, $r=0.450$, respectively).

ROC curve indicated that the optimal cut-off value of CAR to predict UUTI was >12.65, which had a specificity of 97% and sensitivity of 53% (AUC = 0.864; 95% confidence interval (CI): 0.792–0.9363, LR: 24.40; $p < 0.001$). The positive predictive value of CRP/Albumin over 12.65 is 96% and, the negative predictive value is 66%. The accuracy of CAR is 74%. Also, the optimal cut-off value of CRP predicting UUTI was >52, with 97% specificity and 53% sensitivity (AUC=0.856; 95% CI: 0.779-0.933, LR: 24.40; $p<0.001$) and cut-off value for neutrophil was >14750 with 16% specificity and 97% sensitivity (AUC=0.756; 95%CI: 0.659-0.854, LR: 7.51; $p<0.001$), and for WBC the optimal cut-off value was >17290 with 30% specificity and 97%sensitivity (AUC=0.726; CI:0.623-0.829, LR:14.08; $p<0.001$) (Table 2)(Figure 1).

The multiple logistic regression model using a backward stepwise method revealed that CAR (OR =0.897, 95% CI: 0.838-0.960, p =0.002) and ANC (OR =0.182, 95% CI: 0.039-0.841, p =0.029) remained significant predictors of UUTI after adjusting for the other confounding variables, which were either found to be statistically significant in the univariate analysis (Table 3).

Table 1. Baseline characteristics of study patients

	UUTI (n=49)	**LUTI** (n=46)	***p***
Age, months	43.80±45.59	39.52±51.49	0.669
Male/female, n	17/32	24/22	0.085*
CRP/Albumin Ratio	19.89±17.89	5.18±5.54	<0.001
CRP, mg/l	75.40±70.17	9.18±13.91	<0.001
Albumin, g/dl	4.08±0.38	4.14±0.39	0.451
Procalcitonin, ng/ml	0.40±0.18	0.35±0.13	0.101
WBC $X10^3$, mm^3	1.48±7.28	1.00±4.90	<0.001
ANC $X10^3$, mm^3	7.98±5.92	4.07±3.79	<0.001
ALC $X10^3$, mm^3	4.68±2.78	4.76±2.41	0.871
Hb, g/dl	11.29±1.57	11.80±1.85	0.149
Platelet count $x10^3$, mm^3	403.76±212.47	364.51±146.15	0.300
Urine pH	6.23±0.39	6.17±0.55	0.541
Urine density, g/ml	1014±10.62	1015±10,37	0.590

*Chi-Square, Data are presented as mean ± standard deviation
ANC: Absolute neutrophil count, ALC: Absolute lymphocyte count, CRP: C reactive protein, Hb: Hemoglobin, LUTI: Lower urinary tract infection, UUTI: Upper urinary tract infection, WBC: White blood cell count.

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Table 2. Comparison of ROC analyses of parameters to predict UUTI

	AUC	%95 CI	Specificity(%)	Sensitivity(%)	LR	p
WBC	0.726	0.623-0.829	30	97	14.08	<0.001
Neutrophil	0.756	0.659-0.854	16	97	7.51	<0.001
CRP	0.856	0.779-0.993	97	53	24.40	<0.001
CRP/Albumin	0.864	0.792-0.936	97	53	24.40	<0.001

AUC: Area under the curve, CRP: C-reactive protein, CI: Confidence interval, LR: Likelihood ratio, ROC: Receiver operation curve, UUTI: Upper urinary tract infection, WBC: White blood cell count

Table 3. Univariate and multivariate analyses of the study group

Univariate Analysis				Multivariate Analysis		
Statistically Significant Variables	***p***	**OR**	**%95 CI**	***p***	**OR**	**%95 CI**
ANC	<0.001	0.067	0.017-0.264	0.029	0.182	0.039-0.841
CRP/Albumin	<0.001	0.875	0.820-0.935	0.002	0.897	0.838-0.960
WBC	0.001	0.013	0.001-0.155			

All the variables from Table 1 were examined and only those significant at P < 0.05 level and correlated with CRP/Albumin are shown in univariate analysis. Multivariate logistic regression analyses including all the variables in univariate analysis with the enter method. P ≤0.05 was considered statistically significant.
ANC: Absolute neutrophil count, CI: Confidence interval, CRP: C reactive protein, WBC: White blood cell, OR: Odds ratio

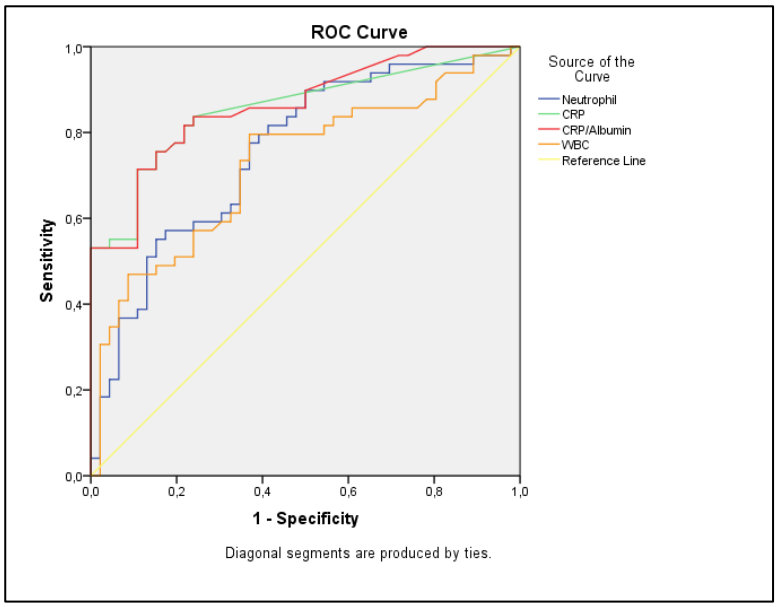

Figure 1. ROC curve analyses of CRP/Albumin ratio, CRP, WBC, and neutrophil for predicting UUTI.

Discussion

In this study, we investigated the relationship between CAR and the UUTI in UTI in children. To the best of our knowledge, this is the first study in which the CAR was used to predict the localization of UTI. We demonstrated that CAR was an independent predictor of UUTI in UTI in children. We also determined an optimal cut-off value for CAR to predict UUTI. We found that a CAR of more than 12.65 predicted UUTI with a sensitivity of 53% and a specificity of 97% with 74% accuracy.

Differentiating acute pyelonephritis from cystitis is important and useful in many ways. Pyelonephritis is one of the UTIs that should be diagnosed and treated as soon as possible due to serious complications such as kidney failure and hypertension. On the other hand, longer-term antibiotherapy is required in pyelonephritis.[6] In infants, it is often necessary to follow up with hospitalization. Besides, close monitoring of patients with recurrent pyelonephritis with antibiotic prophylaxis and imaging is also important in children with urinary tract infections. The gold standard used to distinguish pyelonephritis from LUTIs, such as cystitis, is a DMSA renal scan.[16] However, it does not seem very useful in terms of differential diagnosis due to several reasons such as radiation involvement, cost, increased patient visits, and the need for specialists for evaluation. It is obvious that there is a need for simple, faster, non-invasive, and easier methods. There are many studies in the literature on this subject. In a systemic review evaluating several studies on the power of procalcitonin to distinguish pyelonephritis from cystitis, the accuracy of the prediction was found to show heterogeneity.[17] In our study there was not any difference between the groups in terms of procalcitonin levels. In another review, 24 studies investigating CRP, procalcitonin, and ESR on the separation of pyelonephritis and cystitis were examined, and these tests were found to be sensitive (summary sensitivity values ranged from 0.83 to 0.94) but not very specific (summary specificity values ranged from 0.39 to 0.74).[6] In the same study, 13 studies with 1638 participants in which CRP was examined were examined, and summary sensitivity was found to be 0.94 (0.85 to 0.97) and summary specificity was found to be 0.39 (0.23 to 0.58).

CRP is now one of the markers that can be evaluated in most centers. Evaluation of CRP with albumin may increase its power to be an indicator of inflammation. CRP level increase in response to infection and this increase is proportional to infection severity.[12] In contrast, albumin is a negative acute phase reactant released in inflammation.[10] This may be explained by increased catabolism rate in sepsis and redistribution secondary to increased vascular permeability which causes a capillary leak.[18] The degree of hypoalbuminemia in critically ill patients correlates with the intensity of the inflammatory response triggered by infection.[19] Therefore, the difference between CRP and albumin in infections is gradually widening. Since the use of the ratio between CRP and albumin will include minor reductions in albumin values, it will also change without significant difference in albumin values and provide a value that positively correlates with infection, i.e. the high rate indicates high inflammatory status.[19]

CAR is one of the new markers that have been used in infection and sepsis in recent years.[13,20] In the study of Yang et al.[13] on 214 premature infants, they showed that the high sensitive CRP/albumin ratio (hsCRP/A) could be used in the early diagnosis of intrauterine bacterial infection, and especially that the increase in 48th hour had a better diagnostic sensitivity. Another retrospective study conducted by Sun et al.[20] adult septic patients showed that CAR indicated the prognosis of patients on length of stay. When we scanned the literature, we did not find any study related to CAR in UTI. Based on the idea that inflammation is more prevalent in pyelonephritis than cystitis, we investigated whether the CAR ratio can detect localization in children with UTI. Concordantly, we found that CRP, WBC, and ANC which are among the inflammatory markers, are higher in the UUTI group, and CAR is also higher in the UUTI group and correlated with them. These findings were compatible with Pecile et al.[21] and Gürgöze et al.[22] studies. We evaluated the predictive values of CRP, WBC, and neutrophil for distinguishing UUTI and found that WBC and neutrophil are more sensitive but less specific. When we looked at CRP, we saw that its values were very close to CAR, but AUC was higher in CAR. This supports that it may be more advantageous to take albumin in addition to CRP. We also demonstrated that CAR independently predicts UUTI with a sensitivity of 53% and specificity of 97% with an accuracy of 74%. Undoubtedly, randomized controlled studies with more cases are needed to support this.

The retrospective design and the limited number of cases can be counted as the study limitations. The absence of a control group in our study may be another limitation. Additionally, there is a need for prospectively designed case-control studies with a large number of cases comparing pre and post-treatment values of CRP and albumin.

In conclusion, determining the localization of UTI as soon as possible without available non-invasive methods will ease the patient follow-up, while it will also reduce treatment costs and prevent unnecessary antibiotic use. On the other hand, we believe that the CAR may offer an advantage in clinical practice by virtue of its low cost and ready availability. There is, however, a need for further studies on this subject.

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Conflict of Interest

The authors have no conflict of interest to declare.

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