Evaluation of Immature Platelet Fraction in Lower Respiratory Tract Infections: A Retrospective Study

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Abstract

Introduction

Immature platelet fraction (IPF) is a parameter of an automated hematologic analyzer and is related to platelet size and cytoplasmic RNA content. It reflects thrombopoiesis and is often used as the marker of platelet activity. IPF has been evaluated mostly in hematologic disorders and has also been evaluated in patients with gestational hypertension, sepsis, autoimmune diseases and in hospitalised patients with neutrophilia. Platelets, asides from the maintenance of hemostasis, release inflammatory mediators that can modify leukocyte and endothelial responses to various inflammatory stimuli. Lower respiratory tract infections are the leading cause of death from infections worldwide. The role of platelets in lower respiratory tract infections has been reported in many studies. IPF, which is related to platelet activation, has not been evaluated in patients with lower respiratory tract infections.

Methods

The study involved patients who fulfilled the criteria of community-acquired pneumonia (CAP) and aspiration pneumonia (AP). In addition, age and sex-matched healthy controls were involved. Whole blood samples were collected from healthy controls and from the patients on admission. The mean IPF% and C-reactive protein (CRP) levels were measured in patients with CAP, in patients with AP and in healthy controls. The mean IPF% values in patients with infection were compared to mean IPF% values in healthy controls. The mean IPF% values were compared to mean CRP levels in patients with infection. Additionally, the mean IPF% values in patients that died in the first 14 days were compared to the mean IPF% values in patients that were alive. The statistical analysis of data was performed with the Statistical Package for the Social Sciences (SPSS) for Windows, Version 13.0 (SPSS Inc, Chicago, IL).

Results

The study population consisted of 45 patients (27 patients with CAP and 18 patients with AP), 27 males and 18 females, with a mean age of 72.11 ± 16.4 years and 39 healthy controls, 22 males and 17 females with a mean age of 64.2 ± 14.8 years. The mean CRP levels in patients with infection were 155.2±119.1 mg/dl. The mean IPF% value of patients with infection was 2.76 ± 2.27 and in patients with AP 2.55 ± 2.02 and in patients with AP 3.07 ± 2.64 (p = 0.06). The mean IPF% value in patients with infection had no linear correlation with CRP value in these samples. The mean IPF% value in patients with infection was 3.75 ± 0.595. The mean IPF% value in patients with infection was 2.55 ± 2.02 and in patients with AP 3.07 ± 2.64 (p = 0.06). The mean IPF% value in patients with infection was 3.75 ± 0.595. The mean IPF% value in patients that died in the first 14 days was 5.54 ± 3.17 and in patients with CAP who died in the first 14 days of hospitalisation compared to those who were alive, but not statistically significant.

Conclusions

Mean IPF% value is greater in patients with lower respiratory tract infections, including CAP and AP, compared to healthy controls. There is no linear correlation between IPF values and CRP values in patients with lower respiratory tract infections. In addition, there is a difference in mean IPF% value between patients who died in the first 14 days of hospitalisation compared to those who were alive, but not statistically significant.
Materials And Methods

The study involved patients who fulfilled the criteria of CAP and aspiration pneumonia (AP). The exclusion criteria were: patients <18 years old, patients with a history of solid tumors or hematological malignancy,
patients suffering from disease or receiving therapy that suppresses the bone marrow activity, patients receiving antiplatelet therapy and patients with platelet counts of less than 150 x10³/μl. In addition, age and sex-matched healthy controls without infection, and with platelet counts of more than 150 x10³/μl, were involved. Whole blood samples were collected from healthy controls and from the patients on admission. The mean IPF% and CRP levels were measured in patients with CAP, in patients with AP and in healthy controls. IPF was measured in automated Sysmex XE 2100 hematology analyzer. Serum levels of CRP were determined by immunoturbidimetric assay on Roche Cobas 6000 c501 analyzer. Reference range for IPF% in our laboratory is 1%-5% and normal values for CRP are values less than 6 mg/dl. The mean IPF% values in patients with lower respiratory infection were compared to mean IPF% values in healthy controls. The IPF% values were compared to CRP levels in patients with infection. Additionally, the mean IPF% values in patients who died in the first 14 days of hospitalisation were compared to the IPF% values in patients that were alive. The statistical analysis of data was performed with the Statistical Package for the Social Sciences (SPSS) for Windows, Version 13.0 (SPSS Inc., Chicago, IL). Continuous variables were tested for normality of distribution by the Kolmogorov-Smirnov test. For normally distributed values, descriptive results are presented as mean (standard deviation). The statistical control for normal values performed with: (a) independent samples T test for normally distributed data, (b) one-way ANOVA and (c) Pearson χ² for control of independence of variables. All p-values were two-sided and 5% was chosen as the level of statistical significance.

Results

The study population consisted of 45 patients (27 patients with CAP and 18 patients with AP), 27 males and 18 females, with a mean age of 72.11 ± 16.4 years and 39 healthy controls, 22 males and 17 females with a mean age of 64.2 ± 14.8 years (Table 1).

The mean CRP levels in patients with lower respiratory tract infections were 155.2 ± 119.1 mg/dl (Table 2). The mean IPF% value of patients with lower respiratory tract infections was 2.76 ± 2.27 and the mean IPF% value of controls was 1.72 ± 0.77 (p < 0.006) (Table 2; Figure 1).

<table>
<thead>
<tr>
<th></th>
<th>C, n = 39</th>
<th>AP, n = 18</th>
<th>CAP, n = 27</th>
<th>C versus AP</th>
<th>C versus CAP</th>
<th>AP versus CAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (males/females)</td>
<td>22/17</td>
<td>11/7</td>
<td>16/11</td>
<td>0.738</td>
<td>0.818</td>
<td>0.901</td>
</tr>
<tr>
<td>Age(years) (SD)</td>
<td>64.2 (14.8)</td>
<td>77.5 (13.3)</td>
<td>69.7 (17.1)</td>
<td>&lt;0.01</td>
<td>0.339</td>
<td>0.238</td>
</tr>
<tr>
<td>CRP (mg/dl) (SD)</td>
<td>3.28 (1.05)</td>
<td>188.3 (115.9)</td>
<td>133.2 (118.1)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.092</td>
</tr>
<tr>
<td>IPF (%) (SD)</td>
<td>1.72 (0.77)</td>
<td>3.07 (2.64)</td>
<td>2.55 (2.02)</td>
<td>&lt;0.023</td>
<td>0.148</td>
<td>0.595</td>
</tr>
<tr>
<td>Status (alive/dead)</td>
<td>39/0</td>
<td>10/8</td>
<td>22/5</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.060</td>
</tr>
</tbody>
</table>

TABLE 1: Characteristics of the study population

C, controls; AP, aspiration pneumonia; CAP, community-acquired pneumonia; IPF, immature platelet fraction. Status: alive/dead in the first 14 days of hospitalisation

The mean IPF% and CRP values in patients with infection and healthy controls

<table>
<thead>
<tr>
<th></th>
<th>C, n = 39</th>
<th>Patients, n = 45</th>
<th>C versus patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF (%) (SD)</td>
<td>1.72 (0.77)</td>
<td>2.76 (2.27)</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>CRP (mg/dl) (SD)</td>
<td>3.28 (1.05)</td>
<td>155.2 (119.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

TABLE 2: Mean IPF% and CRP values in patients with infection and healthy controls

C, controls; IPF, immature platelet fraction; CRP, C-reactive protein
The mean IPF% value in patients with CAP was 2.55 ± 2.02 and in patients with AP 3.07 ± 2.64 (p = 0.595) (Figure 2). The IPF% values in patients with lower respiratory tract infections had no linear correlation with CRP values in these patients (r = 0.076, p = 0.62). (Table 3; Figure 3). Thirteen patients died in the first 14 days of hospitalisation (eight patients (61.5%) with AP and five patients (18.5%) with CAP (Figure 4). The mean IPF% value in all patients that died in the first 14 days was 3.75 ± 2.44 and the mean IPF% value in all patients that were alive was 2.35 ± 2.11 (p = 0.06) (Table 4; Figure 5). The mean IPF% value in patients with CAP who died in the first 14 days of hospitalisation was 5.54 ± 3.17 and in patients with CAP who were alive was 1.87 ± 0.72 (p = 0.06). The mean IPF% value in patients with AP who died in the first 14 days of hospitalisation was 2.63±0.85 and in patients with AP who were alive was 5.41 ± 3.51 (p = 0.554) (Table 5).
FIGURE 2: Comparison of IPF% values between groups
11, 30, 51, 56, 74: outliers; 62, 70: extreme values. IPF, immature platelet fraction

<table>
<thead>
<tr>
<th>REGRESSION</th>
<th>r</th>
<th>r^2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/dl) = 2.981-0.001 (IPF (%))</td>
<td>0.076</td>
<td>0.006</td>
<td>0.620</td>
</tr>
</tbody>
</table>

TABLE 3: Correlation between IPF% values and CRP values in patients with lower respiratory tract infections
CRP, C-reactive protein; IPF, immature platelet fraction
FIGURE 3: Correlation between IPF% and CRP values in infected patients.

CRP, C-reactive protein; IPF, immature platelet fraction

FIGURE 4: People alive/dead in each group of infection in the first 14 days.
days of hospitalisation

<table>
<thead>
<tr>
<th>Status</th>
<th>Alive, n =32</th>
<th>Dead, n = 13</th>
<th>Alive versus Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPF (%) (SD)</td>
<td>2.35 (2.11)</td>
<td>3.75 (2.44)</td>
<td>0.06</td>
</tr>
<tr>
<td>CRP (mg/dl) (SD)</td>
<td>141.8 (124.2)</td>
<td>188.3 (102.3)</td>
<td>0.239</td>
</tr>
</tbody>
</table>

TABLE 4: Mean IPF% values in dead and alive patients in the first 14 days of hospitalisation

CRP, C-reactive protein; IPF, immature platelet fraction

FIGURE 5: Comparison of IPF% values between dead and alive patients in the first 14 days

30, 69, 74: outliers; 43, 47, 80: extreme values; IRF, immature platelet fraction
### TABLE 5: Mean IPF% values and mean CRP values in patients with AP and CAP, dead and alive in the first 14 days of hospitalisation

<table>
<thead>
<tr>
<th></th>
<th>Status</th>
<th>Alive, n = 10</th>
<th>Dead, n = 8</th>
<th>Alive versus Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>AP</td>
<td>IPF (%) (SD)</td>
<td>3.41 (3.51)</td>
<td>2.63 (0.85)</td>
<td>0.554</td>
</tr>
<tr>
<td></td>
<td>CRP (mg/dl)</td>
<td>158.6 (119.9)</td>
<td>225.5 (106.3)</td>
<td>0.235</td>
</tr>
<tr>
<td>CAP</td>
<td>Status</td>
<td>Alive n = 22</td>
<td>Dead n = 5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IPF (%) (SD)</td>
<td>1.87 (0.72)</td>
<td>5.54 (3.17)</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>CRP (mg/dl)</td>
<td>134.1 (128.2)</td>
<td>128.9 (66.7)</td>
<td>0.931</td>
</tr>
</tbody>
</table>

AP, aspiration pneumonia; CAP, community-acquired pneumonia; CRP, C-reactive protein; IPF, immature platelet fraction.

### Discussion

According to our results, there was a difference in mean IPF% value between patients with AP compared to the patients with CAP but no statistically significant. However, there was a statistically significant difference in mean IPF% value between all patients with respiratory infections and healthy controls, indicating increased bone marrow platelet production in infected patients. Platelets are anucleate blood cells, with intimate relationship with the lungs, which transit the pulmonary vessels and are present in alveolar capillaries. Megakaryocytes, the cells that are the precursors of platelets, are present in the mammalian lungs. There is evidence that the lungs are sites of thrombopoiesis, and that human lungs are reservoirs for platelets and release them in response to specific stimuli [20]. In addition, there is evidence that platelets regulate vascular permeability in the lungs and the barrier function of the alveolar capillaries. Recent studies indicate that platelets have a key role in pulmonary immune responses and integrity but that these cells can also contribute to injury in lung diseases [20].

As mentioned in the introduction, the platelet activation related to S. pneumoniae has been studied [14]. In addition, platelet activation associated with Staphylococcus aureus and Klebsiella pneumoniae-induced sepsis has been studied in numerous animal models of pulmonary bacterial infections [21]. There is evidence that platelets have an important role in the immune response to respiratory bacterial infection with P. aeruginosa. It has been reported that experimentally-induced platelet depletion leads to increased pulmonary bacterial growth and systemic bacterial dissemination indicating that platelets play a significant role in preventing bacterial lung infections [22]. Besides bacterial infections, the role of platelets in lower respiratory tract viral infections has been reported. Schrottaier et al. described the interaction between platelets and leukocytes and the subsequent alteration in cytokine production as a possible mechanism involved in defense against the respiratory syncytial virus (RSV) [23].

CRP was identified in 1930 and is considered to be an acute-phase protein, indicating infectious or inflammatory disorders [24]. CRP has been studied as a diagnostic tool and as a biomarker for disease severity in lower tract infections and as a marker for prognosis in patients with CAP [25-27]. However, in our study, the IPF% values in patients with lower respiratory tract infections had no linear correlation with CRP values in these patients (r = 0.076, p = 0.62).

Liu et al. studied the correlation between the percentage of immature platelets and infection in 190 patients with a body temperature >37.3°C or <36°C and suspicious of infection, who were hospitalized and concluded that the sensitivity and specificity for diagnosing infection were, respectively, 91.78% and 93.18% when IPF% and CRP were used in combination [28]. IPF% changed dynamically during the course of the infection and recovered to lower than 5.5% at two to seven days before the body temperature was normal.

In our study, there was a difference in mean IPF% value between patients that were alive and patients who died in the first 14 days of hospitalisation, with greater mean IPF % value noticed among patients that died in the first 14 days of hospitalisation, but not statistically significant. These results indicate a greater platelet bone marrow production in patients who died. The association between platelet counts and mortality in patients with lower tract infections has been reported. Mirsaedil et al. in their retrospective cohort study concluded that platelet abnormalities are associated with mortality in patients hospitalized with CAP and evaluating an initial complete blood count test in patients with CAP, an abnormal platelet count is a better predictor of outcome than an abnormal leukocyte count [29]. Brogley et al. in their multicentre observational study reported that thrombocytopenia is an independent predictor of mortality in patients with severe CAP [30].

The study has some limitations. The fact that all the patients included in this study were enrolled in a single
Conclusions
Mean IPF% values are greater in patients with lower respiratory tract infections, including CAP and AP, compared to healthy controls. There is no linear correlation between IPF values and CRP values in patients with lower respiratory tract infections. In addition, there is no statistically significant difference in mean IPF% value between patients that died in the first 14 days of hospitalisation compared to those who were alive. Based on our study, we cannot conclude that IPF is a reliable inflammatory marker or prognostic factor for lower respiratory tract infections. To our knowledge, the current study is the first to evaluate IPF in patients with lower respiratory tract infections. Further studies are needed to establish the role of IPF as a biomarker in these patients.

Additional Information
Disclosures
Human subjects: Consent was obtained by all participants in this study. Animal subjects: All authors have confirmed that this study did not involve animal subjects or tissue. Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/services info: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Financial relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References
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