PLATELET/ LYMPHOCYTE RATIO (PLR) PREDICTIVE VALUE IN I MMUNE THROMBOCYTOPENIC PURPURA PATIENTS

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ABSTRACT

Background: *platelet/lymphocyte ratio (PLR) is a new inflammatory marker, and its level increases in different inflammatory diseases, diabetes, and malignancy. In ITP patients, there is a decrease in platelet count, and theories suggest an inflammatory response from the immune system toward platelets mastered by lymphocytes.*

Aim of the work: *The study aimed to know the relation between platelet /lymphocytes and correlate this ratio to the prognosis of immune thrombocytopenia*

Patients and Methods: ***T****his was a retrospective study conducted on 96 subjects diagnosed with immune thrombocytopenic purpura attending the haematology unit of Ain Shams University, divided into 2 groups (responsive ITP group and resistant/relapsed), with data collected at the time of diagnosis and after 3 months of treatment and follow-up in comparison to 32 subjects in the control group.*

Results: *In comparison between ITP sub-groups at the time of diagnosis, responsive ITP group patients had a significantly higher PLR compared to other groups, while resistant or relapsed ITP patients had a significantly lower PLR. After 3 months of treatment, PLR revealed that resistant or relapsed ITP patients had a significantly lower PLR compared to other groups (P 0.001).*

Conclusion: *A low level of PLR is an indicator of ITP resistance or the development of relapse.*

Keywords: *platelet lymphocyte ratio (PLR), immune thrombocytopenic purpura (ITP), prognostic factor*

INTRODUCTION:

ITP is an immune disease characterized by a immune destruction of platelet by autoantibodies. The diagnosis is usually made by ruling out all known causes of thrombocytopenia. The clinical presentation can be either acute with severe bleeding or insidious with slow progression and mild or no symptoms[(1)]

Complete blood counts, autoimmune markers, virology to detect EBV and CMV, the first laboratory tests performed, Bone marrow aspiration is usually done in certain clinical situation as old age or suspecting malignancy or presence of lymphadenopathy or organomegaly[(2)].

The platelet to lymphocyte ratio (PLR) is now trending inflammatory biomarker, easy to calculate in clinical set , non-expensive and used to predict inflammation and mortality in a wide variety of diseases e.g. inflammatory conditions such as vasculitis and systemic lupus erythematosus, and it can now predict prognosis in diseases such as acute myocardial dysfunction and acute kidney injury. PLR is also simple to calculate in

various malignancy prognostic prediction models, such as those for lung cancer and prostate cancer[3].

AIM OF THE WORK:

The study aimed to know the relation between platelet /lymphocytes and correlate this ratio to the prognosis of immune thrombocytopenia

PATIENTS AND METHOD:

This was a retrospective study conducted on 96 subjects diagnosed with immune thrombocytopenic purpura attending the haematology unit of Ain Shams University, divided into 2 patient groups (the responsive ITP group, which had 64 patients classified according to the treatment plan into 2 subgroups (subgroup A: 32 patients who responded to medical treatment within 3 months, subgroup B: 32 patients who responded after splenectomy) and 32 patients who had relapsed after several lines of medical treatment e.g steroid resistant as first line then resistant to immune-suppression as second line as azathioprine of MMF and resistant to third line Eltrombopag) and data collected at the time of diagnosis and 3 months later after treatment ,follow-up is done also by PLR , in comparison to 32 subjects who were in the healthy control group, and

Inclusion criteria:

Patients aged from 16 to 60 years old with ITP

Exclusion criteria: Patients aged less than 16 years and more than 60 years

1. Patients suffering from other haematological disorders, such as aplastic anaemia, myelodysplasia, or any other haematological cancer
2. Thrombocytopenia from other causes (such as HCV or HIV)
3. Pregnant females

Ethical considerations:

All patients who took part in the study provided written informed consent. The study has been approved by Ain Shams University's Ethical Committee Board and the Helsinki Declaration.

Study tools: At the time of recruitment, all patients are subjected to the following study tools: A complete medical history, physical examination, and lab tests such as a complete blood count, kidney and liver function tests, autoimmunity markers, viral markers, and, if necessary, a bone marrow aspirate are all performed.

Statistical Analysis:

To collect, list, and analyze the data, the Statistical Package for the Social Sciences (SPSS) version 23 was used on an IBM-compatible personal computer.

RESULTS:

This was a retrospective study of 96 subjects with immune thrombocytopenic purpura; 64 were in the responsive ITP group, which was divided into two subgroups based on the treatment plan (subgroup A: 32 patients who responded to medical treatment within 3 months, subgroup B: 32 patients who responded after splenectomy), and the other 32 patients were resistant to many lines of treatment because they were steroid-resistant, plus the second line had been Mycophenolate.

The mean age of included patients was 40.79 ± 12.29 years. Eighteen patients were male and 78 were female. The bleeding was mild in 48 patients, moderate in 30 patients, and severe in 18 patients. The mean age of control subjects was 38.81 14.64 years; 12 subjects were males and 20 were females All patients were free from hepatic and renal disease; in addition, viral and autoimmune markers were negative in all patients**.**

The difference in age, sex, or the comorbidity index was statistically insignificant.

The laboratory parameters for each group are shown in table (1,2).

Table 1. Pre-treatment and 3-months post-treatment CBC results in Responsive ITP group

	Pre-treatment	**3-months post-treatment**	**Paired t-test**	**P-value**
Platelet: Mean ± SD Range	 20.53±3.06 5.0-30.0	 175.53±50.76 105.0-313.0	 17.900	 **<0.001****
lymphocyte: Mean ± SD Range	 1.55±0.66 0.4-2.5	 2.17±0.54 1.2-3.5	Wilcoxon 3.783	 **<0.001****
PLR: Mean ± SD Range	 13.32±1.76 8.7-16.6	 81.01±12.18 61.1-116.8	 32.505	 **<0.001****
TLC: Mean ± SD Range	 6.34±2.38 3.6-14.0	 7.28±1.91 3.9-11.4	Wilcoxon 2.890	 **0.004***
Neutrophils Mean ± SD Range	 4.12±2.76 1.17-12.6	 4.51±1.94 1.16-9.1	Wilcoxon 1.813	 0.070
Hemoglobin Mean ± SD Range	 10.25±1.83 6.8-14.0	 11.07±1.77 7.0-14.3	 6.779	 **<0.001****

**Highly significant (P<0.001)

Pre-treatment and three months after treatment CBC results in the responsive group revealed significantly higher PLR 3 months post-treatment compared to pre-treatment. In addition, platelet, lymphocyte, TLC, and haemoglobin concentrations were significantly higher 3 months post-treatment compared to pre-treatment.

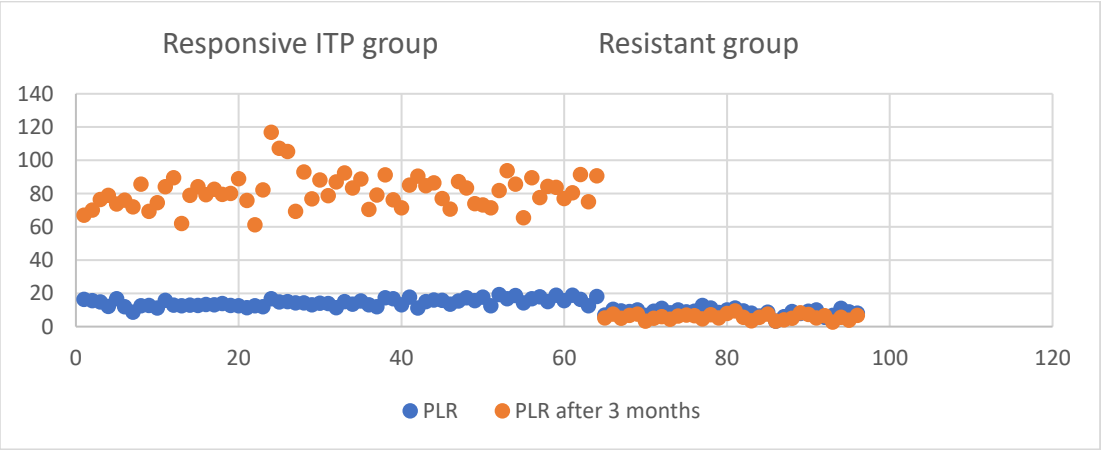

Diagram (1). PLR comparison before and after treatment in study groups

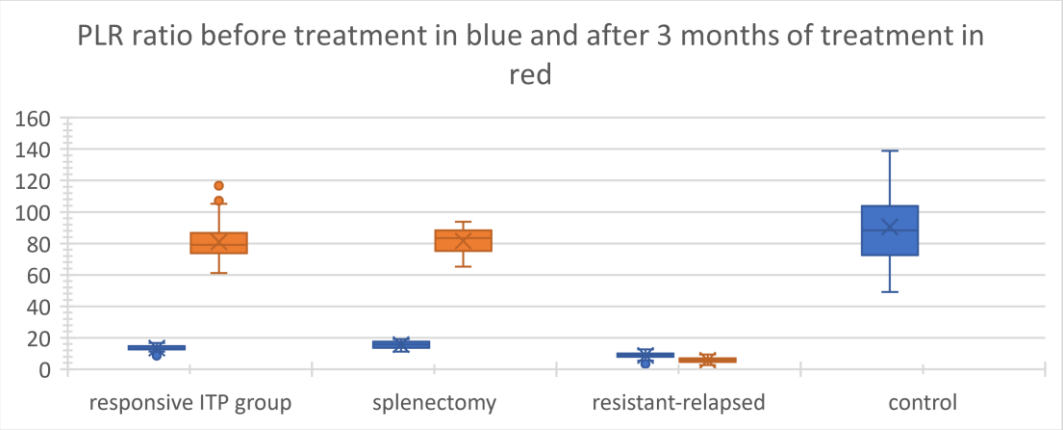

Diagram (2): boxplot diagram shows the difference between platelet to lymphocyte ratio in the responsive group and resistant group

Table2. Pre-treatment and 3-months after treatment CBC results in Resistant-relapsed group

	Pre-treatment	**3-months post-treatment**	**Paired t-test**	**P-value**
Platelet: Mean ± SD Range	 14.50±7.33 4.0-28.0	 17.91±6.45 5.0-30.0	 Wilcoxon 2.227	 **0.026***
lymphocyte: Mean ± SD Range	 1.65±0.74 0.5-3.0	 3.08±0.62 1.9-4.0	 Wilcoxon 4.827	 **<0.001****
PLR: Mean ± SD Range	 8.72±1.93 3.30-12.60	 5.73±1.63 2.6-9.3	 9.071	 **<0.001****
TLC: Mean ± SD Range	 5.69±1.12 3.0-8.0	 7.55±1.42 5.3-11	 6.938	 **<0.001****
Neutrophils Mean ± SD Range	 3.45±0.98 1.4-5.7	 3.94±1.16 1.2-6.9	 1.827	 0.077
Hemoglobin Mean ± SD Range	 9.90±2.34 5.0-12.0	 10.81±1.99 6.5-13.0	 8.414	 **<0.001****

**Highly significant (P<0.001)

Pre- and 3-month post-treatment CBC results in the resistant-relapsed group revealed that PLR was significantly lower 3 months post-treatment compared to pretreatment.

We found a significant difference between the PLR of responsive ITP patients and that of relapsed or resistant ITP patients who are not responsive to therapy

The PLR associated with relapsed ITP was significantly below the starting ratio, and this could be explained by either the prolonged use of the immunosuppressant drug or the underlying pathology of ITP itself. There is not too much data in this area, and a few studies have researched only the PLR ratio in newly diagnosed ITP patients.

Table 3. ROC curve for PLR at baseline as a predictor for disease prognosis in each ITP sub-group against the control group

PLR at baseline		
	Responsive group	Resistant-relapsed
Cut-off point	≤ 61.90%	≤ 56.55%
Accuracy	100%	100%
Sensitivity	100%	100%
Specificity	90.6%	93.7%
Significance	<0.001	<0.001

AUC: Area under the curve

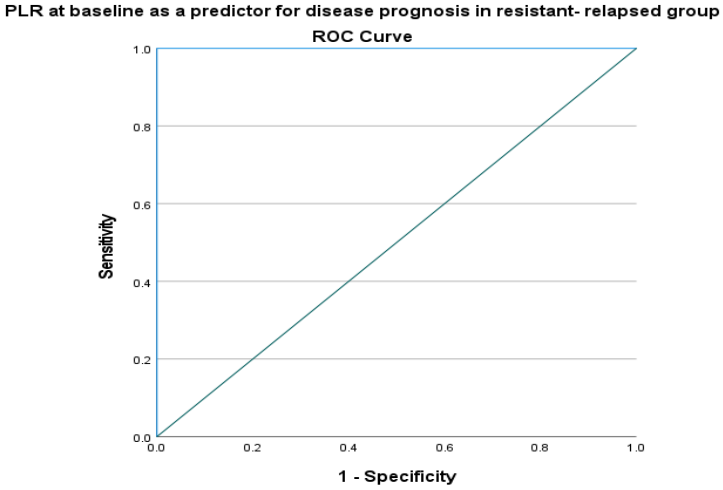

Diagram 3: ROC curve of the sensitivity of PLR in the responsive, resistant, and relapsed groups

The correlation between PLR and other CBC parameters in ITP cases at baseline showed a significant positive correlation between PLR and platelet count and haemoglobin concentration, and a significant negative correlation between PLR and lymphocyte count.

DISCUSSION:

ITP is an immune disorder characterised by the presence of platelet glycoprotein anti bodies. Treatment of ITP has made considerable progress over the last decade, particularly with the use of thrombopoietin analogues and immunosuppressants. Unfortunately, the causes and risk factors for recurrence in ITP patients are still unknown with high risk of relapse or recurrence[4].

The CBC and platelet counts, as well as the patients' symptoms, are usually used to predict ITP relapse; no lab test can detect relapse in those patients, relapse is most common during the first year, but it can happen at any time.

Qin et al. (2016) investigated the role of PLR in systemic lupus erythematosus (SLE) and discovered that SLE patients had significantly higher PLR than controls. Furthermore, SLE patients with nephritis had higher PLR levels than those without[10].

Song et al. 2019 and **Wang et al. 2019** had studies to detect relapse using the PLR parameter (platelet to lymphocyte ratio) and it is novel inflammatory biomarker that may play a key role in predicting the prognosis of several inflammatory, autoimmune, and infectious diseases.

Sisti et al. (2019) investigated PLR in preeclampsia and correlate it with disease severity, they found PLR was lower in patients with severe PE than in the control group and the differences were statistically significant. Furthermore, serum PLR levels in pregnant women with HELLP syndrome were found to be significantly lower than in pregnant women with normal pregnancies[(8)].

Another study done by **Qu et al. (2020),** to study effect of PLR as inflammatory marker in COVID-19 patients, they found that higher PLR levels are associated with more severe COVID-19 cases and a longer hospital stay[(9)].

To our knowledge, this is the first study to assess PLR across various ITP categories (responsive and resistant).

This retrospective study, we aimed to find the relationship between PLR at baseline and ITP recurrence at 3-month follow-up. We chose two groups, one that was responsive to treatment and the other that was resistant to treatment, while minimizing demographic differences to maximize the study impact of PLR.

PLR in the responsive group ranged from 8.7-16.6 (mean=13.32) before treatment and increased to 61.1-116.8 (mean=81.01) after treatment, with a high statistical p-value ($p < 0.001$).

Before starting the therapy, the resistant group had a range of 3.30-12.60 (mean=8.72), which unexpectedly decreased after treatment to a range of 2.6-9.3 (mean=5.73) with a high statistical p-value ($p < 0.001$).

Although there is a scarcity of published data from studies on the relationship between PLR and ITP recurrence, **Jung, et al.2016** reported initial platelet and lymphocyte counts to be of prognostic value , Platelet counts >6.950/mm3 and absolute lymphocyte counts ≤2.050/mm3 were associated with a significant risk of developing chronic ITP [(11)].

Ahmed et al. (2010) reported in a larger study that chronic ITP patients with a persistent course of disease for more than 6 months had lower TLC and lymphocyte count than patients who recovered from the disease in less than 6 months. As a result, the authors concluded that TLC is a statistically significant predictor of the development of persistent or chronic ITP patients.

Furthermore, **Akbayram et al. (2017)** found that in children, a decrease in absolute lymphocyte counts at the time of diagnosis is associated with a significant risk of developing chronic ITP. For acute and chronic ITP, the mean presenting absolute lymphocyte counts were 3.380 ±1.920 mm3 and 2.820 ±1.580 mm3, respectively. With statistically significant ($p = 0.002$), low absolute lymphocytic count at presentation was associated with an increased risk of developing persistent ITP after 12 months.

Based on the PLR value at diagnosis, haematologists can develop more individual treatment protocols and precisely assess the prognosis in different subgroups.

To assess patient response over 3 months, an increase in PLR level indicates a solid response to therapy, and if PLR begins to decline, it can predict relapse or resistance.

However, it should be noted that this result was only observed in this study, and more research is needed to validate our findings and clarify the underlying mechanisms.

We used the ROC curve to assess the prognostic value of PLR, which yielded a PLR cut-off of 61.9 for the responsive group and 56.5 for the resistant/relapsed group, revealing 100% accuracy and sensitivity in diagnosing all studied patients

Wang et al. (2019) investigated whether PLR is independently linked with glucocorticoid (GC)-resistant ITP and the effect of PLR on treatment response. PLR level was found to be inversely related to GC non-response. When PLR exceeds 5.08, a

unit increase in PLR is associated with a 19% reduction in GC resistance.

Another study done by **Augène et al., 2019,** they had same conclusion they used Generalized linear Model between PLR and ITP relapse, implying that using PLR to assess the risk of ITP recurrence and compare it with other covariates , with 95% confidence intervals, results indicated that higher PLR was statistically associated with a lower risk of ITP relapse, implying that clinicians can directly assess the risk of recurrence of ITP patients based on PLR due to the lesser influence of other covariates.

Conclusion: PLR is a good predictor of ITP patient response; when it rises, there is a good prognosis; when it falls, there is a bad prognosis and resistance.

Declarations:

Consent for Publication:

I confirm that all authors accept the manuscript for submission.

Availability of data and materials:

Competing interests:

none

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Conflicts of Interest:

The authors declare no conflicts of interest regarding the publication of this paper.

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القيمة التنبؤية لنسبة الصفائح الدموية / الخلايا الليمفاوية في مرضى فرفرية نقص الصفيحات المناعي

إيناس عبد المعطي محمد وعصام عبد الواحد حسن واية عاطف السيد ورنا زكريا عباس

قسم الطب الباطني وأمراض الدم الإكلينكية، كلية الطب - جامعة عين شمس

الخلفية: نسبة الصفائح الدموية / الخلايا الليمفاوية هي علامة التهابية جديدة ، ويزداد مستواها في الأمراض الالتهابية و المناعية المختلفة والسكري والأورام الخبيثة. في مرضى الفرفرية (النقص المناعي للصفائح الدموية) هناك نظريات تشير الى وجود حدوث استجابة التهابية من الجاز المناعي تجا الصفائح الدموية حيث يتم تكسيرها بواسطة الخلايا الليمفاوية..

الهدف من العمل: هدفت الدراسة إلى معرفة العلاقة بين الصفائح الدموية / الخلايا الليمفاوية وربط هذه النسبة بتكهن قلة الصفيحات المناعية.

المرضى والطرق: كانت هذه دراسة بأثر رجعي أجريت على ٩٦ شخصًا تم تشخيص إصابتهم بفرفرية نقص الصفيحات المناعية في وحدة أمراض الدم بجامعة عين شمس ، مقسمة إلى مجموعتين(المجموعة المستجيبة للعلاج سواء علاج دوائي او جراحي باستئصال الطحال و يبلغ عدد المرضي بها ٦٤مريضا) و المجموعة التي تقاوم العلاج و يبلغ عدد المرضي بها ٣٢مريضا بالمقارنة مع الجموعة الضابطة و عددهم ٣٢شخصا.

النتائج: بالمقارنة بين المجموعات الفرعية في وقت تشخيص المرض فإن مستوي الصفائح الدموية / الخلايا الليمفاوية يبدو عاليا في مرضي الفرفرية مقارنة بالاشخاص الطبيعين والمجموعة المقاومة للعلاج و كذلك فإن أعاد قياس نسبة الصفائح الدموية / الخلايا الليمفاوية بعد ثلاثة اشهر من العلاج اثبتت نفس النتيجة ز

الخلاصة: انخفاض مستوى الصفائح الدموية / الخلايا الليمفاوية أحد علامات الإنذار السيئة حيث تعني انتكاسة المرض او مقاومة الجسم للعلاج