Diagnostic Sensitivity and Specificity of Spectral Color Doppler Ultrasound Indices in Juvenile Idiopathic Arthritis

Devesh K. Bhagwani, Afsana Jahan, Tribhuvan P. Yadav, Soumya Dey, Namrita Sachdev

Abstract

Objective: Subjectivity in diagnosing arthritis by clinical parameters has led to the use of power color Doppler Ultrasonography (USG) indices color fraction and resistive index (RI) to objectively assess synovitis. Cut off levels of these USG parameters have also been derived in adult patients with rheumatoid arthritis. This study was performed in children with juvenile idiopathic arthritis (JIA) using power color Doppler to find out diagnostic cut off values of color fraction and RI in diagnosing arthritis.

Methods: A cross sectional observational study was conducted. Forty children of JIA having active arthritis and thirty four age and sex matched healthy controls were evaluated by power color and spectral USG. Their mean color fraction and resistive index (RI) were derived and compared. Using ROC curve, cut off values of these indices was derived. Finally, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of these cut off values were calculated.

Results: A total of 187 diseased joints and 200 healthy joints were evaluated by power color Doppler and spectral Doppler USG. Color fraction was significantly higher and RI significantly lower among cases than controls when both pooled and individual joint data were compared. Cut off level of color fraction and RI of all joints pooled together was 1.00 and 0.711 respectively. Similarly cut off value of individual joint group of these two indices and sensitivity, specificity, PPV and NPV were derived. Conclusion: A highly significant difference was observed in color fraction and RI between cases and controls. Color Fraction and RI were found to be very sensitive and specific in diagnosing arthritis in JIA patients with very high PPV and NPV.

Key words: Juvenile idiopathic arthritis, color fraction, resistive index, sensitivity, specificity, negative predictive value, positive predictive value

Introduction

Juvenile idiopathic arthritis (JIA) is a chronic debilitating disease of childhood characterized by periods of remission and disease activity. It is diagnosed primarily on history and clinical examination. Early diagnosis of the disease and early treatment is beneficial for a better outcome [1].

Clinically, at times it might be difficult to detect minimal synovial inflammation,
which suggests the onset of arthritis or relapse of JIA. Though Erythrocyte sedimentation rate (ESR) and C Reactive protein (CRP) have been reported to increase during active disease; they lack specificity [2]. Thus deriving objective parameters to detect minimal synovial inflammation would be of immense help in clinical practice. It might help to objectively document synovitis, relapse and remission and most importantly, rule out presence of active arthritis.

In the past few years, Ultrasonography (USG) has gained momentum in evaluation of musculoskeletal diseases especially rheumatoid arthritis (RA) [3, 4]. Moreover, it is cost effective, widely available, and easy to perform and has the ability to evaluate multiple joints in a single sitting.

Color fraction, a measure of local vascularity in the area of interest and resistive index (RI), a measure of peripheral resistance, are the two indices in spectral color Doppler USG which have added objectivity in evaluation of synovial inflammation in RA patients [5].

The sensitivity, specificity and cut off values for these two indices for diagnosing arthritis in RA patients have been published [6]. The present study was planned with the aim to evaluate color Doppler indices viz: color fraction and RI in JIA patients and to find out their cut off values and their sensitivity and specificity in diagnosing arthritis.

**Methods**

**Study Design and sample size calculation**

A Cross sectional observational study was conducted in the Department of Pediatrics and Radiology, Post Graduate Institute of Medical Education and Research and associated Dr. Ram Manohar Lohia Hospital, New Delhi, from November 2010 till January 2012.

Sample size was calculated keeping the study by Terslev et al as reference [6]. They evaluated the sensitivity and specificity of Doppler ultrasound in diagnosing arthritis of wrists and hand in adult RA patients. They found RI and color fraction of 0.80 ± 0.17 and 0.16 ± 0.18 respectively in diseased joints as compared to 1.00 ± 0.05 and 0.006 ± 0.03 in healthy joints of wrists and hands. Sample size was calculated to have a power of 90% in a 2 sided students’ t test to compare RI, color fraction of JIA patient’s versus age, sex matched controls. To estimate the sensitivity and specificity of these indices with a 10% relative error margin and 95% confidence interval, 175 affected joints of JIA patients as well as age and sex matched controls would be required.

**Patient enrolment**

Forty patients with JIA (as per ILAR classification criteria) having active arthritis (defined as a joint having swelling and/ or tenderness score between +1 to +3) who were attending the paediatric Rheumatology clinic and thirty four age and sex matched controls were enrolled after obtaining written informed parental consent/child’s assent. Ethical clearance was obtained from the institute’s ethical committee. Those with connective tissue disorder; an obvious infection and fever due to any cause other than systemic onset JIA or who did not give consent were excluded from the study.

**Data collection**

1. **Clinical assessment**

   Age, sex, ILAR category, age of onset and duration of disease were recorded and clinical evaluation was performed for swelling and tenderness score by the same investigator. The severity of joint swelling was graded as: Grade 0: None, Grade +1: Mild (Definite swelling but no blurring of normal skeletal outlines), Grade +2: Moderate (Definite obscuring of skeletal landmarks), Grade+3: Severe (No discernible skeletal landmarks). Tenderness score was graded as: Grade 0: no tenderness, Grade +1: complained of pain, Grade +2: complained of pain and winced, Grade +3: complained of pain, winced and withdrew).

2. **Laboratory assessments**

   Laboratory assessment done on the same day of clinical evaluation included determination of hemoglobin, total leukocyte count, differential leukocyte count, ESR,CRP, antinuclear antibody (ANA), and rheumatoid factor (RF). ESR was calculated by automated machine Alifax Spa Padova-Italy. A value of more than 10 mm / hr was considered increased. CRP was estimated by latex agglutination test and values more than 8 mg /dl were considered increased. ANA test was done by the Biolatex LE-EKO latex agglutination method and if positive, it was confirmed by an immunoflorescence method using Hep -2 cells. RF estimation was also done by Latex agglutination method.

3. **Ultrasound Examination**
A PHILIPS HD11 ultrasound system was used for ultrasound examination using a 5-12 MHz linear array transducer and was performed by the same trained radiologist. The target joint was scanned at a predefined transducer position for that particular joint and the synovial membrane examined longitudinally and transversally. On the USG image the synovial membrane appeared predominantly as a hypoechoic layer, covering the bone surfaces adjacent to the joint and superficially bound from the subcutaneous tissue by a thin white strand, the fibrous capsule. The joint and transducer position employed for the ultrasonographic evaluation of different joints was as per standard guidelines [7].

(a) Power color Doppler examination and calculation of color fraction

The settings of power color Doppler were the same for all joints and all participants, with a gain setting just below the noise level using setup for low flow : Nyquist limit + 0.014 m/s and 7 MHz Doppler frequency. With this setup all the color pixels in the image corresponded to motion, i.e., blood flow. The synovial vascularisation in the joints was visualized by color Doppler and the image with maximum color activity (if any) was selected for analysis. The digitally stored color Doppler image in DICOM format was transferred to a processing program (Adobe Photoshop). The synovium was traced indicating the region of interest (ROI). Using a color recognition function, number of color pixels as well as the total amount of pixels in the ROI were counted and expressed in relation to the total number of pixels in the region of interest as the color fraction. If there was no color activity, the synovium was taken as non-inflamed.

(b) Spectral Doppler and calculation of resistive index

Using color Doppler as guidance, the spectral Doppler probe was placed over an intrasynovial artery and the spectrum was obtained. An intramuscular artery in the thenar muscles was kept as reference. The US unit traced the Doppler spectrum electronically, and identified the cardiac cycles, peak systolic flow, and end diastolic flow. RI was calculated as (peak systolic flow minus end diastolic flow)/peak systolic flow; a degree of peripheral resistance. Wherever possible, the RI was determined in 3 arteries within the synovial membrane and a mean value was derived. Low values of RI meant low resistance indicating inflammation whereas high value meant high resistance, which was normal in the musculoskeletal system. We used a maximum value of 1.00 for the RI, because the analysis was limited to one side of the Doppler baseline to avoid obscuration by venous signals. When spectral Doppler measurements could not be measured due to lack of detectable vascularisation in the examined joint, the RI was taken as 1.00, since the resistance in the synovial arteries was presumed to be the same as extra synovial musculoskeletal flow. The examination time for each joints using color Doppler and spectral Doppler procedure was 30-40 minutes.

Statistical analysis was performed by the SPSS program for Windows, version 17.0 (SPSS, Chicago, Illinois). Continuous variables are presented as mean ± SD, and categorical variables are presented as absolute numbers and percentage. The comparison of normally distributed continuous variables between the groups was performed using Student’s t test. Nominal and categorical data between the groups were compared using Chi-squared test or Fisher’s exact test as appropriate. Pearson correlation was applied to see the relationship between swelling score, tenderness score, duration of disease and that of color fraction and RI. ANNOVA was applied to test significance between swelling and tenderness score and USG indices. A receiver operating characteristics (ROC) analysis was used to determine optimal cut-off values of color fraction and RI for different joints and all joints pooled together. The area under the curve, sensitivity, specificity, positive and negative predictive values was calculated to analyze the diagnostic value of color fraction and resistive index. For all statistical tests, a p value less than 0.05 was taken to indicate a significant difference. The aim of curve analysis was to minimize the number of false positives and false negatives, thereby maximizing the sensitivity and specificity. In an ROC curve, if the test generates a straight line it does not yield any predictive information whereas a test that discriminates well between two groups will have a high rate of true positive results and low rates of false positive results yielding an elliptical curve. A point on this elliptical curve nearest to upper left corner would be good first choice of a cut off value for a test. This was how the cut off value for different Ultrasonography indices has been calculated along with area under the curve. After deriving the cut off
value, the sensitivity, specificity, positive predictive value and negative predictive value were calculated using a 2 × 2 contingency table for different joints individually and pooled together.

## Results

### Demographic profile and biochemical indices

Forty patients with JIA and thirty four age and sex matched controls were included in the study. Male: female ratio in cases and control group were 1.2:1 and 1:1 respectively. The patients ranged from 1 to 16 years in age with mean of 9.14 ± 3.65 years. Most of the cases (85.3%) were in the age range of 5 to 15 years. Of all the patients with JIA, sixteen (40%) were of Systemic onset, seven (17.5%) were Oligoarticular, six (15%) each of RF negative Polyarticular and Enthesitis related arthritis (ERA) and five (12.5%) of RF positive Polyarticular JIA. ANA was positive only in one patient. The mean hemoglobin level was found to be significantly lower but total TLC: Total leukocyte count; ESR: Erythrocyte sedimentation rate; CRP: C Reactive Protein.

<table>
<thead>
<tr>
<th>Joint</th>
<th>SOJIA</th>
<th>POJIA RF –VE</th>
<th>POJIA RF+VE</th>
<th>ERA</th>
<th>OJIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>%</td>
<td>Frequency</td>
<td>%</td>
<td>Frequency</td>
</tr>
<tr>
<td>Knee</td>
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<td>32.1</td>
<td>11</td>
<td>26.2</td>
<td>5</td>
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<td>Ankle</td>
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<td>26.9</td>
<td>12</td>
<td>28.6</td>
<td>7</td>
</tr>
<tr>
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<td>19.2</td>
<td>9</td>
<td>21.4</td>
<td>7</td>
</tr>
<tr>
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<td>11.5</td>
<td>8</td>
<td>19</td>
<td>4</td>
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<tr>
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<td>10.3</td>
<td>2</td>
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<td>Total</td>
<td>78</td>
<td>100</td>
<td>42</td>
<td>100</td>
<td>25</td>
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</tbody>
</table>

SOJIA: Systemic onset juvenile idiopathic arthritis; RF –VE/ +VE: Rheumatoid factor negative/ positive; POJIA: Poly articular juvenile idiopathic arthritis. ERA: Enthesitis related arthritis; OJIA: Oligo articular juvenile idiopathic arthritis.

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leukocyte count; ESR and CRP were significantly higher among cases than controls. (Table 1)

Knee joint and ankle joint were involved most commonly in ERA followed by oligoarticular and RF negative polyarticular JIA. The wrist joint was most commonly involved in RF positive polyarticular JIA. Pattern and frequency of different joint involvement in various subsets of JIA is depicted in table 2.

The duration of disease was less than one year in fifteen, 1-2 years in fourteen, 2-3 years in eight and more than 3 years in three patients.

USG evaluation of joints: RI and color fraction

A total of 187 healthy joints and 200 joints in controls were studied by USG. Most common joints evaluated were knee (cases: 59; controls: 68) followed by ankle (cases: 55; controls: 68), wrist (cases: 34; controls: 55), elbow (cases: 22; controls: 6) and small joints (cases: 17; controls: 5).

When 187 diseased and 200 healthy joints were pooled together for USG indices, the mean color fraction was significantly higher in cases (0.31±0.09) as compared to controls (0.033±0.006) (table 3). Analysis of the USG indices of the knee, ankle and wrist joint separately also revealed a significant difference in mean color fraction of diseased joints as compared to healthy controls. Even though the number of elbow joints and small joints of hand evaluated were less, mean color fraction in diseased joints was significantly higher.

The mean resistive index was found to be significantly lower in all diseased joints pooled together (0.62±0.07

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>(I) Swelling Score</th>
<th>(J) Swelling Score</th>
<th>Mean Difference (I-J)</th>
<th>SE</th>
<th>p Value</th>
<th>F Value</th>
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</thead>
<tbody>
<tr>
<td>Color Fraction</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>1.000</td>
<td>0.533</td>
</tr>
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<td></td>
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<td>0.018550</td>
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<td>0.019053</td>
<td>0.018493</td>
<td>.913</td>
<td></td>
</tr>
</tbody>
</table>

SE: Standard error; RI: Resistive index

Figure 1a. ROC curve for RI. 1b. Color fraction when all joints were pooled together.

Table 4. Test of significance between swelling score and ultrasound indices (Color fraction and RI)
versus 0.79±0.08 p< 0.001) as well as in each diseased joint group as compared to the controls (Table 3).

Correlation of color fraction, RI and swelling, tenderness grade and duration of disease

Eighty three joints had a tenderness and swelling grade 1, eighty six had swelling and tenderness grade 2 and eighteen had grade 3. On analyzing the color fraction and RI with different grades of swelling and tenderness, not much difference or correlation was seen in value of color fraction and RI with different grades of swelling and tenderness (data not shown). On applying ANNOVA to 187 diseased joints it was found that there was no significant difference in color fraction or RI with increasing grades of swelling (Table 4).

Similarly no significant correlation was found between duration of disease and color fraction (r=0.0138; p=0.394) or RI (r= -0.021; p=0.900).

Cut off values of color fraction and RI and their sensitivity, specificity, PPV and NPV

When all the joints were pooled together, the cut off for color fraction was 0.100 which corresponded to a point nearest to upper left corner of ROC curve (Figure 1a) and area under ROC curve was 0.954 (95% CI 0.940- 0.968).The sensitivity, specificity, PPV and NPV of color fraction in diagnosing arthritis were 93.6%, 94%, 93.6%, and 94% (Table 5).

On individual joint group analysis, the cut off values of both color fraction and RI were derived for knee, ankle, wrist, elbow and small joints of hands separately. The sensitivity, specificity, PPV, NPV for all joints were found to be significantly high (Table 5).

**Discussion**

USG evaluation of the musculoskeletal system has been in use since the eighties; initially with gray scale, real time and later with color Doppler, power color and spectral Doppler; as advances in the machine occurred. Real time high resolution USG has been used in pediatric patients to evaluate hip effusion [8-10], wrist swelling and tendon sheaths [11] and cartilage thickness in JIA patients [12].The drawback of gray scale USG was its inability to detect hyperemia or blood flow. Power color Doppler USG could detect increased vascularity in synovium. It has been widely evaluated in rheumatoid arthritis patients by either counting color pixels in the synovium [13] or detecting power Doppler signal with arbitrary grading [14] or by studying pulsatility [15]. With more advanced USG machines, a quantitative evaluation of joint inflammation was made possible by power color Doppler and spectral USG (using color fraction and RI as quantitative indices). These have been used in adult RA patients in diagnosing arthritis [16]; assessment of disease activity [17] and evaluating response

<table>
<thead>
<tr>
<th>USG indices</th>
<th>Joint</th>
<th>Cut off</th>
<th>AUC (95% CI)</th>
<th>Sensitivity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color Fraction</td>
<td>Pooled</td>
<td>0.100</td>
<td>0.954(0.940-0.968)</td>
<td>92.5</td>
<td>90.6</td>
<td>92.9</td>
</tr>
<tr>
<td></td>
<td>Knee</td>
<td>0.107</td>
<td>0.961(0.926-0.997)</td>
<td>94.9</td>
<td>93.3</td>
<td>95.5</td>
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<td></td>
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<td>0.109</td>
<td>0.944(0.901-0.988)</td>
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<tr>
<td></td>
<td>Wrist</td>
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<td>80</td>
<td>95.8</td>
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<td>Elbow</td>
<td>0.095</td>
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<tr>
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<td>Small joint</td>
<td>0.107</td>
<td>0.956(0.936-0.976)</td>
<td>94.1</td>
<td>100</td>
<td>83.3</td>
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<tr>
<td>Resistive Index</td>
<td>Pooled</td>
<td>0.711</td>
<td>0.965(0.953-0.977)</td>
<td>93.6</td>
<td>93.6</td>
<td>94</td>
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<tr>
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<td>Knee</td>
<td>0.707</td>
<td>0.966(0.916-1.000)</td>
<td>96.6</td>
<td>95</td>
<td>97</td>
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<td>Ankle</td>
<td>0.728</td>
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<td>91.7</td>
<td>100</td>
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<tr>
<td></td>
<td>Wrist</td>
<td>0.711</td>
<td>0.912(0.848-0.975)</td>
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<td>0.988(0.976-1.000)</td>
<td>94.1</td>
<td>100</td>
<td>83.3</td>
</tr>
</tbody>
</table>

AUC: Area under curve. PPV: Positive predictive value; NPV: Negative predictive value; CI: Confidence interval.
to treatment [16,18]. Terslev et al then derived cut off values of both the indices to distinguish between normal and abnormal joints in adults [6]. Few studies which have been done in JIA patients with power color Doppler USG (using semi-quantitative indices) have evaluated disease activity [2,19], therapy [19-21] or even detected subclinical synovitis [22,23]. Studies have also suggested that laboratory tests like ESR and CRP were not sufficiently sensitive for prediction of active disease [2] and found USG to be more sensitive in detecting synovitis than clinical examination [21-23]. Color fraction and RI have not been studied earlier in children. We evaluated these indices in 187 joints in JIA patients and 200 healthy joints in all joints pooled together and in individual joint groups.

The color fraction was found to be significantly higher and resistive index significantly lower in diseased joints as compared to healthy joints; in all the joints pooled together and in individual joint groups. Since it has not been studied earlier in pediatric patients, we could not compare our results with any study; however our results were comparable to those of RA patients [6]. We did not find any correlation between grades of swelling or tenderness and color fraction or RI. This would mean that these indices are not affected by degree of swelling and tenderness. The correlation of these indices with disease activity scores could be a scope for future studies.

In JIA, like in RA, there is hyperplasia and h ypervascularization of the synovium. The hyperemia of synovitis is detected by color USG as increased color pixels in the region of interest but this is not sufficient to quantify synovial inflammation. This is supplemented by estimating abnormal synovial perfusion in the inflamed synovium by spectral Doppler by detecting the type of flow in the vessels visualized in the inflamed synovium by power color Doppler [6,16]. RI is a measure of type of blood flow. Decreased RI implies a low resistance flow in vessels in inflamed synovium.

Since the color fraction increased and RI decreased significantly in an inflamed joint, it would be beneficial to determine a cut off value for these to distinguish abnormal from normal.

We found a cut off level 0.100 for color fraction and 0.711 for RI in all the joints pooled together with a very high diagnostic sensitivity, specificity, PPV and NPV. The cut off value for knee, ankle, wrist, elbow and small joints of hand were also derived individually. The cut off values for color fraction and RI might be helpful in certain clinical situations. In patients where clinically it is difficult to diagnose arthritis the cut off values would be helpful in detecting synovitis e.g. if an ankle arthritis is doubtful then a color fraction of more than 0.109 and RI of less than 0.728 would indicate that the joint is diseased. The cut off values might also be helpful in documenting remission or relapse objectively. These also might help in detecting subclinical synovitis and possibility change the classification of patient subsets. However these findings need to be further validated globally before arriving at universally acceptable cut off values in different joints with a larger sample size for individual joints specially elbow and small joints.

Though the results of our study were quite encouraging but there were some limitations. Dynamic MRI has been reported in adult patients to diagnose arthritis with high sensitivity and specificity. We could not use it to compare with Power Doppler Ultrasonography because of its limitations like need for sedation, high cost, difficult to perform in children, allergic reactions to contrast and difficult to evaluate multiple joints in a short time. Secondly, the number of small joints evaluated was limited. To conclude, we believe, that power color and spectral Doppler has a role in evaluation of JIA patients objectively.

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