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Original Article

A Novel Biomarker for Bell's Palsy: The Pan-Immune-Inflammation Value

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BACKGROUND: The pan-immune-inflammation value (PIV) is a recently described novel biomarker obtained from complete blood count parameters. Systemic biomarkers have been investigated in a number of studies aimed at confirming the role of the inflammatory process in the etiology of Bell's palsy (BP) and elucidating the association with prognosis. This study investigated the relationship between PIV and BP.

METHODS: Sixty patients aged 18-75 years presenting with BP and 51 healthy controls with similar age and sex profiles were included in this retrospective study. Pan-immune-inflammation value and systemic immune-inflammation index (SII) values were calculated and compared between the 2 groups. The severity of paralysis in the BP group was recorded according to the House–Brackmann (HB) grading system and compared between the 2 groups.

RESULTS: Both PIV and SII values were significantly higher in the BP group ($P < .001$). Intra-group comparisons based on paralysis grading revealed a significant difference in SII values in grades IV and V ($P = .04$).

CONCLUSION: The findings suggest that PIV may represent a useful and readily available biomarker reflecting systemic inflammation in patients with BP. However, larger prospective studies are now required to confirm its diagnostic and prognostic values.

KEYWORDS: Bell's palsy, facial paralysis, inflammatory markers, pan-immune-inflammation value, systemic immune-inflammation index

INTRODUCTION

Bell's palsy (BP), characterized by acute facial muscle weakness, is the most common cause of facial paralysis, with an incidence of 11.5-53.3 in 100 000 members.[1] Bell's palsy is an exclusion diagnosis, which can be confirmed once underlying causes such as trauma, neoplasm, and congenital and syndromic diseases have been ruled out.[2] The etiology of BP is not yet fully understood, although various theories have been proposed, including viral infection, inflammation, ischemia, autoimmune diseases, and acute cold exposure.[1] Various electrophysiological tests and imaging methods are employed for diagnosis and predicting prognosis.

Various systemic inflammatory markers, such as the systemic immune-inflammation index (SII), the neutrophil/lymphocyte ratio (NLR), the platelet lymphocyte ration (PLR), and mean platelet volume, are obtained from complete blood cell subtypes. These have been investigated in different infectious and inflammatory diseases, cardiovascular diseases, autoimmune diseases, and malignancies and have been found to be useful in terms of both diagnosis and prognosis.[3] The pan-immune-inflammation value (PIV) is a recently described biomarker obtained from platelet, lymphocyte, neutrophil, and monocyte counts. It has been examined in various malignant diseases, such as head and neck, colorectal, and breast cancers, and has been described as a significant factor in terms of prognosis.[4] In addition, PIV has also been investigated in patients with inflammatory etiologies such as rheumatoid arthritis and systemic lupus erythematosus, and has been shown to be of prognostic value again.[5,6]

Systemic biomarkers have been investigated in a number of studies aimed at confirming the role of the inflammatory process in the etiology of BP and elucidating the association with prognosis.[7,8] However, despite these findings, evidence regarding the role of the PIV in patients with BP remains limited. To the best of the authors' knowledge, the present study is one of the first to investigate PIV in patients with BP and the first to evaluate the PIV together with the SII in the same patient cohort. The authors aimed to compare PIV and SII values between patients with BP and healthy controls and to evaluate the association of these inflammatory markers

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with House–Brackmann (HB) grades. This was intended to yield additional evidence regarding the potential clinical utility of the PIV and its complementary role alongside SII in cases of BP.

METHODS

This retrospective case-control study was conducted at the Department of Otorhinolaryngology of Erzincan Binali Yıldırım University Mengucek Gazi Training and Research Hospital between January 2020 and September 2024. Approval for the research was obtained from the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (Approval No: 2024-14/03; Date: 24.10.2024). The study was conducted in accordance with the principles of the Declaration of Helsinki. Sixty patients with BP aged 19-75 years presenting to the Erzincan Binali Yıldırım University Mengucek Gazi Training and Research Hospital Ear, Nose, and Throat (ENT) Clinic and 51 healthy controls with similar age and sex distributions were enrolled. Patients with available complete blood count results obtained during the acute phase of BP, with documented age and sex-related data, and with recorded HB grades were included.

Bell's palsy was diagnosed clinically as acute unilateral peripheral facial nerve paralysis following the exclusion of identifiable causes such as trauma, otitis media, Ramsay Hunt syndrome, parotid or middle ear neoplasms, and central nervous system disorders. Patients presenting to the ENT clinic with complaints of facial asymmetry and weakness and whose detailed medical histories and physical examination findings were available in the medical records were enrolled in the study. Patients who presented more than 5 days after symptom onset, with histories of previous ear surgery, with accompanying hearing loss suggestive of an alternative diagnosis, with clinical findings suggestive of rheumatological or autoimmune diseases, with active infection, who were receiving medications capable of affecting complete blood count parameters, or with active malignancy were excluded. The control group consisted of individuals without BP and with no known acute or chronic inflammatory, infectious, or systemic diseases, as determined by a retrospective review of hospital records and available laboratory data.

Patients' complete blood count parameters were calculated using an automatic hematology analyzer (XN-2000-Hematology-analyzer-Sysmex Corporation, Japan) and subjected to analysis. Complete blood samples obtained at the initial presentation, before the initiation of corticosteroid therapy, were used to calculate SII and PIV values. The SII was calculated using the formula platelet × neutrophil / lymphocyte, and the PIV was calculated using the formula platelet × neutrophil × monocyte / lymphocyte. Following blood sample collection, all patients received oral methylprednisolone at a dose of 1 mg/kg/day, tapered every 3 days according to the standard departmental treatment protocol. Gastric protection was provided during corticosteroid therapy, blood glucose levels were monitored, and all patients received standard eye protection, including artificial tear eye drops and eye care instructions. Patients' HB grades were calculated based on standardized clinical criteria routinely used in otorhinolaryngology practice and recorded. The SII and PIV values were compared between the BP and control groups to determine the presence of any statistically significant differences. Patients with BP were classified according to the HB grading system, and the relationships between HB grades and inflammatory markers were analyzed. The primary outcome of the study was the difference in PIV values between patients with BP and healthy controls. Secondary outcomes included differences in SII values and the association between both inflammatory markers and HB grades.

Patients with missing complete blood count results, demographic information, or HB grades were excluded from the study and no missing data imputation was therefore performed. Statistical analyses were performed on Statistical Package for Social Sciences for Windows version 20.0 software (SPSS Inc., Armonk, NY, USA). The Kolmogorov–Smirnov test was applied to determine the distribution of the variables. Non-normally distributed continuous variables were analyzed using the Mann–Whitney *U*-test. Spearman's correlation analysis was applied to evaluate relationships. Comparisons among more than 2 groups were performed using the Kruskal–Wallis test. When a significant overall difference was detected, pairwise comparisons were performed using the Mann–Whitney *U*-test with Bonferroni correction. *P* values < .05 were considered statistically significant.

RESULTS

Sixty patients with BP and 51 healthy controls were included in the study. Mean ages were 52.6 ± 17.0 years in the BP group and 51.0 ± 15.0 years in the control group. Thirty-two patients (53.3%) in the BP group and 27 (52.9%) in the control group were female, with no significant differences in age or sex distributions being observed between the groups ($P > .05$). The right side of the face was affected in 35 patients (58.3%) and the left side in 25 (41.7%). Eight cases (13.3%) were grade II according to the HB system, 23 were (38.3%) grade III, 11 were (18.3%) grade IV, 16 were (26.7%) grade V, and 2 were (3.3%) grade VI (Table 1).

Since SII and PIV values in the patient and control groups were not normally distributed, comparisons between the 2 groups were performed using the non-parametric Mann–Whitney *U*-test. Both mean and median SII and PIV values were significantly higher in the BP group than in the control group ($P < .001$) (Tables 2 and 3).

When the patients with BP were grouped according to their disease grades, the Kruskal–Wallis test revealed a significant difference in SII values ($P = .04$). The Mann–Whitney *U*-test was applied to identify the group responsible for the difference, and *P* values were presented with the application of Bonferroni correction. Post hoc analysis demonstrated that the significant difference was primarily attributable to patients with HB grades IV and V ($P = .04$) (Table 4). Analysis revealed no significant difference between these groups' PIV values ($P = .46$) (Table 5).

MAIN POINTS

- The pathogenesis of Bell's palsy (BP) is not fully understood, but is generally idiopathic.
- Inflammation is one of the main theories proposed to account for the pathogenesis of BP.
- The pan-immune-inflammation value (PIV) is a recently described biomarker obtained from platelet, lymphocyte, neutrophil, and monocyte counts. It has been investigated in patients with inflammatory etiologies.
- The PIV may represent a useful biomarker reflecting systemic inflammation in patients with BP.

Table 1. Demographic and Baseline Clinical Characteristics of the Patients with Bell's Palsy and Healthy Controls

Characteristic	BP Group (n = 60) (%)	Control (n = 51) (%)
Age (years), mean ± SD	52.6 ± 17.0	51.0 ± 15.0
Female	32 (53.3)	27 (52.9)
Male	28 (46.7)	24 (47.1)
Right side affected	35 (58.3)	–
Left side affected	25 (41.7)	–
HB grade II	8 (13.3)	–
HB grade III	23 (38.3)	–
HB grade IV	11 (18.3)	–
HB grade V	16 (26.7)	–
HB grade VI	2 (3.3)	–

BP, Bell's palsy; HB, House–Brackmann; SD, standard deviation.

DISCUSSION

Facial paralysis is a neuropathy resulting from dysfunction of the seventh cranial nerve.[9] Although it can occur at any age and in both sexes, it is more common in diabetic patients, following upper respiratory tract infections, and in pregnant women. Bell's palsy is the most common cause of facial paralysis and is the term used for idiopathic paralyses.[10] The condition generally develops within a few days, and may be accompanied by symptoms such as auricular or postauricular pain, facial numbness, hyperacusis, taste impairment in the anterior part of the tongue, and decreased tear production.

Although the etiology of BP is not yet fully understood, the current emphasis is on viral agents, inflammation, and ischemia. Several agents, including Varicella zoster virus, herpes simplex virus type-1 (HSV-1), and human herpesvirus 6, have been investigated to examine the relationship between BP and viral agents. Herpes simplex virus type-1, the most studied of these, is reported to be reactivated around the geniculate ganglion.[11] Ischemia refers to the interruption of nutrition to the facial nerve, and paralysis is reported to become permanent if this interruption develops into tertiary ischemia.[12] Inflammation is the principal point of focus in the etiology of BP. This etiology was first established by Liston and Kleid's[13] histopathological study. Several subsequent studies then corroborated that hypothesis. Yılmaz et al[14] investigated cytokines such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha in serum samples from patients with BP and reported higher concentrations than in a control group. Another study investigating T lymphocyte sub-units in patients with BP also reported findings supporting inflammation.[15] These findings regarding the etiology of BP represent the basis for investigation of numerous markers potentially capable of representing inflammatory markers in the disease.

A number of values obtained from blood cells have been the subject of numerous studies investigating inflammatory processes in various diseases and conditions. These parameters have been described as useful for several purposes, including estimating prognosis and predicting survival in cancers, in the diagnosis and follow-up of rheumatological and inflammatory diseases, and in estimating the severity of infectious diseases. Neutrophils, a white blood cell subgroup, represent innate immunity, while lymphocytes adapt to eliminate infected tissues, some pathologies, and malignant cells.[16] Monocytes play an important role in the innate immune reaction to infections and are the most vital cells in the release of pro-inflammatory and pro-oxidant cytokines.[17] Jin et al[18] investigated the monocyte high-density lipoprotein ratio in patients with BP and described it as useful in both diagnosis and prognosis. The PIV, calculated using monocyte values, is a relatively novel marker used in various recent studies. Recently, it has been investigated in areas such as malignancies, rheumatological diseases, and autoimmune diseases and has been described as a significant factor in diagnosis and predicting prognosis.[19,20]

Table 2. A Comparison of PIV Values in the Bell's Palsy and Control Groups

	Mean ± SD	Median	Mean Rank	*P*
Patient	385.6 ± 406	288	67.22	<.001
Control	216.1 ± 112.5	184	42.80	

PIV, pan-immune-inflammation value.

Table 3. A Comparison of SII Values in the Bell's Palsy and Control Groups

	Mean ± SD	Median	Mean Rank	*P*
Patient	662.4 ± 682	520	70.16	<.001
Control	335.7 ± 130.4	346	39.34	

SII, systemic immune-inflammation index.

Kınar et al[21] investigated 88 patients with BP and reported significantly higher PLR, NLR, and SII values compared to a control group. Additionally, those authors concluded that SII values may represent a useful parameter for predicting prognosis in patients with the condition. Another study involving 54 pediatric BP cases reported that NLR and PLR values are easily accessible from pediatric patients and may represent useful prognostic markers.[22]

To the best of the authors' knowledge, this is one of the first studies to investigate PIV in patients with BP, and the first to evaluate the PIV together with SII in the same patient cohort. Both PIV and SII values were higher in the patients with BP than in the control group. When the groups were examined on the basis of paralysis grading, grade IV and V patients exhibited significantly higher SII values than the other subgroups.

Sivrice et al[23] recently published a retrospective case-control study evaluating the PIV in patients with BP. Consistent with the present findings, they reported significantly higher PIV values in the BP group compared with healthy controls, although no association was observed between PIV and HB grades. These consistent findings further support the role of systemic inflammation in the pathogenesis of BP and suggest that the PIV may serve as a useful biomarker reflecting inflammatory activity. In contrast to Sivrice et al, the

Table 4. A Comparison of SII Values by Grades in the Patient Group

	Mean ± SD	Median	Mean Rank	*P*
HB grade II	727 ± 699	510	31.38	.04
HB grade III	511 ± 210	448	26.65	
HB grade IV	464 ± 254	360	21.91	
HB grade V	1000 ± 1141	749	41.31	
HB grade VI	521 ± 72	521	32.00	

HB, House–Brackmann; SII, systemic immune-inflammation index.

Table 5. A Comparison of the Bell's Palsy Group PIV Values by HB grades

	Mean ± SD	Median	Mean Rank	*P*
HB grade II	360 ± 122	355	36.38	.46
HB grade III	345 ± 202	294	30.35	
HB grade IV	349 ± 307	194	24.91	
HB grade V	502 ± 704	318	33.28	
HB grade VI	214 ± 69	214	17.25	

HB, House–Brackmann; PIV, pan-immune-inflammation value.

authors simultaneously evaluated both the PIV and SII in the same patient cohort, thus permitting a more comprehensive assessment of systemic inflammatory biomarkers.

Atan et al[8] reported higher NLR and PLR values in 99 patients with BP than in a control group, but observed no association with prognosis. Similar research investigating NLR values in pediatric BP patients also concluded that this parameter might be significant in diagnosis, but it exhibited no relationship with HB grading.[24] The present study also determined no correlation between PIV values and severity of paralysis. This suggests that while PIV may be useful as a marker reflecting the presence of systemic inflammation in BP, it may be of more limited value in predicting disease severity or clinical grading. Therefore, the PIV should be interpreted as a supportive biomarker, rather than a prognostic indicator. Considered together, these findings are consistent with the concept that systemic inflammatory biomarkers, particularly the PIV and SII, may complement clinical assessment in cases of BP, although they should not replace established clinical evaluation and grading systems.

The limitations of this study include its retrospective nature, and the fact that scanning was performed via the patient files, meaning that accompanying comorbidities could only be investigated through the hospital record system. In addition, the retrospective, single-center design may have introduced selection bias. Due to the study design, subclinical inflammatory conditions and certain comorbidities or lifestyle factors (such as body mass index and smoking status) may not have been fully captured, which may, in turn, have influenced baseline inflammatory marker levels. In addition, the relatively small sample size, particularly within certain HB grade subgroups, may have reduced the statistical power to detect differences and limited the generalizability of the findings. Furthermore, since this retrospective study was designed to evaluate inflammatory biomarkers only at initial presentation, no longitudinal assessment of clinical outcomes or treatment response was performed. Finally, imaging findings, audiological parameters, and patient-reported outcome measures were not included in the study design; therefore, the prognostic value of the PIV cannot be evaluated.

CONCLUSION

The findings of this study suggest that the PIV may represent a useful and readily available biomarker reflecting systemic inflammation in patients with BP. However, larger prospective studies are now required to confirm its diagnostic and prognostic values.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received from the Erzincan Binali Yıldırım University Clinical Research Ethics Committee (Approval No: 2024-14/03; Date: 24.10.2024).

Informed Consent: The informed consent was waived due to the retrospective nature of the study.

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