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Neutrophil to Lymphocyte Ratio Predicts Glucocorticoid Resistance in Polymyalgia Rheumatica

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Author Contributions

Author CO designed the study, collected the patient data and was chiefly responsible for writing the manuscript. Author CM analyzed and interpreted all data presented. Author DL proposed further study of NLR and PLR in PMR and together with authors JL, AS and RB improved several iterations of the manuscript. All authors read and approved the final product.

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Conflict of Interest Statement

Author CO has received speaking honoraria from Roche, Janssen, Novartis and Pfizer, and meeting sponsorship from Roche. Author CM declares no conflict of interest. Author DL declares no conflict of interest. Author JL has received a speaking honorarium from Abbvie and meeting sponsorship from Gilead. Author AS declares no conflict of interest. Author RB declares no conflict of interest.

ABSTRACT

Aim: Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) correlate with disease activity in several rheumatic diseases, however their utility in polymyalgia rheumatica (PMR) remains unclear. This study evaluated their relationship with disease activity and glucocorticoid resistance in PMR.

Method: Data for disease activity (PMR-AS) and full blood examination was obtained from a prospective observational cohort comprising newly diagnosed, steroid-naïve PMR patients treated with low-dose glucocorticoid therapy. Glucocorticoid resistance was defined as non-response to prednisolone 15mg/day or initial response followed by flare (PMR-AS ≥ 9.35 or $\Delta \geq 6.6$) upon weaning to 5mg/day. Univariable Bayesian linear regression analysis of the relationship between PMR-AS (baseline and mean) and NLR and PLR was performed. Predictors of glucocorticoid resistance were identified using a multivariable outcome model, with variables derived from Bayesian model selection.

Results: Of the 32 included patients, 16 (50%) fulfilled the primary outcome measure of glucocorticoid resistance. These participants were older, typically female, and had higher baseline CRP than their glucocorticoid-responsive counterparts. A statistically significant relationship was identified between PMR-AS and both NLR (OR 28.1 [95% CI 1.6 – 54.7]) and PLR (OR 40.6 [95% CI 10.1 – 71.4]) at baseline, with PLR also found to correlate with disease activity during follow-up (OR 15.6 [95% CI 2.7 – 28.2]). Baseline NLR proved a statistically significant predictor of glucocorticoid-resistant PMR (OR 14.01 [95% CI 1.49 – 278.06]).

Conclusion: Baseline NLR can predict glucocorticoid resistance in newly diagnosed PMR patients. Both NLR and PLR may be reliable biomarkers of disease activity in PMR.

Key Words: polymyalgia rheumatica; neutrophils; lymphocytes; glucocorticoids; prognosis.

Trial registration: Australian New Zealand Clinical Trials Registry (<http://www.anzctr.org.au>) – trial identification ACTRN1261400696695, registered 2/7/2014.

Polymyalgia rheumatica (PMR) is an inflammatory condition characterised by subacute-onset shoulder and hip pain, and stiffness. Oral glucocorticoids represent the treatment mainstay and whilst cessation of therapy is the ultimate goal, up to 50% of patients still require prednisolone 2-3 years after diagnosis.¹ A higher baseline erythrocyte sedimentation rate (ESR) has been associated with disease relapse and lower probability of glucocorticoid discontinuation, however these findings have not been consistently reproduced.² To date, a reliable and readily accessible biomarker to measure disease activity and predict resistance to standardised low-dose glucocorticoid therapy has not been identified in PMR.

Neutrophil, platelet and lymphocyte counts undergo temporary changes in an active inflammatory state. Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) can be calculated from a routine full blood examination (FBE) using the neutrophil count or platelet count divided by the lymphocyte count. In oncology, high NLR and PLR are associated with poor prognostic outcomes across a range of solid organ malignancies.^{3, 4} These indices have similarly been found to correlate with disease activity in several rheumatic diseases including most recently PMR, but their role in predicting treatment response in this condition is less well-defined.⁵⁻⁸

In this study, we sought to prospectively characterize the relationship between NLR and PLR, and disease activity in patients with newly diagnosed PMR. The ability of NLR and PLR to predict resistance to standardised low-dose glucocorticoid therapy was also evaluated.

METHOD

Patients

Patients with newly diagnosed, steroid-naïve PMR according to the 2012 EULAR/ACR classification criteria⁹ were prospectively recruited from primary care, community and hospital rheumatology practices. Participants with symptoms suggestive of giant cell arteritis (GCA) including headache, jaw claudication, scalp tenderness or visual disturbance were excluded, along with cases of cancer within the past 5 years, neuromuscular disease, active infection, other inflammatory conditions (eg. rheumatoid arthritis [RA]) and chronic pain syndromes. The study was approved by the Austin Health Human Research Ethics Committee (HREC/14/Austin/158) prior to commencement and registered with the Australian New Zealand Clinical Trials Registry (trial identification ACTRN1261400696695).

Following written consent, demographic and clinical data were collected and the health assessment questionnaire–disability index (HAQ-DI) completed. A standard physical examination was undertaken including measurement of the shoulder range of motion (elevation of upper limb score). In order to measure disease activity using the PMR-activity score (PMR-AS)¹⁰, participants marked a visual analogue scale indicating pain severity and the investigator provided a physician global assessment. Relevant differential diagnoses were excluded by testing creatine kinase, thyroid function, rheumatoid factor, anti-citrullinated peptide antibodies (ACPA) and anti-neutrophil cytoplasmic antibodies. FBE, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were performed at baseline and each subsequent visit. A whole body ¹⁸F-Fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT) scan (Gemini-TF64 or Ingenuity-TF128 PET/CT system; Phillips, Cleveland, OH, USA) from skull vertex to toes was also undertaken in all participants within 7 days of study enrolment.

Treatment Protocol

Participants were treated with a standardised schedule of low-dose glucocorticoid therapy as outlined in the British Society of Rheumatology (BSR) guideline.¹¹ Follow-up visits were scheduled at weeks 4, 8, 16, 24, 32 and 46 (the minimum duration of this treatment protocol) and disease activity was re-calculated. A PMR-AS score of ≥ 9.35 in a patient who had achieved clinical remission (PMR-AS < 9.35) or increase in PMR-AS by ≥ 6.6 if the participant had been previously responding to treatment (PMR-AS ≥ 9.35 but falling between successive visits) constituted the definition of disease relapse. When this occurred, the patient's prednisolone dose was increased to the previous higher dose for 4 weeks and an additional study visit performed to determine if the weaning schedule could be reinstated. If relapse occurred on

more than two occasions, methotrexate was commenced as a steroid-sparing agent, and the participant was withdrawn from the study.

Glucocorticoid Resistance

Glucocorticoid resistance has been previously defined by Mori et al. in PMR as non-response to an initial prednisolone dose of 15mg/day or initial response followed by disease relapse upon weaning prednisolone to 5mg/day.¹² This definition was accordingly utilised as the primary outcome measure for glucocorticoid-resistant disease in our study.

Statistical Analyses

All statistical analyses were conducted using R version 3.5.2 and the package *rstanarm*.^{13, 14} Results for continuous variables are reported as mean \pm standard deviation or median (interquartile range). NLR and PLR, both right-skewed distributions, were log-transformed prior to analysis. Univariable Bayesian linear regression was used to analyse the relationship between NLR and PLR, and PMR-AS (baseline and mean). Several multivariable, Bayesian logistic regression models were compared using leave-one-out cross-validation – from the *loo* package¹⁵ – to select predictors of resistance to low-dose glucocorticoid therapy. All outcomes are reported as odds ratios (OR) with 95% credible intervals (CI).¹⁶ Weakly-informative prior distributions were applied using student t-distribution with 7 degrees of freedom.¹⁷

RESULTS

Thirty-two of the 35 patients (91.4%) recruited at baseline were suitable for inclusion in the final analysis (Table 1): one patient was excluded due to large vessel vasculitis on whole body PET/CT consistent with concomitant GCA; another patient's final diagnosis was revised to Parkinson's disease; and the third patient required a modified schedule of glucocorticoid therapy due to a history of prednisolone-induced central serous retinopathy.

Twenty-five/32 participants (78.1%) relapsed during the 46-week follow-up period. Relapse most commonly occurred at week 24, at which point in time patients were taking a median prednisolone dose of 7mg. Three participants required the initiation of methotrexate as dictated by the study protocol.

Sixteen patients (50%) fulfilled the primary outcome measure of resistance to low-dose glucocorticoid therapy; their demographic details compared with those participants with glucocorticoid-responsive PMR are presented in Table 2.

Glucocorticoid-resistant patients were older and typically female compared with their glucocorticoid-responsive counterparts. Baseline CRP, but not ESR, and disease activity (PMR-AS) were also higher. In terms of haematologic parameters, median white cell count (WCC), neutrophil and platelet counts were similar between the two groups, but the median lymphocyte count was lower in glucocorticoid-resistant patients (1.7 [1.6 – 1.8] cf. 2.1 [1.9 – 2.3]). Consequently, values for mean log-transformed NLR (1.20 ± 0.48) and PLR (5.37 ± 0.37) were higher in this group than the glucocorticoid-responsive cohort (NLR 0.87 ± 0.38 ; PLR 5.12 ± 0.38).

A statistically significant relationship was identified between disease activity (PMR-AS) and both NLR (OR 28.1 [95% CI 1.6 – 54.7]) and PLR (OR 40.6 [95% CI 10.1 – 71.4]) at baseline. During follow-up, PLR correlated with mean PMR-AS (OR 15.6 [95% CI 2.7 – 28.2]), with a trend towards significance observed between NLR and mean PMR-AS (OR 10.1 [95% CI -0.9 – 21.3]).

Using Bayesian outcome modelling, baseline NLR was found to be a statistically significant predictor of glucocorticoid-resistant PMR during follow-up (OR 14.01 [95% CI 1.49 – 278.06]). A trend towards significance was also noted for baseline PLR (OR 5.02 [0.49 – 71.54]), along with age (OR 1.14 [95% CI 1.00 – 1.34]) and female sex (OR 2.98 [0.54 – 18.39]). There was no correlation between baseline CRP and glucocorticoid resistance after adjusting for demographic factors (OR 1.02 [95% CI 0.99 – 1.05]). Figure 1 illustrates the relationship between baseline laboratory values for CRP, ESR and NLR, and glucocorticoid-resistant PMR.

DISCUSSION

In a cohort of 32 patients with newly diagnosed PMR, 16 (50%) had a disease course characterized by resistance to low-dose glucocorticoid therapy, with baseline NLR proving a distinct predictor of this outcome. A trend towards significance was also observed between NLR and disease activity, with a statistically significant correlation found between PLR and PMR-AS both at baseline and during follow-up. All participants were steroid-naïve at study enrolment, glucocorticoid therapy thus having no bearing upon baseline haematologic parameters.

An increasing body of evidence now refutes historical opinion that PMR is a self-limiting, perpetually steroid-responsive entity. In a recent population-based study, around 25% of patients required more than 4 years of continuous prednisolone.¹⁸ Significant morbidity is known to arise from this treatment paradigm whereby glucocorticoid monotherapy is advocated

in the first instance and steroid-sparing agents are only initiated following recurrent relapse.^{11, 19} On whole-body magnetic resonance imaging (MRI) however, a complete patient-reported response to prednisolone has been shown to correlate with an extra-capsular pattern of inflammation, thereby confirming the existence of discrete phenotypic differences between glucocorticoid-responsive and -resistant PMR cases.²⁰ Identification of baseline NLR as a predictor of later glucocorticoid-resistance in this study therefore has certain clinical relevance. Not only does it add to the paucity of recognized adverse prognostic indicators in this condition (such as female sex, peripheral joint involvement and high ESR)², but it also further characterizes the subset of patients with relapsing PMR whom may benefit from early disease modifying anti-rheumatic drug (DMARD) initiation.

Relying upon systemic markers of inflammation to assess disease activity in PMR can be problematic. Normal CRP and ESR results are observed in 14 and 27% of relapses respectively.²¹ There is consequently an unmet need for a novel biomarker that accurately reflects the underlying inflammatory state in PMR. In research settings, the PMR-AS is considered a valid and reliable measure of disease activity; a value ≥ 9.35 is associated with a sensitivity of 96.6% and specificity of 90.7% for flare diagnosis.²² The composite nature of this scoring system is however less conducive to use in everyday clinical practice. In this study, a statistically significant relationship existed between PMR-AS and both NLR and PLR at baseline, with PLR also being found to correlate with disease activity during follow-up. We therefore propose that these indices, which can be simply calculated from an FBE, represent readily accessible and inexpensive biomarkers with the potential to measure PMR disease activity more reliably than conventional inflammatory markers like CRP and ESR.

Several other studies have recently investigated trends in haematologic parameters in PMR. In their retrospective analysis of 94 PMR patients contrasted with 242 RA patients, Jung et al. found NLR and PLR to be significantly higher among PMR cases.⁸ These levels subsequently diminished with treatment and were found to correlate with other measures of disease activity including CRP, however an association between NLR or PLR and a relapsing disease course was not identified in this instance. A Japanese study has however reported thrombocytosis as an adverse prognostic factor in PMR.²³ Using hierarchical cluster analysis, participants with a platelet count $>450 \times 10^9/L$ were found to be less likely to exhibit a response to glucocorticoid therapy at one month. Finally, a change in leukocyte dynamics among patients with PMR and GCA compared with healthy and infection controls has been newly documented by van Sleen et al., with a shift towards the production of myeloid-lineage leukocytes noted prior to the commencement of prednisolone.²⁴ This bias ultimately persisted during treatment

with a weaning schedule of glucocorticoid therapy and was even maintained in patients achieving drug-free remission.

Taken together, these results suggest that the inflammatory milieu which characterises PMR directly impacts neutrophil and platelet production within the bone marrow. As other authors have previously hypothesised, this likely occurs secondary to high levels of the key cytokine interleukin-6, given this pro-inflammatory mediator is additionally an independent regulator of granulopoiesis and stimulates thrombopoiesis through thrombopoietin.^{25, 26} It is therefore entirely conceivable that haematologic parameters reported on an FBE may provide an accurate representation of underlying disease activity in PMR.

Whilst the precise mechanism behind the association of high NLR with adverse survival in cancer patients is not known, neutrophilia as an inflammatory response is understood to suppress other immune cells including lymphocytes, activated T cells and natural killer cells, whose infiltration of tumors is otherwise associated with positive cytotoxic treatment outcomes.⁴ In RA, where a recent meta-analysis has demonstrated a consistent relationship between NLR and PLR, and the presence of active disease, these indices are similarly thought to reflect the pathogenic mechanisms at play rather than being surrogate measures of the body's overall inflammatory state.²⁷

The pathogenesis of PMR remains comparatively unclear though – it is hypothesized to arise from an aberrant immune response that follows an interaction between environmental factors, possibly viral, and the innate immune system in genetically predisposed individuals.²⁸ Activated macrophages predominate in both synovial and arterial samples taken from PMR patients. In the related condition GCA however, neutrophils have been implicated as the promoters of an escaped proinflammatory disease phenotype.²⁹ More specifically, a subset of neutrophil granulocytes capable of suppressing T cell activity following the institution of high-dose prednisolone therapy have been demonstrated to lose this ability upon glucocorticoid weaning in the context of rising IL-17 and IL-6 levels. Loss of this neutrophil suppressor function is thought to result in unchecked T cell proliferation within the vessel wall and eventual disease relapse.

Whilst this mechanism provides a biologically plausible explanation for a predominance of neutrophils enabling an adverse prognostic outcome in PMR, baseline neutrophil counts for glucocorticoid-resistant patients in our study were not substantially different from their glucocorticoid-responsive counterparts. Rather, lymphocyte counts were lower in this subset thereby producing higher NLR values. In general, no difference in total lymphocyte numbers is

observed when PMR cases are compared with healthy controls.³⁰ Circulating B-cell lymphopaenia secondary to redistribution or intravascular marginalization of predominantly pro-inflammatory B-effector cells has however been established to exist in newly diagnosed, steroid-naïve PMR.³¹ This disturbance in B cell homeostasis corrects with glucocorticoid therapy and is sustained in clinical remission but reoccurs upon disease relapse. Unfortunately, we did not undertake lymphocyte subset testing as part of this study, hence it is unclear whether lower lymphocyte counts at baseline in glucocorticoid-resistant patients represented an exaggeration of this previously described B cell phenomenon. Further investigation of lymphocyte subsets and their association with glucocorticoid resistance in PMR is now planned.

There are several other limitations to this study. It involves a relatively small number of participants and consequently the results may not be generalizable to a larger, more heterogeneous PMR cohort. As glucocorticoids have the potential to impact upon measured neutrophil and platelet counts, it is similarly not known if NLR can predict glucocorticoid-resistant disease in PMR if calculated from an FBE obtained once the patient has commenced prednisolone. Finally, this study provides proof-of-concept for the utility of NLR and PLR in measuring PMR disease activity and predicting treatment response. For use in everyday practice however, cut-off values to aid clinical decision-making would be ideal. Unfortunately, this was beyond the scope of the current pilot and hence further validation of these biomarkers in a large, multi-center trial is necessary.

CONCLUSION

Baseline NLR represents a readily accessible and inexpensive biomarker that can predict glucocorticoid resistance in newly diagnosed PMR. This finding further characterizes a distinct subgroup of patients with relapsing disease in whom early initiation of DMARD therapy may be appropriate. In addition, both NLR and PLR appear to be reliable measures of PMR disease activity, outperforming conventional inflammatory markers like CRP and ESR. Further studies are now needed to validate these biomarkers for implementation in routine clinical practice.

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Table 1 – Baseline demographic information: values are means \pm standard deviation, unless otherwise stated; median values are reported with 25% and 75% quartiles.

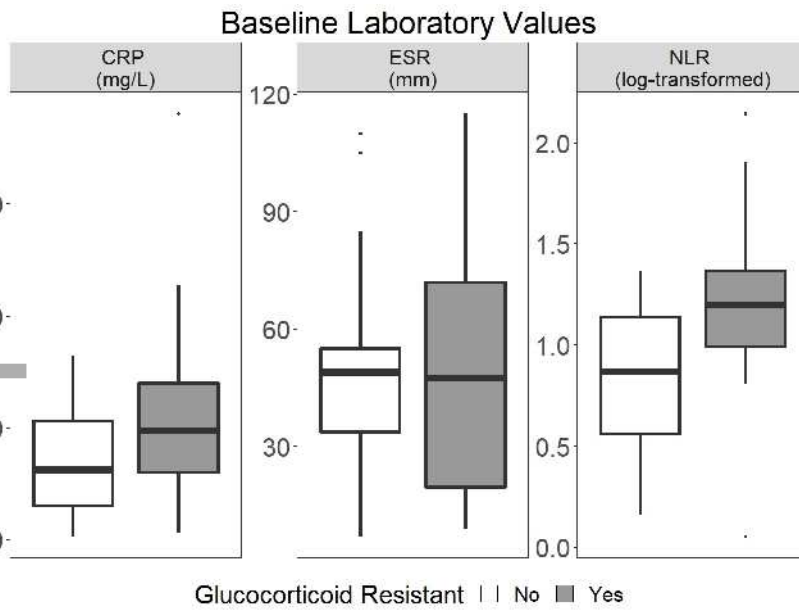
Demographic	Patients (n=32)
Age (years)	69.0 \pm 7.2
Male	17 (53.1%)
Caucasian	31 (96.9%)
BMI (kg/m²)	27.7 \pm 5.1
Shoulder Pain	32 (100%)
Hip Pain	28 (87.5%)
Median EMS (mins)	120 (67.5 – 195)
EULAR/ACR Clinical Algorithm Score	5.2 \pm 0.6
Median CRP (mg/L)	42.9 (21.8 – 65.7)
Median ESR (mm)	47.5 (30.5 – 68)
PMR-AS	74.2 \pm 35.7
Median HAQ-DI	1.7 (1.1 – 2.1)

Abbreviations: BMI – body mass index; EMS – early morning stiffness; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; PMR-AS – polymyalgia rheumatica-activity score; HAQ-DI – health assessment questionnaire-disability index.

Table 2 – Demographic comparison of glucocorticoid-resistant and -responsive patients: values are means \pm standard deviation, unless otherwise stated; median values are reported with 25% and 75% quartiles.

Abbreviations: CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; PMR-AS – polymyalgia rheumatica-activity score; WCC – white cell count; NLR – neutrophil to lymphocyte ratio; PLR – platelet to lymphocyte ratio.

Demographic	Glucocorticoid-Resistant (n=16)	Glucocorticoid-Responsive (n=16)
Age (years)	71.9 \pm 7.0	66.1 \pm 6.4
Gender:		
- Female	10 (62.5%)	5 (31.25%)
- Male	6 (37.50%)	11 (68.75%)
CRP (mg/L)	59.3 \pm 46.0	36.4 \pm 27.6
ESR (mm)	50.7 \pm 28.6	49.4 \pm 30.1
PMR-AS	85.3 \pm 35.3	63.0 \pm 33.7
Median WCC (x10⁹/L)	8.55 (7.4 – 9.25)	7.95 (7.0 – 9.23)
Median neutrophils (x10 ⁹ /L)	5.5 (4.9 – 6.73)	5.1 (3.8 – 5.9)
Median lymphocyte (x10 ⁹ /L)	1.7 (1.6 – 1.8)	2.1 (1.9 – 2.3)
Median platelets (x10⁹/L)	362 (297 – 409)	332 (264 – 448)
NLR (log-transformed)	1.2 \pm 0.4	0.8 \pm 0.4
PLR (log-transformed)	5.37 \pm 0.37	5.12 \pm 0.38



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