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Do Haematological Laboratory Data Associate with Tumour Size, Cavernous Sinus Invasion, and Sellar Erosion in Patients with Pituitary Adenoma?

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Abstract

Background: Pituitary adenomas (PAs) are the most prevalent neuroendocrine tumour. Inflammation, both within the tumour microenvironment and systemically, plays a role in tumour biology. Haematological laboratory data serves as an initial and cost-effective approach. This study explores the association between haematological indices (e.g., NLR, PLR, LMR) and PA characteristics (tumour size, sellar erosion, cavernous sinus invasion).

Methods: A retrospective study (2018–January 2023) analysed preoperative haematological data (such as neutrophil to lymphocyte ratio [NLR], platelet to lymphocyte ratio [PLR], and lymphocyte to monocyte ratio [LMR]) from PA patients. The haematological data was analysed based on tumour characteristic with $p<0.05$ considered significant.

Results: Among 64 patients (mean age 45.55±14.67), 20–40% had elevated NLR, PLR, and LMR. Tumour characteristics included 60.9% macroadenomas and 39.1% giant PAs, with 43.8% showing sellar erosion and 42.2% cavernous sinus invasion. Monocyte counts were significantly higher in giant PAs vs. macroadenomas (7.48 ± 1.91 vs. 6.49 ± 1.95, p=0.040), and platelet counts were higher in sellar erosion vs. enlargement (336,710 ± 90,460 vs. 284,720 ± 89,766, p=0.016).

Conclusion: Our study found that patients with giant PAs had significantly higher monocyte counts.

Keywords: Pituitary adenoma, systemic inflammation index, monocyte, tumour size.

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INTRODUCTION

Pituitary adenomas (PA) are benign neoplasms originating in the anterior pituitary cells, that represent 15–20% of all intracranial tumors.[1] The incidence of PA is estimated to be about 3.9–7.4 cases per 100,000 people per year.[2] The peak incidence is in the fourth and fifth decades of life, and PAs are more common in women than in men.[1,3,4] PAs are benign by histology but with high morbidity caused by their complications.[1,5,6] PA cause hypersecretion of pituitary hormones resulted in acromegaly due to growth hormone (GH) and insulin-like growth factor 1 (IGF-1) excess.[7] In addition, mass effect caused by PA often compress surrounding structure leads to impaired visual acuity or pituitary hormones deficiency.[1] It is well established that long-lasting GH/IGF-1 axis hypersecretion leads to systemic complications, especially in development of cardiovascular (CV) diseases.[8-10]

Recent studies revealed that local and systemic inflammation may modulate and promote several tumorigenic processes, such as tumour proliferation, migration, invasion, and immune cells chemoattraction in different cancer.[9,11-13] Excessive dose of GH and IGF-1 initiated inflammation process via T-cells, B-cells, and monocyte overproduction.[9] It is proven to have crucial role in bi-directional network between endocrine and immune system in PA patients.[8]

Haematological laboratory data has been favoured over past decades by most clinicians due to cost-effective, easily accessible, and commonly used indices.[14,15] Furthermore, several studies have demonstrated that blood markers like white blood cell (WBC) count, neutrophils, monocytes, as well as ratios such as neutrophil–to–lymphocyte ratio (NLR), platelet–to–lymphocyte ratio (PLR), and lymphocyte–to–monocyte ratio (LMR) exhibit significant alterations in different malignant tumour cases.[16-19] Moreover, these parameters have been proposed as potential biomarkers to differentiate malignant from benign neoplasms preoperatively, predicting prognosis and response to treatment.[20-22]

However, there is limited data regarding haematological parameters and its correlation with PA patients' characteristics. This study aims to investigate the association between haematological laboratory data and tumour size, sellar erosion, and cavernous sinus invasion in patients with PA.

MATERIAL AND METHODS

We collected patients' data from 2018 to January 2023 through medical records. The criteria for selecting patients included those diagnosed with PA based on radiology or histopathology, patients over 18 years old, patients with complete radiology and haematology data (including routine blood tests and differential counts), patients undergoing their first PA surgery, and patients without a history of haematological disorders and other malignancies.

Preoperative haematological data, including routine blood parameters (haemoglobin, haematocrit, erythrocyte, leukocyte, and platelets) and leukocyte differential counts (eosinophils, basophils, bands, segmented neutrophils, lymphocytes, and monocytes) were collected. We measured the NLR (calculated by dividing the neutrophil count by the lymphocyte count), the PLR (calculated by dividing the platelet count by the absolute lymphocyte count), and the LMR (calculated by dividing the lymphocyte count by the monocyte count). These indexes were used to assess the level of systemic inflammation in the study.

From the radiological imaging, we collected the anteroposterior, craniocaudal, and laterolateral dimensions of the largest tumour diameter. We also evaluated the Hardy Classification (Grade 0-4 and Grade A-E), and KNOSP classification (Grade 0-4). We divided the subject into three population; (I) based on its tumour size which were categorized as pituitary microadenoma (PMic), with diameter <10 mm, pituitary macroadenoma (PMac) with diameter >10 mm and <40 mm, or giant pituitary adenoma (GPA) with diameter >40 mm; (II) Based on its sellar erosion and enlargement, which categorized by Hardy Score classification ≤ 2 to be enlargement and ≥ 3 to be erosion; (III) Cavernous sinus invasion, which categorized from KNOSP classification grade 4 or Hardy Classification grade E.

A statistical analysis was performed to analyse the leukocyte, platelet, neutrophils, lymphocytes, monocytes, NLR, PLR, LMR, based on its population by using independent sample T-test or Mann-Whitney Test. A p value <0,05 was considered significant, and variable with significant result will be performed receiving operator characteristic (ROC) analysis. All data was analysed by using SPSS for Windows ver. 26 (IBM, USA).

This research has received ethical approval from institutional review board with number 1481/EC/KEPK/RSDK-2023.

RESULTS

Table 1. Demographic and haematology data of the subjects

Parameters	Result (n = 64)
Age (years)	45.55 ± 14.67
Sex	
Male	31 (48.4%)
Female	33 (51.6%)
Routine blood parameters	
Haemoglobin (g/dL)	12.92 ± 1.81
Haematocrit (%)	38.75 ± 5.13
Erythrocyte (10^6/µl)	4.54 ± 0.58
Leukocyte (10^3/µl)	8.94 ± 4.31
Platelet (10^3/µl)	307.46 ± 93.05
Leukocyte differential counts (%)	
Eosinophils (%)	3.28 ± 3.57
Basophils (%)	0.19 ± 1.18
Bands neutrophils (%)	0.52 ± 0.85
Segment neutrophils (%)	60.63 ± 10.93
Lymphocytes (%)	27.85 ± 9.52
Monocytes (%)	6.88 ± 1.98
Absolute lymphocyte count (10^3/µl)	2.33 ± 0.89
Absolute neutrophile count (10^3/µl)	5.64 ± 3.78
Absolute Monocyte count (10^3/µl)	0.62 ± 0.36

Data presented in mean ± SD or n (%)

During the study period, a total of 64 subjects met our criteria. The average age the subjects was 45.55±14.67. Female patients comprised slightly more of the study population than male patients (51.6% vs. 48.4%). The routine blood parameters and leukocyte differential counts of the subjects were found to be within normal limits. The data is shown in Table 1.

Systemic inflammation indexes revealed that the NLR showed an average of 3.05±3.15, which was higher than the range observed in the healthy normal population (0.43–2.75 for males and 0.37–2.87 for females).[23] A total of 17 subjects (26.6%) exhibited an elevated NLR, while 47 subjects (73.4%) had a normal NLR. Similarly, the PLR showed an average of 153.79±88.6, slightly higher than the range observed in the healthy normal population (36.63–149.13 for males and 43.36–172.68 for females).[23] Among the subjects, 21 individuals (32.8%) showed an increased PLR, while 43 subjects (67.2%) had a normal PLR. The LMR showed an average of 4.44±2.36, within the normal range observed in the healthy population (ranging from 2.62 to 4.56). Of the subjects, 25 (39.1%) exhibited a higher LMR, 29 (45.3%) had a normal LMR, and 10 (15.6%) had a lower LMR compared to the healthy population.[24]

Table 2. The tumour characteristic data of subjects

Variables	Result (n = 64)
Tumor Size	
AP (mm)	31.32 ± 11.41
CC (mm)	34.22 ± 12.45
LL (mm)	36 ± 12.95
Hardy Classification	
Sellar	
Grade 1	0 (0%)
Grade 2	36 (56.3%)
Grade 3	11 (17.2%)
Grade 4	17 (26.6%)
Extension	
Grade A	0 (0%)
Grade B	5 (7.8%)
Grade C	28 (43.8%)
Grade D	10 (15.6%)
Grade E	21 (32.8%)
Knops Classification	
Grade 0	3 (4.6%)
Grade 1	2 (3.2%)
Grade 2	19 (29.7%)
Grade 3	17 (26.6%)
Grade 4	23 (35.9%)

Data presented in mean ± SD or n (%); AP, anteroposterior; CC, craniocaudal; LL, laterolateral

Regarding tumour size, all diameters measured over 30 mm, resulting in 39 (60.9%) subjects being categorized as macroadenomas and 25 (39.1%) subjects as giant pituitary macroadenomas. No patients were classified as microadenomas. The most cases in the Hardy classification were grade 2 (36, 56.3%), and grade C accounted for 28 (43.8%) cases. In the KNOSP classification, grade 4 was the most common, with 23 (35.9%) cases. Thus, sellar erosion was present in 28 (43.8%) subjects, and sellar enlargement in 36 (56.3%) subjects. Additionally, 27 (42.2%) subjects exhibited cavernous sinus invasion. The tumour characteristic data are presented in Table 2.

Haematological Laboratory Data against tumour size, sellar erosion, and cavernous sinus invasion

According to Figure 1, a significant difference was observed only in the monocyte variable. GPA showed a higher average monocyte count compared to PMac (7.48 ± 1.91 vs. 6.49 ± 1.95, p=0.040). No significant differences were found in the other variables.

According to Figure 2, a significant difference was observed only in the platelet variable. Sellar erosion

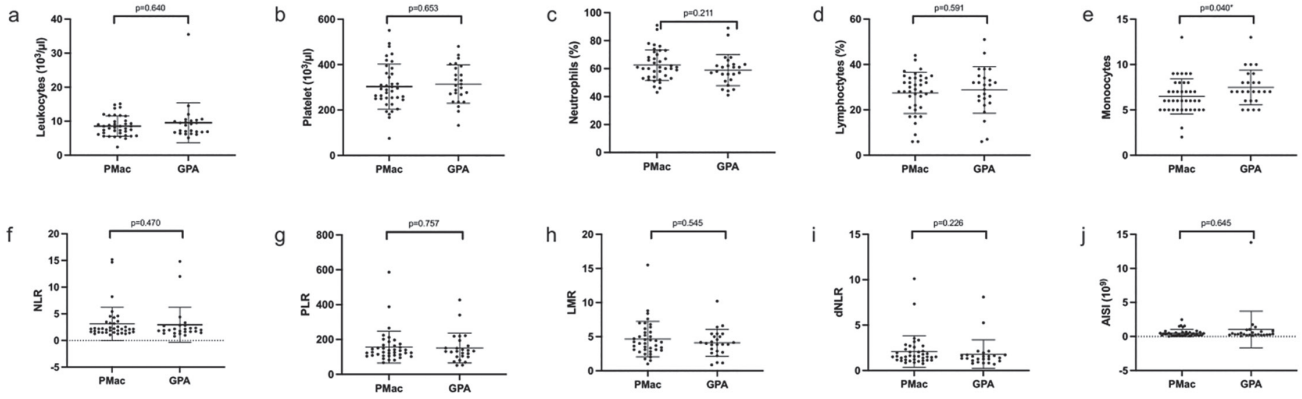

Figure 1. Comparison of (a)leukocyte, (b)platelet, (c)neutrophil, (d)lymphocyte, (e)monocyte, (f)NLR, (g)PLR, (h)LMR, (i)dNLR, (j)AISI based on PMac (n = 39) and GPA (n = 25)

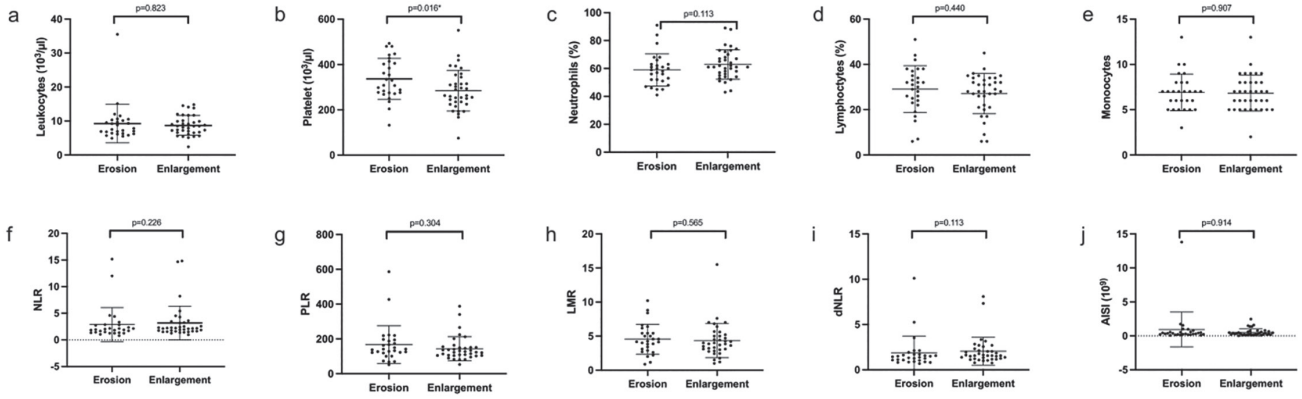

Figure 2. Comparison of (a)leukocyte, (b)platelet, (c)neutrophil, (d)lymphocyte, (e)monocyte, (f)NLR, (g)PLR, (h)LMR, (i)dNLR, (j)AISI based on pituitary sellar erosion (n= 28) vs. sellar enlargement (n = 36)

showed a higher average platelet count compared to sellar enlargement (336,710 ± 90,460 vs. 284,720 ± 89,766, p=0.016). No significant differences were found in the other variables. Furthermore, in the analysis of cavernous sinus invasion, no significant differences were identified in any of the variables.

ROC curve analysis

According to Figure 3 (a), the ROC analysis curve indicates that with a monocyte cut-off value of 6.5%, it has a sensitivity of 72% and a specificity of 56.4% (area under the curve/AUC=0.650). According to Figure 3 (b), the ROC analysis curve indicates that with a platelet cut-off value of 288,500, it has a sensitivity of 47.2% and a specificity of 39.3%. However, the AUC is 0.323.

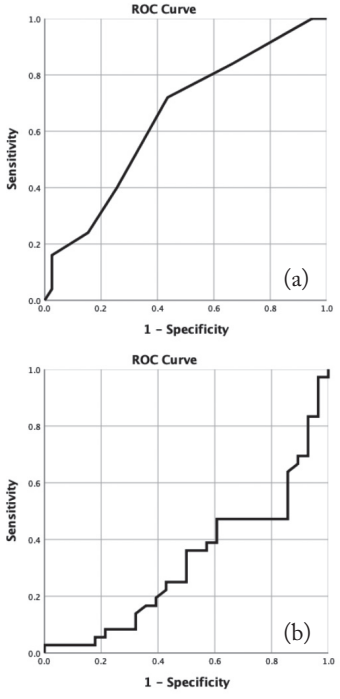

Figure 3. CROC curve analysis of monocytes against GPA (a) and platelets against sellar erosion (b)

DISCUSSION

The present study investigated the association between haematological laboratory data and tumour size, sellar erosion, and cavernous sinus invasion in patients with PA. The results showed that only monocyte count and platelet count were significantly associated with GPA and sellar erosion, respectively.

Our study revealed a significant increase in monocyte count among GPA patients, highlighting the potential association between monocytes and tumour biology. Monocytes serve as precursor cells to macrophages, which play a multifaceted role in tumour development. In the pituitary tumour, current research has focused on Tumour-Associated Macrophages (TAMs).[25]

TAMs divide into the M1-TAMs and M2-TAMs subgroups, which are both related to lymphocyte-secreted factors, fibrosis, metabolic stress, and hypoxia. [25-27] M2-TAMs plays critical role in PAs; which they can suppress the immune system by upregulating interleukins (IL); IL-10, IL-13, and transforming growth factor-β (TGF-β); affect epithelial-mesenchymal transition and proliferation through CCL17; increase vascularization through increased vascular endothelial growth factor (VEGF) expression; and affect extracellular matrix through the expression of matrix metalloproteinases (MMP); MMP-2 and MMP-9. [28-31] Additionally, another recent study documented that PAs with higher levels of CD68+ cells in their tumours were associated with larger tumour sizes and aggressiveness, suggesting a potential role for macrophages in the growth of PAs.[29, 32, 33]

There were no studies concerning platelets to sellar erosion were found, leading us to hypothesize that the observed sellar erosion in our study might be associated to the tumour size instead. The low AUC values of the ROC curve suggested that platelet count are not good predictors for sellar erosion. Nevertheless, our study finding of significant increase in monocyte count among GPA patients serves as supporting findings in TAMs of PA.

In systemic inflammation indexed, our results showed no significant difference between PMac and GPA, even though approximately 20-40% of our study population showed increased NLR, PLR, and LMR. In contrast, previous study comparing PAs patient's vs healthy populations showed a positive relationship between NLR, PLR, with the presence of non-functional PAs.[16] Another study found that compared to Non-Functional PAs, individuals with acromegaly had higher NLR, PLR, and neutrophil counts, while also having lower lymphocyte counts.[9] In studies of other brain tumours such as meningioma and glioma, NLR, PLR, and LMR showed an association.[17-19]

The present study had several limitations, as the diagnosis of PA is often late in Indonesia, the variation of the sample population was lacking as most patients had arrived at the PMac and even GPA stages. In addition, we also did not classify functional and non-functional PAs due to limited examination instruments.

CONCLUSION

In conclusion, our study found that patients with GPA had significantly higher monocyte counts. This suggests that monocytes may play a role in PA tumour growth and size. Further research is recommended to be conducted on the relationship between monocytes and various functional PA patients, as this may contribute to the development of effective therapeutic strategies.

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None of the authors has any conflict of interest.
The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Informed consent was obtained from all the patients included in the study.

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