Mean platelet volume, Immature platelet fraction and disease activity in Juvenile Idiopathic arthritis: a cross sectional study.

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Research Article

Keywords: Juvenile idiopathic arthritis, mean platelet volume, immature platelet fraction, inflammatory activity tests, disease activity, platelet parameters

Posted Date: April 10th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2701871/v1

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Abstract

Objective

To test correlation between mean platelet volume (MPV), immature platelet fraction (IPF) with disease activity in a group of patients with juvenile idiopathic arthritis (JIA) defined by JADAS 71. Determine sensitivity, specificity, positive and negative predictive value.

Methods

A cross sectional study was performed in JIA patients with oligoarticular and polyarticular rheumatoid factor negative subtypes, classified with active or inactive disease activity by JADAS 71. Other subtypes and patients with acute infection, neoplastic diseases, macrophage activation syndrome, other thrombocytopenias, other inflammatory diseases, and use of antiplatelet and anticoagulant medications were excluded. All blood parameters were processed in a SYSMEX XN 1000 haematology analyser.

Results

Twenty-five active and 21 inactive JIA disease patients were included. Oligoarticular were 76%, 73,9% were female sex and 95,6% were caucasian. The median age was 10,30 [4,77–14] years and the median disease duration was 57 months [24–90,7]. The median JADAS 71 was 1,35 [0–10,25] with active disease above 1. There was no correlation between MPV and JADAS 71 (rho = 0,204 e p = 0,185). There was no correlation between IPF and JADAS 71 (rho = 0,192 e p = 207). Sensitivity was 13% and specificity was 4,80%. Positive predictive value (PPV) was 75% and negative predictive value (PNV) was 50%. Sensitivity was 4,22%, and specificity was 0,0%, PPV was 36,8% and PNV was 100%.

Conclusions

MPV and IPF had no correlation with JADAS 71 in a group of JIA patients

Background

Evaluation of disease activity is essential in Juvenile idiopathic arthritis (JIA) care. Inflammatory tests available in routine as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are unspecific and have many interferes (1). In JIA, there are observational studies suggesting that(2) ESR seems to have greater responsiveness to initial therapy compared to CRP. Other retrospective study, ESR was also more associated to uveitis in 358 children with polyarthritis rheumatoid factor negative (PFRN) and oligoarthritis(1). One prospective longitudinal study showed there are patients with persistent elevated tests in despite of the absence of clinical arthritis and vice-versa (3).
There is vast scientific evidence pointing at the role of platelets in outbreak and maintenance of inflammatory process and, at the same time, the appearance of new platelet parameters (4). Platelets are fragments of cytoplasm megakaryocytes full of membrane receptors and inner granules filled with preformed molecules that interact directly with immune system (5). During their vital cycle, a reduce in their size occurs. Younger platelets have greater size and are more metabolic active (6). In inflammatory systemic diseases, IL-6 stimulates thrombopoiesis intensively leading to a reduce in platelet volume(7)(8)(9).

The new haematological analysers introduced new platelet parameters that are accessible in routine and could improve this evaluation. Mean platelet volume (MPV) is measurement of platelet dimensions during the morphologic analysis phase (9). The presence of RNA in platelet cytoplasm is the immature platelet fraction (IPF) is another parameter of interest (10). There are no studies exploring IPF in JIA patients to our knowledge.

We aim to study the role of these parameters in the routine disease activity evaluation in JIA.

**Methods**

This study was approved by our institution ethics committee (CAAE: 27069019.1.0000.5336). Forty-six patients diagnosed with JIA according to the ILAR criteria, oligoarticular and polyarticular rheumatoid factor negative, assisted in the Paediatric Rheumatology outpatient clinic of Saint Lucas Hospital of Pontifical Catholic University of Rio Grande do Sul, Brazil were included. Inclusion occurred after signed consent by parents and signed assent by patients. JADAS 71 cut-off for inactive disease in oligoarticular and polyarticular subtypes is a result below or equal to 1. Other subtypes were excluded and patients with acute infection, neoplastic diseases, macrophage activation syndrome, other thrombocytopenias, other inflammatory diseases, and use of antiplatelet and anticoagulant medications. Immediately after the clinical evaluation, blood samples were obtained by vacutainers (BD Vacutainer® K$_2$ EDTA 13 x 75 mm) containing 3 ml de EDTAK$_2$ (ethylenediaminetetraacetic acid). All blood samples were processed in less of 120 minutes to avoid the effect of EDTAK$_2$ in platelet size in a SYSMEX XN 1000 haematology analyser in our institution. For ESR optical photometry method was used and for CPR, dry chemistry technic was used. For IPF, there is a specific platelet channel and Fluorocell PLT® dye with 0,003% of oxazine and 99,9% de ethylene glycol was used.

All parameters are continuous variables and were presented by median and interquartile range. Categorical data were reported in terms of absolute frequencies and percentages. Associations between numerical variables were evaluated by spearman coefficient. A receiver operating characteristic curve analysis (ROC) was produced to find the most precise level to identify patients with active disease. The level of significance defined was $p \leq 0.05$. Sensitivity, specificity, positive and negative predictive value were calculated.

**Results**
Twenty-five active and 21 inactive JIA disease patients. Oligoarticular patients were 76% with 73,9% were female sex and 95,6% were caucasian. The median age was 10,30 [4,77–14] years and the median disease duration was 57 months [ 24–90,7]. The median JADAS 71 was 1,35 [ 0–10,25] with active disease above 1. Uveitis was present in 17,3% with only two patients being of polyarticular type. Antinuclear antibody was present in 56,5% of patients. There were no patients on non-steroidal anti-inflammatory therapy, 17,4% were in regular use of steroids. Methotrexate was used in 26,1%, leflunomide was used in 32,6% and 41,3% were taking anti-TNF therapy (26,1% adalimumab, 13% etanercept e 2,2% tocilizumab).

There was not significant difference between active and inactive patients for sex, age, subtype, presence of uveitis or drugs (table 1).

There were no significant differences in blood variables between active and inactive patients (Table 2).

There was no correlation between MPV and JADAS 71(rho = 0,204 e $p = 0,185$). There was no correlation between IPF and JADAS 71 (rho = 0,192 e $p = 207$). There was good correlation between MPV and IPF (rho = 0,866 e $p = 0.000$). The receiver operating characteristic curve analysis (ROC) for MPV and JADAS-71 showed an under the curve area (UCA) of 0,412 (IC 95% 0,240–0,580), with an ideal cut-off of 8,15 fL (Fig. 1). Sensitivity was 13% and specificity was 4,80%. Positive predictive value (PPV) was 75% and negative predictive value (NPV) was 50%. The ROC curve analysis for IPF and JADAS 71 showed an UCA of 0,427 (IC 95% 0,258–0,595) with an ideal cut-off of 0,35% (Fig. 2). Sensitivity was 4,22%, and specificity was 0,0%, PPV was 36,8% and NPV was 100%.

**Discussion**

JIA is primarily clinical and exclusion diagnostic imposing difficulties to the clinician (11). The introduction of biologic therapy forced an improvement in tools for these purposes and creation of JADAS reflects that set, with significant improvement (12). To test and validate for new inflammatory laboratorial tests is always challenging in Paediatrics because of biological variability, and access to low cost and reproducible methods. That is a universal challenge (13). Platelet parameters satisfy those requirements and might have a potential as new inflammatory markers.

In relation to MPV in JIA, a retrospective review of digital records, compared 64 active disease patients, 51 inactive patients and 64 health sex and age matched controls and found elevated MPV in active patients(14). In another cross-sectional study with 55 JIA patients, MPV seemed to distinguish systemic subtype from oligoarticular an polyarticular patients(15). A case-control study found no significant differences in JIA patients when compared to controls (16). It is important emphasize that, beyond different designs, there were also important heterogeneity of patients, analysers used, definitions of disease activity and analytical phase procedures that might have influenced results in these studies.

We tried to contribute on this field with a cross-sectional design, with a clear definition of disease activity by using JADAS-71 in a more uniform group of patients obtained by the exclusion of other subtypes of
JIA. We observed analytical attention, by use of EDTA, time for processing blood samples and clear exclusion criteria applied. We believe that our population study is representative of what is related in literature, with most of patients being female and oligoarticular subtype. We tried to minimize the potential interferences observed in other studies.

We found a poor performance of MPV and IPF to detect active patients defined by JADAS 71, in opposition to published studies. We believe that this result might be explained by the selection criteria used and by the fact that those might be screening parameters and shall only be used together with routine tests available. MPV and IPF had no correlation with ESR and CRP. To our knowledge, this is the first study to explore IPF in JIA.

Our limitations were the absence of a control group and the small number of patients. The cross-sectional design does not allow to observe response to therapy in JIA.

**Conclusions**

In conclusion, our findings suggest the MPV and IPF were not sensible and specific parameters to distinguish active and inactive patients in JIA. To our knowledge, this is the first study to explore IPF in JIA.

**Abbreviations**

MPV: Mean platelet volume

IPF: Immature platelet fraction

JIA: Juvenile idiopathic arthritis

CRP: C reactive protein

ESR: Erythrocyte sedimentation rate

PFRN: Polyarthritis rheumatoid factor negative.

IL-6: interleukin 6

EDTA K\textsubscript{2}: Ethylenediaminetetraacetic acid

ROC: Receiver operating characteristic curve

UCA: under the curve area

PPV: Positive predictive value

PNV: Negative predictive value
Declarations

Authors’ contributions

MMP and LCB contributed to design of the study, patients’ assessment, writing the manuscript, draft revision and statistical work.

All authors read and approved the final manuscript.

Funding

No funding resources for this work.

Availability of data and material

Please contact author for data request.

Ethics approval and consent to participate.

All participants gave their informed consent to participate.

Consent for publication

Obtained.

Competing interests

All the authors declare no competing interests.

References


Tables

Table 1. Active and inactive characteristics:
Table 2: Paraclinical comparison between groups - median [P25 – 75].

<table>
<thead>
<tr>
<th>Variables</th>
<th>Actives n=25</th>
<th>Inactives n=21</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years) [P25 – 75]</td>
<td>8.5 [4.6 – 13.2]</td>
<td>11 [ 7.8 – 14.25]</td>
<td>0.206</td>
</tr>
<tr>
<td>Sex – (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (28)</td>
<td>5 (23.8)</td>
<td>0.528</td>
</tr>
<tr>
<td>Female</td>
<td>18 (72)</td>
<td>16 (76)</td>
<td>NS</td>
</tr>
<tr>
<td>Subtype – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oligoarticular (35)</td>
<td>18 (72)</td>
<td>17 (48.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Polyarticular (11)</td>
<td>7 (28)</td>
<td>4 (19)</td>
<td>NS</td>
</tr>
<tr>
<td>Uveitis – n (%)</td>
<td>4 (16%)</td>
<td>5( 23%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**NS:** Non-significant, data not shown.

Table 2: Paraclinical comparison between groups - median [P25 – 75].

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Active</th>
<th>Inactive</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm/h)</td>
<td>6 [2 – 11]</td>
<td>10 [ 5 – 37]</td>
<td>0.84</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>0.6 [0.5 – 8.9]</td>
<td>0.5 [0.5 – 1]</td>
<td>0.95</td>
</tr>
<tr>
<td>MPV (fL)</td>
<td>9.6 [8.9 – 10.7]</td>
<td>9.4 [8.9 – 10.1]</td>
<td>0.318</td>
</tr>
<tr>
<td>IPF (%)</td>
<td>2 [1.3 – 3.8]</td>
<td>2 [ 1 – 2.5 ]</td>
<td>0.400</td>
</tr>
</tbody>
</table>

ESR: erythrocyte sedimentation rate, CPR: C reactive protein, MPV: Mean platelet volume, IPF: Immature platelet fraction.

**Figures**
Figure 1

MPV and JADAS ROC curve
1 – specificity

Figure 2

MPV and JADAS ROC curve