CLINICOPATHOLOGICAL AND PROGNOSTIC SIGNIFICANCE OF PLATELET TO LYMPHOCYTE RATIO IN DIFFUSE LARGE B-CELL LYMPHOMA: A META-ANALYSIS

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Background: Nowadays, there is a significant but variable correlation between the diffuse large B-cell lymphoma (DLBL) and the platelet-lymphocyte ratio (PLR). This meta-analysis will assess this association.

Methods: A thorough search was done up until June 2022, and 11 research revealed 2284 patients with DLBL. They discovered a connection between DLBL and the PLR. A fixed or random-effect model was used to construct odds ratios (ORs) with 95% confidence intervals (CIs) and examine the prognostic significance of the PLR on overall survival, progression-free survival, and a variety of clinicopathological characteristics.

Results: Poor 5-years overall survival (OR, 0.59; 95% CI, 0.36-0.98, p<0.001), poor 2-years progression-free survival subjects (OR, 0.42; 95% CI, 0.27-0.67, p<0.001), and poor 5-years progression-free survival (OR, 0.50; 95% CI, 0.34-0.72, p<0.001) were all significantly correlated with high the PLR. In a similar manner, a high PLR was strongly correlated with the presence of B-symptoms (OR, 2.22; 95% CI, 1.69-2.93, p<0.001), a high lactate dehydrogenase level (OR, 2.98; 95% CI, 2.19-4.06, p<0.001), a higher tumour stage (OR, 1.84; 95% CI, 1.08-3.13, p=0.03). Nevertheless, there was no significant correlation between a high the PLR and a high Eastern Cooperative Oncology Group performance status ≥2 (OR, 1.44; 95% CI, 0.69-3.02, p=0.33), a high bone marrow infiltration (OR, 1.02; 95% CI, 0.60-1.74, p=0.94), a person’s gender (OR, 1.20; 95% CI, 0.93-1.55, p=0.17); age (OR, 0.89; 95% CI, 0.69-1.15, p=0.37); and cell of origin (OR, 1.00; 95% CI, 0.71-1.39, p=0.98).

Conclusions: The impact of the PLR on DLBL may be substantial as a technique to enhance prognosis. Patients with DLBL who have a high the PLR may be at an independent risk for having a poor prognosis. To prevent potential problems, we advise keeping track of patients with a high platelet-to-lymphocyte ratio.

Keywords: platelet to lymphocyte ratio; Diffuse large B-cell lymphoma; overall survival; progression-free survival; B symptoms; elevated lactate dehydrogenase; higher tumor stage; Eastern Cooperative Oncology Group performance status; international prognostic index; Infiltration of bone marrow

INTRODUCTION

A typical non-Hodgkin lymphoma subtype that makes up 30–40% of lymphomas worldwide is diffuse large B-cell lymphoma (DLBL)¹². In terms of clinical and biological characteristics, DLBL is a cancer that is aggressive and diverse³. More than 60% of DLBLs are cured with the conventional treatment Rituximab (R)-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), but 30% are recurrent⁴. Prognostic biomarkers have a crucial role in determining treatment options and predicting survival. The International Prognostic Index (IPI), albeit frequently employed in the prediction of DLBL, needs to have better predictive power⁵. Therefore, it is critical to find affordable and accessible prognostic biomarkers. Inflammatory reactions take place during different stages of cancer progression. Indicators derived from haematological factors

Received in 15/11/2022 & Accepted in 8/1/2023

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have recently been researched for cancer prediction. The ratio of platelet counts to lymphocyte counts is known as the platelet-lymphocyte ratio (PLR). The PLR is a prognostic indicator for a number of cancers, including ovarian cancer, esophageal cancer, DLBL, and head and neck squamous cell carcinoma. Despite the fact that a number of recent retrospective studies found a predictive role for the PLR in DLBL, their results were erratic and conflicting.

In people with DLBL, the PLR was examined to determine whether it was associated with survival. The meta-analysis performed here was to evaluate whether different levels of the PLR are related to higher odds of DLBL prognosis. The study aimed to recognize the relationship between PLR and DLBL subjects’ survival.

**METHODS**

The study performed here followed the meta-analysis of studies in the epidemiology statement, which was conducted following an established protocol.

**Study selection**

The included studies met the statistical criteria for the relationship between the PLR and DLBL (odds ratio [OR] with 95% confidence intervals [CIs]).

Only human studies in any language were considered. Inclusion was not limited by study size or publication type. Publications excluded were review articles and commentary and studies that did not deliver a measure of association. Figure 1 shows the whole study process.

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**Fig. 1:** Flowchart of the study process.
Identification

Based on the PICOS concept\textsuperscript{23}, we created a search strategy protocol, which we designated as \textit{P} (population): people with DLBL. \textit{I} (intervention/exposure): different PLR, \textit{C} (comparison): comparisons between persons with DLBL who had differing PLR as a reference (high and low) \textit{O} Poor survival was the outcome of the study and \textit{S} (study design) had no restrictions\textsuperscript{24}. Using a combination of keywords and related terms, we first conducted a thorough search of the China Knowledge Resource Integrated Database (CNKI), Embase, PubMed, Cochrane Library, OVID, and Google Scholar up until June 2022. Based on the inclusion and exclusion criteria, all discovered publications were compiled in an EndNote file. Duplicate papers were removed, and the titles and abstracts were updated to omit studies that did not demonstrate a connection between PLR and DLBL. We searched the remaining studies for relevant information.

Screening

Based on study- and topic-related criteria, data were condensed into a specified form. The surname of the first author, the length of the trial, the location of the practise, the research design, the type of study, the sample size, the patient demographics, the method of treatment, the number of participants who had DLBL, the management characteristics, the PLR, the time period for evaluating the PLR with regard to DLBL, the method of evaluation, the information source, and the outcome examination\textsuperscript{25}. When there were different data from one study, we extracted them independently. The risk of bias in these studies; individual studies were evaluated using the quality in prognosis studies tool, which evaluates validity and bias in studies of prognostic factors across 6 domains: participation, attrition, prognostic factor measurement, confounding measurement, and account, outcome measurement, and analysis and reporting\textsuperscript{26}. Any inconsistencies were addressed by a reevaluation of the original article.

Eligibility

The main discovery focused on the PLR and how it relates to DLBL. Patients with DLBL had their PLR gathered.

Inclusion

Sensitivity studies were limited to articles that discussed the relationship between patients with DLBL and PLR. With different PLR as benchmarks for subcategories and sensitivity analyses, we assessed DLBL participants (high and low).

If the following inclusion criteria were satisfied, the publications were included in the meta-analysis:

1. A retrospective or randomized controlled study design was used for the investigation.
2. The intended subjects consist of those who have DLBL.
3. Patients with DLBL had their PLR assessed as part of the treatment plan.
4. The study used a reference group of patients with DLBL who had different PLR (high and low).

Statistical analysis

The dichotomous method was used to determine the OR on a random or fixed effect model with a 95% confidence interval. The range of the (I2) index was 0 to 100%. The I2 index scale's heterogeneity is classified as zero, low, moderate, and high, or 0%, 25%, 50%, and 75%, respectively\textsuperscript{14}. This is thought to be a Random-effect if I2 > 50% and a Fixed-effect if I2 < 50%. By stratifying the results of the initial evaluation into several outcome categories, a subgroup analysis was carried out at the beginning of the evaluation. If the p-value is less than 0.05, the outcome is regarded as statistically significant. The Egger regression test measured publication bias and evaluated it subjectively (if p \geq 0.05). The odds ratios' logarithmic funnel plot is therefore contrasted with its standard errors\textsuperscript{16}. Utilizing Reviewer Manager version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark), statistics and graphs were produced.
RESULTS AND DISCUSSION

Results
Of the 986 studies found, 11 were included because they satisfied the study’s inclusion requirements (between January 2015 and December 2019). In the 11 articles, there were 2284 cases of DLBL. In every study, a PLR was connected to DLBL.

Participants in the trial who had DLBL ranged in number from 59 to 515 at the outset. However, as shown in Table 1, we exclude the Melchardt et al. 2015 study since its cut-off value for the platelet-lymphocyte ratio was higher than three times that of the other ten studies (453 vs. 150, respectively). Due to their usage of a high cut-off value, we believed that its outcomes might have an impact on the results of the meta-analysis. With regard to overall survival (OS), 10 studies published data stratified patients by the PLR, and ten studies with regard to progression-free survival (PFS). Additionally, the correlation of the platelet to lymphocyte and clinicopathological characteristics were included; seven studies for B-symptoms, six for lactate dehydrogenase level, seven for tumour stage, seven for the international prognostic index (IPI), six for gender, six for age, four for Eastern Cooperative Oncology Group (ECOG) performance status (PS), three for infiltration of bone marrow, and three studies for the tumour microenvironment.

High PLR was significantly related to poor 5-years overall survival (OR, 0.59; 95% CI, 0.36-0.98, p<0.001) with high heterogeneity ($I^2 = 81\%$), poor 2-years overall survival (OR, 0.37; 95% CI, 0.24-0.56, p=0.005) with moderate heterogeneity ($I^2 = 63\%$), poor 5-years PFS (OR, 0.50; 95% CI, 0.34-0.72, p<0.001) with moderate heterogeneity ($I^2 = 63\%$), and poor 2-years PFS subjects (OR, 0.42; 95% CI, 0.27-0.67, p<0.001) with moderate heterogeneity ($I^2 = 73\%$) as shown in Figure 2.

### Table 1: Characteristics of the selected studies for the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>PLR Cut-off</th>
<th>Duration</th>
<th>Country</th>
<th>Ethnicity</th>
<th>Sample size</th>
<th>Sex (Males/Females)</th>
<th>Age (year)</th>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periša, 2016 [16]</td>
<td>162.3</td>
<td>2006-2015</td>
<td>Croatia</td>
<td>Caucasian</td>
<td>103</td>
<td>37/66</td>
<td>63 (22-87)</td>
<td>I-IV</td>
<td>R-CHOP</td>
</tr>
<tr>
<td>Han, 2018 [18]</td>
<td>300</td>
<td>2006-2012</td>
<td>China</td>
<td>Asian</td>
<td>361</td>
<td>203/158</td>
<td>55 (12-91)</td>
<td>III-IV</td>
<td>R-CHOP</td>
</tr>
</tbody>
</table>

R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; PLR: platelet-to-lymphocyte ratio.
Fig. 2: A forest plot of the PLR in relation to DLBL in a) 5-years overall survival, b) 2-years of overall survival, c) 5-years of PFS, and d) 2-years without progression.
Elevated PLR was significantly related to the presence of B-symptoms (OR, 2.22; 95% CI, 1.69-2.93, p<0.001) with low heterogeneity ($I^2 = 41\%$); high lactate dehydrogenase (OR, 2.98; 95% CI, 2.19-4.06, p<0.001) with low heterogeneity ($I^2 = 26\%$); higher tumor stage (OR, 1.84; 95% CI, 1.08-3.13, p=0.03) with moderate heterogeneity ($I^2 = 72\%$); and high international prognostic index (OR, 2.41; 95% CI, 1.49-3.91, p<0.001) with moderate heterogeneity ($I^2 = 64\%$) as shown in Figure 3. However, high PLR was not significantly correlated with high ECOG performance status (PS) (OR, 1.44; 95% CI, 0.69-3.02, p=0.33) with moderate heterogeneity ($I^2 = 56\%$); high infiltration of bone marrow (OR, 1.02; 95% CI, 0.60-1.74, p=0.94) with no heterogeneity ($I^2 = 0\%$); gender (OR, 1.20; 95% CI, 0.93-1.55, p=0.17) with no heterogeneity ($I^2 = 17\%$); age (OR, 0.89; 95% CI, 0.69-1.15, p=0.37) with no heterogeneity ($I^2 = 0\%$); or cell of origin (OR, 1.00; 95% CI, 0.71-1.39, p=0.98) with no heterogeneity ($I^2 = 0\%$) as shown in Figure 4.

Stratified analysis of studies that did and did not adjust for different time of PLR detection was not performed because no studies reported or adjusted for this factor or whether higher PLR is related to all cancers or with exact type of cancer.

According to the visual funnel plot analysis and the quantitative Egger regression test evaluation, publication bias was not found (p = 0.88).
Fig. 3: A forest plot of the PLR in relation to DLBL of the following factors: a) DLBL international prognostic index (IPI) >2; b) DLBL tumour stage (> II); c) DLBL infiltration of bone marrow; d) DLBL B-symptoms; and e) lactate dehydrogenase.
Fig. 4: A forest plot of the PLR in relation to DLBL of the following data: a) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) > 2; b) male gender; c) age > 60 years; and d) cell of origin [germinal center B cell (GCB)].
**Discussion**

Inflammation has a crucial role in the growth of tumours. Variable results were found when the PLR was examined for the prognosis of patients with DLBL. In patients with DLBL, the PLR has been shown to be predictive, though the results have been mixed.

We found a higher risk of inadequate overall survival and PFS associated with a high PLR based on 11 studies involving 2284 patients with DLBL. According to the statistics, DLBL patients with a high PLR often had poor overall and PFS.

The only previous meta-analysis on this topic that we could locate stated that DLBL patients with a high PLR have poor overall survival but not PFS. The high the PLR cut-off value from Melchardt et al. 2015's study was included in their meta-analysis. This value (453 compared to 150, respectively) was more than thrice that of their other seven studies' lowest the PLR cut-off value. The results of their meta-analysis might have been impacted by the results of this study due to the high the PLR cut-off value.

The results also showed a relationship between clinicopathological traits indicative of substantial cancer aggression and the PLR. In this study's DLBL patients, the PLR was a highly significant predictor factor for inadequate overall survival and invasiveness.

A high PLR did not, however, correlate with a high Eastern Cooperative Oncology Group performance. This may be because there were so few studies that met the inclusion criteria for our investigation on the relationship between PLR and Eastern Cooperative Oncology Group performance. The results might be different if other studies with a similar association were found because there was a strong correlation between a high international prognostic score and an elevated PLR. It is suspected that the inflammatory response affects the angiogenesis, growth, and metastasis of cancer. However, the exact mechanism underlying the link between a high PLR and a poor prognosis in patients with DLBL is yet unknown. High platelet counts and low lymphocyte counts can lead to a high PLR. Both the early and late stages of cancer angiogenesis have been linked to platelets. That was obvious in our results where the a high the PLR was strongly correlated with the presence of B-symptoms, a high lactate dehydrogenase level, a higher tumour stage. In the cancer microenvironment, platelets can release a variety of biological chemicals that promote angiogenesis. In addition, platelets start converting growth factor-1 to work with cancer cells to improve pathways connected to the epithelial-mesenchymal transition and promote further metastasis. Immune responses against cancer are negatively impacted by lymphocytes. Cancer cell growth and metastasis can be slowed by lymphocyte-invading tumours, such as CD3+ T cells, CD8+ T cells, and Th1 CD4+ T cells. Therefore, it makes sense to use the PLR as a limit to forecast survival rates in cancer cases.

Changes in PLR measurements may therefore be more useful in predicting DLBL's future stages. People having a higher PLR than those with a lower ratio experienced DLBL with greater power. The need to improve the use of such a crucial haematological marker in predicting DLBL is thus critically raised. Data on the PLR are becoming more readily available and could be utilised as a tool for prognosis and early screening. As a tool for improving early prognosis and therapeutic recommendations in DLBL and identifying those at risk of aggressive DLBL, the PLR is anticipated to have a substantial influence. Changes in PLR measurements may therefore be more useful in predicting the progression of patients with DLBL in the future.

There is a lack of evidence linking an elevated PLR to all cancers or even just some of them.

However, given the results of this study, we advise extending the use of the PLR for DLBL screening and prognosis because it is a simple method for identifying the likelihood of developing DLBL and preventing any unfavourable consequences.

**Limitations**

The individuals in the 11 studies that were chosen for inclusion were all of the same ethnicity, and all of the investigations were retrospective in nature. We were unable to examine the effects of additional PLR measurements on the stages of DLBL. Furthermore, we were unable to ascertain whether a higher PLR is related to a particular
type of malignancy or all malignancies. The distribution of low and high PLR groups may have been influenced by the fact that different studies used different PLR cut-off values. We were unable to find a significant correlation between a high PLR and Eastern Cooperative Oncology Group performance status due to the dearth of papers exhibiting such a link.

Conclusions
There is a link between a high PLR and a higher likelihood of poor overall survival and PFS. The PLR could be used as a stratification variable in interventional research. Data on the PLR is readily available. Increasing the use of PLR for DLBL screening and prognosis allow early detection of the possibility of risk of DLBL and opposing any possible negative outcome. The PLR was also related to the presence of B-symptoms, high lactate dehydrogenase, higher tumor stage, and high international prognostic index. Large prospective studies with a uniform cut-off value of PLR are needed to validate these findings.

List of abbreviations
- CI: confidence interval.
- HR: hazard ratio.
- R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone.
- ECOG PS: Eastern Cooperative Oncology Group performance status.
- DLBL: diffuse large B-cell lymphoma.
- PLR: platelet-lymphocyte ratio.
- PFS: progression-free survival.
- IPI: international prognostic index.

REFERENCES
12. V. Periša, Prognostička vrijednost upalnih bodovnih sustava I širine distribucije eritrocita U bolesnika S B-velikostaničnim limfomom. 2017, Josip Juraj Strossmayer University of Osijek. Faculty of Medicine.


17. X. Hao, Y. Wei, X. Wei, L. Zhou, Q. Wei, Y. Zhang, W. Huang, and R. Feng, "Glasgow prognostic score is superior to other inflammation-based scores in predicting survival of diffuse large B-cell lymphoma", *Oncotarget*, 8(44), 76740 (2017).


نوان الأممية الإكلينيكية والتشخيصية لنسبة الصفائح الدموية إلى الخلايا الليمفاوية في سرطان الغدد الليمفاوية B-клетي: الخلايا الكبيرة المنتشرة: التحليل التلوي

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في الوقت الحاضر، هناك ارتباط كبير ولكن متغير بين سرطان الغدد الليمفاوية الكبيرة B-cell المنتشر ونسبة الصفائح الدموية إلى الخلايا الليمفاوية. سيقوم هذا التحليل التلوي هذا الارتباط.

تم إجراء بحث شامل حتى يونيو 2022، وكشف 11 بحثًا عن 1288 مريضاً مصاباً بـ سرطان B-CELL الغدد الليمفاوية الكبيرة المنتشر. اكتشافاً ووجود صلة بين سرطان الغدد الليمفاوية الكبيرة المنتشر ونسبة الصفائح الدموية إلى الخلايا الليمفاوية. تم استخدام نموذج الأثر الثابت أو العشوائي لإنشاء نسب الأرجحية (ORs) وفحص الأممية التن denneية لـ نسبة الصفائح الدموية إلى الخلايا الليمفاوية على البقاء على قيد الحياة بشكل عام، والمدى الخالي من التقدم، ومجموعة متنوعة من الخصائص الإكلينيكية المرضية.

المبلغ على قيد الحياة مُسنِّب لمدة ٥ سنوات (OR = ٠.٥٠، CI = ٠.٣٦ - ٠.٣٨)، ونسبة البقاء على قيد الحياة القفز الخاليا من سرطان B-CELL بالكمية لمساواة (CI = ١.١٧ - ١.٧٧). وفي السنوات الخمسة (٠.٣٥ - ١.٢٧)، كلما مرتبطة بشكل كبير مع ارتفاع معدل النمو، وبطرية مماثلة، ارتباط ارتفاع نسبة الصفائح الدموية إلى الخلايا الليمفاوية ارتباطًا وثيقًا بوجود أعراض (p = ٠.٩٨، OR = ٢.٢٢ - ٢.٧٣). و بحث (OR = ٠.٠٠، CI = ١.٦١ - ٠.١٩) ، معدل نازعة هيدروجينات (OR = ٠.٤٨ - ٠.٩٨)، مرحلة ورم أعمى (OR = ٢.٥٠، CI = ١.٠٨ - ٣.٠٣).

ومع ذلك، لا يمكن هناك ارتباط كبير بين نسبة الصفائح الدموية إلى الخلايا الليمفاوية المرتفع ونسبة البقاء على قيد الحياة القفز الخاليا من سرطان B-CELL بالكمية لمساواة (OR = ٠.٨٥ - ٠.٩٠، CI = ٢.٣٣ - ٠.٥٠). تشمل مرتبطة المعالجة (OR = ٠.١١ - ١.٢٠، CI = ١.٢٠ - ٠.٣٠) في الخصائص المرضية، معدل نازعة هيدروجينات (OR = ٦.٤٤، CI = ١.٢١ - ٥.٢٠، p = ٠.٤٨). B-CELL قد يكون تأثير نسبة الصفائح الدموية إلى الخلايا الليمفاوية على سرطان الغدد الليمفاوية الكبير المنتشر جوهريًا كأساس لتحسين التشخيص. قد يكون المرض الذي يعانون من سرطان الغدد الكبيرة المنتشر الذين لديهم ارتفاع في نسبة الصفائح الدموية إلى الخلايا الليمفاوية B-CELL
معرضين لخطر مستقل لسوء التشخيص. لمنع حدوث مشاكل محتملة، ننصح بمتابعة المرضى الذين يعانون من ارتفاع نسبة الصفائح الدموية إلى الخلايا الليمفاوية.