

# Impact of hematological markers in prediction of severity of cutaneous drug eruptions

Rezvan Amiri, Behzad Iranmanesh, Mina Amiri\*, Saman Mohammadi, Maryam Khalili, Mahin Aflatoonian

Department of Dermatology, Kerman University of Medical Sciences, Iran.

\* General Practitioner, Kerman University of Medical Sciences, Iran.

## Abstract

**Background** Recognition of parameters to predict severity of drug eruptions can be helpful in early intervention in severe cases. In this study, we evaluate the role of hematological factors including neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte (PLR) ratio in prediction of severity in cutaneous drug reactions.

**Methods** This is a retrospective cross-sectional study on 46 hospitalized patients with drug eruptions and 46 healthy individuals as control group. NLR/PLR was compared between patients with drug eruptions and healthy control group by independent t test. Moreover, the values of these hematological markers were compared between serious and non-serious types of drug eruptions by independent t test.

**Results** Serious drug eruptions constitute nearly one-fourth of total drug eruptions. The mean values of NLR in case and control groups were  $3.91 \pm 2.87$  and  $2.30 \pm 1.62$ , respectively ( $P=0.001$ ). The mean values of PLR in case and control groups were  $155.35 \pm 90.60$  and  $125 \pm 45.64$ , respectively ( $P=0.045$ ). Females with drug eruptions had significantly higher PLR compared to males ( $P=0.02$ ). Furthermore, there was no significant correlation between NLR/PLR in serious and non-serious types of drug reactions.

**Conclusion** NLR/PLR was significantly higher in patients with drug eruptions compared to control group. There was no significant correlation between NLR/PLR with either demographic features of patients or severity of drug eruption; except significantly higher PLR in female with drug eruptions compared to males.

## Key words

NLR; PLR; Drug eruption.

## Introduction

Adverse drug reactions (ADRs) consist of approximately 3% of hospital admissions and 5% of mortalities. Furthermore, they can lengthen duration of admission and burden additional cost on healthcare system. Cutaneous

ADR (CADR) is one of the most common type of reactions; with wide spectrum from self-limited benign types (such as exanthematous drug reaction, urticaria and erythema multiforme) to severe cutaneous drug reactions (SCARs) including Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), generalized fixed drug eruption (FDE), drug rash with eosinophilia and systemic symptoms (DRESS)/ drug-induced hypersensitivity syndrome (DIHS), acute generalized exanthematous pustulosis (AGEP) and anaphylaxis. SCARs can result in organ failure,

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## Address for correspondence

Dr. Mahin Aflatoonian  
Dermatology Department,  
Afzalipour Hospital, Kerman Medical University,  
Kerman, Iran. Post code: 761614111.  
Ph: 09125987542  
Email: maafatoonian@gmail.com

and may even lead to fatal complications.<sup>1-5</sup> Several factors such as age, sex, human leukocyte antigen (HLA) susceptibility, underlying diseases, immune system status and number of taken drugs by patients can influence severity of drug eruptions. Recognition of predictive parameters of severity of drug eruptions can be helpful in early diagnosis and management of SCARs, in order to reduce serious complications such as sepsis, organ failure and mortality<sup>3-8</sup>. In this study, we evaluate the role of hematological factors (NLR and PLR) in prediction of severity of drug reactions.

## Methods

This is a retrospective cross-sectional study on 46 hospitalized patients with drug eruption and 46 healthy individuals as control group. Exclusion criteria were patients with other dermatologic or serious systemic diseases (such as diabetes mellitus, cardiovascular diseases, malignancy, renal insufficiency, liver dysfunction, pulmonary disease and thyroid abnormalities). Drug reactions were classified into two groups as serious (SCARs) and non-serious cases. Firstly, demographic features of the patients (age and sex), type of drug eruption, culprit drug and type of treatment were recorded. Then, hematological markers including NLR and PLR were calculated by dividing neutrophil or platelet to lymphocyte, respectively. Ultimately, NLR/ PLR was compared between patients with drug eruption and healthy control group. Moreover, the values of these hematological markers were compared between serious and non-serious cases of drug eruption. This proposal was approved with ethical code IR.KMU.AH.REC.1399.104.

**Statistical analysis** Data was analyzed by SPSS 16 (software IBM, Armonk, NY, USA). Qualitative and quantitative data was

represented by percentage as well as mean and standard deviation, respectively. Comparison mean NLR/PLR between patients with drug eruption and control group was performed by independent t test. Furthermore, correlation mean NLR/PLR based on severity of drug eruption was evaluated by independent t test.

## Results

Ninety-two participants were enrolled the study (forty-six in each group). Mean age of the patients with drug eruption and control group was  $38\pm 15.89$  (range 9-82) years and  $34.5\pm 10.52$  (range 10-60) years, and the difference was not statistically significant ( $P=0.216$ ). The majority of participants in case and control groups were female (67.4% and 71.7%, respectively), with no significant difference between two groups ( $P=0.65$ ).

The most common culprit drugs were antibiotics (37%), anticonvulsants (32.6%) and pain killers (8.7%). Types of drug eruption in descending order included exanthematous (45.7%), erythema multiforme (17.4%), SJS (15.2%), urticaria (13%), TEN (4.3%) and DRESS (3.4%). SCARs constitute 23.9% of drug eruptions. Oral corticosteroids, topical corticosteroids, antihistamines and intravenous immunoglobulin (IVIg) were prescribed in 95.7%, 48.8%, 39.1% and 4.3% of the patients, respectively.

The mean values of NLR in case and control groups were  $3.91\pm 2.87\%$  (range 0.62-13) and  $2.30\pm 1.62\%$  (0.56%-6.92%), respectively, and the difference was statistically significant ( $P=0.001$ ). The mean values of PLR in case and control groups were  $155.35\pm 90.60\%$  (range 25.58%-469.48%) and  $125\pm 45.64\%$  (55.10%-228.7%), respectively, and the difference was significant ( $P=0.045$ ). There was no significant correlation between NLR/PLR and demographic

**Table 1** Mean NLR/PLR in both groups based on sex.

Variables		Case group	P. value	Healthy control	P. value
NLR	Female	4.10 ± 0.54	0.524	2.22 ± 0.28	0.633
	Male	3.52 ± 0.67		2.48 ± 0.46	
PLR	Female	176.47 ± 17.52	0.02	123.80 ± 7.91	0.780
	Male	111.69 ± 14.03		128.04 ± 13.26	

**Table 2** Correlation of NLR/PLR ratio based on age in both groups.

Variables	Case group		Control group	
	Pearson coefficient	P. value	Pearson coefficient	P. value
NLR	-0.047	0.757	-0.112	0.457
PLR	0.152	0.313	-0.171	0.255

**Table 3** Comparison NLR/PLR ratio between patients with SCARs and non-serious drug eruptions.

Variable	Non-serious drug eruption	SCARs	P. value
	Mean±SD	Mean±SD	
NLR	3.92±0.77	3.91±0.48	0.992
PLR	129.54±17	166.47±19.33	0.236

features in both groups; except between sex and PLR in patients with drug eruption (**Table 1, 2**). Females with drug eruptions had significantly higher PLR compared to males (P=0.02). Furthermore, there was no significant correlation between NLR/PLR in serious and non-serious types of drug reactions (**Table 3**).

**Discussion**

Drug eruptions can have benign course; with spontaneous regression of eruptions with or without discontinuation of culprit drug, or they might have more serious course; with permanent organ failure or even fatal outcome. Early recognition of severe drug eruptions for initial intervention can be helpful in management and prevention of serious complications.<sup>1-4</sup> To date, there are a few scoring systems that predict prognosis and severity of drug eruptions.<sup>3-8</sup> SCORTEN has important role for identifying patients with TEN who have higher risk of mortality rate. It includes factors such as age, hearth rate, percentage of body surface involvement, concurrent history of malignancy as well as levels of blood glucose and bicarbonate.<sup>9,10</sup> Another prognostic tool in

patients with TEN is ABCD-10 that includes age, blood bicarbonate level, concurrent cancer, needs to dialysis and percentage of body surface involvement.<sup>11</sup> In addition, increased level of cytokines such as interleukin (IL)-15 can correlate with severity of drug reactions, especially in TEN.<sup>12</sup> Quinn *et al.* reported that severe dermal infiltrations associates with poor survival rate in patients with TEN.<sup>13</sup> In addition, factors such as facial involvement, eosinophil count, age, sex and presence of atypical lymphocytes in peripheral blood smear might predict severity of DRESS.<sup>5,14</sup> Histological characteristics including severe dermal infiltration, eosinophilia, interface dermatitis and necrotic keratinocytes are indicators of poor prognosis and internal organ involvement in DRESS.<sup>14</sup> Recognition of reliable and simple prognostic tools that can expeditiously and precisely assess severity of drug eruptions and survival rate of the patients is always required.<sup>3-8</sup>

Recently, role of NLR and PLR has been recognized in early determination of chronic inflammatory status, autoimmune diseases and infectious conditions. Moreover, it has been demonstrated that increased level of NLR can be associated with poor prognosis and higher mortality rate in patients with ischemic heart disease, end stage renal diseases and COVID-19 infection.<sup>15-17</sup> In the current study, hospitalized patients with drug eruptions had significantly higher percentage of NLR/PLR compared to healthy control. Furthermore, patients with

SCARs had higher ratio of PLR compared to patients with less serious drug eruptions; however the difference was not statistically significant. Moreover, NLR was nearly equal in patients with both types of serious and non-serious drug reactions.

Dundar *et al.* in a retrospective study evaluated impact of NLR in patients with drug eruptions referring to emergency department. They reported significantly higher NLR in patients who need to be hospitalized than discharged ones (6.13 and 3.69, respectively). However, there was no association between NLR and duration of admission in hospitalized patients with drug eruptions. They also demonstrated higher NLR in TEN/SJS and urticaria/anaphylaxis patients (8.3 and 5.4, respectively). The lowest NLR belonged to patients with fixed drug eruption, exanthematous drug eruption and AGEP (3.3, 4.2 and 4.2, respectively). It was concluded that NLR can be a beneficial factor to predict cases that need to admit for special care and urgent intervention.<sup>18</sup> Wang *et al.* demonstrated significantly higher NLR and PLR in patients with TEN compared to control group (5.67 vs. 1.83; 167.31 vs. 117.84, respectively). They also indicated association of higher mortality rate with NLR value of over 5.79. Furthermore, sensitivity and specificity of 85.7% and 63.6% was estimated for NLR in comparison to SCORTEN for prediction of mortality due to drug eruptions.<sup>19</sup> Komatsu-Fujii *et al.* demonstrated higher ratio of NLR in DRESS compared to exanthematous drug eruptions (18.5 and 4.5, respectively).<sup>20</sup>

This study was done retrospectively and on small number of patients with drug eruptions; thereby, further prospective studies with larger sample size are recommended to assess reliability and validity of hematological markers for recognition of more serious drug eruptions and prediction of morbidity and mortality rate.

## Conclusion

This study demonstrated high levels of hematological markers (NLR/PLR) in patients with drug eruptions compared to control group. Although PLR ratio was higher in SCARs compared to non-serious drug eruptions; however the difference was not statistically significant. Moreover, there was no significant difference in NLR based on severity of drug eruptions. There was no significant correlation between NLR/PLR ratio with demographic features of patients; except significantly higher PLR ratio in female with drug eruptions compared to males.

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