Neutrophil Lymphocyte Ratio in Estimating Response to Corticosteroid Treatment in Immune Thrombocytopenia Patients

Nötrofil Lenfosit Oranı Immün Trombositopeni Hastalarında Kortikosteroid Tedavisine Yanıtı Öngörebilir mi?

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ABSTRACT

Introduction: We aimed to investigate the association between neutrophil lymphocyte ratio (NLR) and response and loss of response to corticosteroid treatment in immune thrombocytopenia patients (ITP).

Methods: We retrospectively analyzed the data of 47 ITP patients treated with corticosteroid therapy at Istanbul Training and Research Hospital Clinic of Hematology between 2007 and 2016. NLR was calculated using complete blood count of patients at the time of diagnosis. The cut-off score for NLR was determined at 2.5 according to median NLR level.

Results: Twenty-three (48.9%) patients had NLR <2.5 and 24 (51.1%) patients had NLR ≥2.5. There was no statistically significant relationship between NLR and treatment response, response duration and loss of response (p=0.74, p=0.869, p=0.315, respectively).

Conclusion: Although NLR was found to be associated with the prognosis and activity of various diseases in several studies, we could not verify such an association between NLR and response to corticosteroid therapy in ITP patients.

Keywords: Corticosteroid, immune thrombocytopenia patients, neutrophil lymphocyte ratio

Introduction

Immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by isolated thrombocytopenia which is attributed to enhanced destruction and impaired production of platelets, often without a definable specific stimulus (1-3). Despite the implementation of novel agents such as thrombopoietin receptor agonists, corticosteroids (CSs) are still the first line recommended therapy for ITP patients who need treatment (1,3,4). Initial response rate to CS treatment is promising, varying from 50 to 90%; however, durable platelet response could be maintained in only 10-30% of patients, when the CS treatment is tapered off or ceased (5).

Inflammation is known to have a significant role in the course of many benign (6) and malignant diseases (7). Neutrophil lymphocyte ratio (NLR), being an inexpensive and easily available parameter, has been used frequently as a marker of systemic inflammation in recent years (6). Neutrophil lymphocyte ratio (NLR), being an inexpensive and easily available parameter, has been used frequently as a marker of systemic inflammation in recent years (6).

The association between elevated NLR and the disease course, prognosis and treatment response has been established in several benign (8-14) and malignant (15,16) diseases.
Even though ITP is an autoimmune disease, the data regarding the relationship between ITP and inflammatory markers is not sufficient. Also, there is limited data with respect to the factors affecting response to CS treatment (17-19). So, we aimed to investigate the association between NLR and response, and loss of response to CS treatment in ITP patients who needed treatment.

Methods
We retrospectively analyzed the data of 47 ITP patients treated with CS therapy at Istanbul Training and Research Hospital, Clinic of Hematology between 2007 and 2016. The data including age, gender, bleeding history, complete blood count at the time of diagnosis, NLR at the time of diagnosis, treatment response, loss of response, and duration of response were recorded for each patient. ITP diagnosis and treatment demand were defined according to The American Society of Hematology practice guidelines (1). We started treatment for patients with platelet count below 30x10^3/L or patients with bleeding. Response to treatment was assessed according to the recommendations of the international working group (20). Response was defined as a platelet count greater than 30x10^3/L and no response was defined as a platelet count less than 30x10^3/L, while loss of response (LOR) was defined as a platelet count less than 30x10^3/L or a less than 2-fold increase in the platelet count from baseline or the presence of bleeding. We did not further evaluate the patients according to complete remission, since the cohort was not large enough for such a detailed analysis. Forty-five patients received methylprednisolone and 2 patients received dexamethasone as first line therapy. NLR was calculated using complete blood count from baseline or the presence of bleeding. We did not further evaluate the patients according to complete remission, since the cohort was not large enough for such a detailed analysis. Forty-five patients received methylprednisolone and 2 patients received dexamethasone as first line therapy. NLR was calculated using complete blood count of patients at the time of diagnosis. The cut-off score for NLR was assigned as 2.5 according to the median NLR level. Twenty-three (48.9%) patients had NLR <2.5 and 24 (51.1%) patients had NLR ≥2.5. There was no statistical significant difference between two groups regarding age, gender, treatment response, response duration and LOR (p=1, p=0.92, p=0.74, p=0.869, p=0.315) (Table 2). Also there was no correlation between NLR and response duration (p=0.918, r=0.018).

Statistical Analysis
Statistical analysis was performed using SPSS version 24 (IBM Corp., Armonk, NY, USA) software. Data were described as numbers and percentage or median and range, where appropriate. Chi-square test or Fisher’s exact test was used for correlation analysis. A p value of <0.05 was considered statistically significant.

Results
Patient characteristics are summarized in Table 1. The median age of the patients at the time of diagnosis was 44 years (range, 18-74). Twenty-seven (57%) patients were female and 20 (43%) were male. Ten (21.3%) patients had a history of bleeding at the time of diagnosis. The median age of the patients at the time of diagnosis was 44 years (range, 18-74). Twenty-seven (57%) patients were female and 20 (43%) were male. Ten (21.3%) patients had a history of bleeding at the time of diagnosis. The median age of the patients at the time of diagnosis was 44 years (range, 18-74). Twenty-seven (57%) patients were female and 20 (43%) were male. Ten (21.3%) patients had a history of bleeding at the time of diagnosis. The median age of the patients at the time of diagnosis was 44 years (range, 18-74). Twenty-seven (57%) patients were female and 20 (43%) were male. Ten (21.3%) patients had a history of bleeding at the time of diagnosis. The median white blood cell count was 7,850/mm^3 (4,710-21,090/mm^3), hemoglobin level was 13.2 g/dL (8.3-17.80 g/dL), platelet count was 9,000/mm^3 (0-37,000/mm^3), neutrophil count was 5,200/mm^3 (2,210-16,900/mm^3), and lymphocyte count was 1,970/mm^3 (610-5,430/mm^3). Thirty-five (74.5%) patients responded to first line treatment, however, LOR developed in 19 (54.2%) of these patients during follow-up. The median NLR was 2.51 (range, 1.15-11.35), and the cut-off for NLR was 2.5 according to the median NLR level. Twenty-three (48.9%) patients had NLR <2.5 and 24 (51.1%) patients had NLR ≥2.5. There was no statistical significant difference between two groups regarding age, gender, treatment response, response duration and LOR (p=1, p=0.92, p=0.74, p=0.869, p=0.315) (Table 2). Also there was no correlation between NLR and response duration (p=0.918, r=0.018).

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NLR &lt;2.5, n=23</th>
<th>NLR ≥2.5, n=24</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>13 (57%)</td>
<td>14 (58%)</td>
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</tr>
<tr>
<td>Male</td>
<td>10 (43%)</td>
<td>10 (42%)</td>
<td></td>
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<tr>
<td>Age, years, median, (range)</td>
<td>44 (18-73)</td>
<td>44 (26-74)</td>
<td>0.92</td>
</tr>
<tr>
<td>Response to corticosteroid therapy, n, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18 (78.3%)</td>
<td>17 (70.8%)</td>
<td>0.740</td>
</tr>
<tr>
<td>No</td>
<td>5 (21.7%)</td>
<td>7 (29.2%)</td>
<td></td>
</tr>
<tr>
<td>Response duration to corticosteroids, months, median, (range)</td>
<td>8.5 (1-60)</td>
<td>7 (1-105)</td>
<td>0.869</td>
</tr>
<tr>
<td>Loss of response, n, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (44.4%)</td>
<td>11 (64.7%)</td>
<td>0.315</td>
</tr>
<tr>
<td>No</td>
<td>10 (55.6%)</td>
<td>6 (35.3%)</td>
<td></td>
</tr>
</tbody>
</table>


Table 2. Comparison of patients with neutrophil lymphocyte ratio <2.5 and neutrophil lymphocyte ratio ≥2.5
Discussion

While impaired platelet production plays a role in the pathogenesis of ITP, the fundamental step in occurrence of the disease is the production of abnormal autoantibodies specific to platelet membrane antigens. Subsequently, those antibodies bind to the membranes of circulating platelets (2,3,21). Autoantibody-bound platelets induce Fc receptor-mediated phagocytosis by macrophages primarily in spleen, leading to increased destruction of platelets (2,3,21). The triggering event in the development of antibody production remains unclear; however direct interaction of monocyte subgroups with T helper/T regulatory lymphocytes has been implicated in eliciting the events (22,23). This autoimmune nature of the disease makes Cs as the first-line therapy, which acts through decreasing the production of autoantibodies and suppressing the reticuloendothelial phagocytosis of antibody-coated platelets in ITP (2,24). Of note that, the response rate particularly sustained plateau response to Cs is not excellent different than anticipated (2,5). Nowadays, identifying risk factors has become important for tailoring individualized treatments in the majority of the diseases. Several factors such as age (17), gender (17), platelet count at diagnosis (17), abnormal platelet morphology (18) were investigated whether they affected response to corticosteroid treatment or not in ITP patients. Among them, abnormal platelet morphology was found to be associated with poor response to CS therapy. Although the data about the factors affecting the response to CS treatment is not obvious, infectious agents like H. pylori, human immunodeficiency virus, hepatitis C virus, cytomegalovirus (CMV), have been reported to augment thrombocytopenia in refractory ITP patients (3). In our study, we evaluated the association of NLR with response to CS treatment in ITP patients and we did not find an association. While 35 (74.5%) patients responded to first line treatment, LOR developed in 19 (54.2%) of these patients during follow-up.

The association of elevated NLR with advanced disease and prognosis has been elucidated quite well in various malignancies (15,16). In addition, NLR has been elevated in autoimmune diseases like systemic lupus erythematosus (SLE) (9,25,26), rheumatoid arthritis (RA) (10), Sjögren’s syndrome (27), and autoimmune thyroiditis (28,29). Also, increased NLR was shown to be an indicator of disease activity in SLE (26), RA (10,30), and Sjögren syndrome (27). On the contrary, the data concerning the role of NLR in some other autoimmune diseases such as Behçet’s disease (11,12) and psoriasis (13,14) is conflicting. According to our knowledge, the role of NLR in adult ITP patients has not been explored previously. On the other hand, the association of low lymphocyte and leukocyte count with disease course in pediatric ITP patients were studied in two studies (31,32). Ahmed et al. (31) showed that low lymphocyte and leukocyte count at the time of diagnosis was a predictive parameter for persistence in pediatric ITP patients. Nevertheless, the treatment details of the patients were not noted in the study. Similarly, Deel et al. (32) found that low lymphocyte count at 3rd month was correlated with progression to chronic ITP. Also, majority of the patients were not treated with steroids in that study. In the current study, when we compared ITP patients who responded to first-line therapy with non-responders, we did not find a significant difference in NLR values between two groups. Accordingly, several issues can be proposed to explain the insignificant results in our study. First, we did not have adequate data concerning the infection history of the patients, particularly H. pylori and CMV infection, which might have played a role in refractoriness. Secondly, subsets of lymphocytes asserted to have role in the pathogenesis of the disease constitutes only minority of the lymphocytes (33), thus any structural or quantitative abnormality in these cells would not allow alteration in lymphocyte count and also NLR. Unfortunately, we could not evaluate these factors due to the retrospective nature of the study. Lastly and the most important one according to us is that, ITP is not a systemic disease affecting the other organs leading to systemic inflammation.

Conclusion

In conclusion, although NLR was found to be associated with the prognosis and activity of various diseases in several studies, we could not verify such an association between NLR and response to corticosteroid therapy in ITP patients.

Ethics Committee Approval: The study protocol has been approved by the Istanbul Training and Research Hospital Ethics Committee (date: 06.01.2017 no: 924).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer-reviewed.


Conflict of Interest: No conflict of Interest was declared by the authors.

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References


