Pituitary (2021) 24:334–350
https://doi.org/10.1007/s11102-020-01112-5

Pre-operative serum inflammation-based scores in patients with pituitary adenomas

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Accepted: 12 November 2020 / Published online: 24 November 2020

Abstract

Objective Full blood count (FBC) and serum inflammation-based scores reflect systemic inflammation and predict outcomes in cancer, but little is known in pituitary adenomas (PAs). We aimed to characterise FBC and inflammation-based scores in PA patients and investigate their usefulness in predicting challenging disease course.

Methods We studied 424 PA patients first operated at our centre with available pre-operative biochemical data. Patients with infection, malignancies, autoimmune or haematological conditions were excluded. Inflammation-based scores studied: Neutrophil-to-Lymphocyte Ratio (NLR), Platelet-to-Lymphocyte Ratio (PLR), Lymphocyte-to-Monocyte Ratio (LMR), Systemic Immune-Inflammation Index (SII), Neutrophil-Platelet Score (NPS), Prognostic Nutrition Index (PNI), and Glasgow Prognostic Score (GPS).

Results Cushing's disease patients had more platelets, leucocytes, neutrophils and monocytes, and higher NLR, NPS and SII. Serum inflammation-based scores didn't differ among non-Cushing PA subtypes. The glucocorticoid excess severity influenced leucocyte, eosinophil, basophil and platelet counts, and GPS in Cushing's disease. Patients with functioning non-Cushing PAs with suprasellar extension, cavernous sinus invasion and hypopituitarism had GPS ≥ 1, while NPS ≥ 1 was associated with suprasellar extension. More invasive and difficult to treat corticotrophinomas were associated with fewer platelets pre-operatively ($< 299.5 \times 10^9$/L predicting multimodal treatment). Non-functioning PA patients who suffered apoplexy had more leucocytes, neutrophils and monocytes, higher GPS ≥ 1 and fewer platelets; re-operated cases had fewer lymphocytes, higher NLR and PLR.

Conclusions Serum inflammation-based scores may predict invasive/refractory PAs: GPS and PNI in non-functioning and functioning non-Cushing PAs; NPS in functioning non-Cushing PAs; NLR and PLR in non-functioning PAs. Platelets $< 299.5 \times 10^9$/L predict multimodal treatment in Cushing's disease. Further studies are needed to confirm these observations.

Keywords Pituitary adenoma · Systemic inflammation · Serum inflammation-based scores · Serum inflammatory biomarkers

Introduction

Pituitary adenomas (PAs) account for 15% of all intracranial tumours, being the third most common intracranial neoplasm after meningiomas and gliomas, and the vast

Pedro Marques and Friso de Vries have contributed equally to this manuscript.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11102-020-01112-5) contains supplementary material, which is available to authorized users.

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majority of PAs are benign and follow an indolent course, although they can be associated with significant morbidity due to mass effects on surrounding tissues and/or excessive or insufficient hormone secretion (caused by both the tumour mass effects and therapeutical approaches such as surgery and radiotherapy) [1]. A subset of PAs present a challenging disease course being refractory to the conventional treatments, and may recur/regrow after surgical or medical therapy requiring multiple or multimodal treatment. Although upfront discrimination of an aggressive PA is not straightforward, some markers of PA aggressiveness have been identified, including radiological invasiveness (into cavernous or sphenoid sinus), and histological markers such as Ki-67, mitotic count, p53 staining and certain histiotypes including Crooke's adenoma, sparsely-granulated somatotrophinomas or null-cell PAs [2, 3]. However, to date it is still not possible to reliably predict the prognosis or recurrence in patients with PAs, and therefore new prognostic markers would definitely fulfil an important unmet clinical need.

Inflammation plays an important role in tumour biology, not only in the local tumour microenvironment [4], but also systemically [5, 6]. Responses to systemic inflammation include alterations in haematopoiesis and in secretion of acute-phase proteins, cytokines, growth factors and hormones [7, 8]. Full blood count (FBC), C-reactive protein (CRP), albumin and serum inflammation-based scores can reflect the systemic inflammatory status and predict outcomes in cancer patients [5]. Different pre-operative serum inflammation-based scores have been used and can easily be calculated from FBC data (Table 1): Neutrophil-to-Lymphocyte Ratio (NLR) [5, 9, 10], Platelet-to-Lymphocyte Ratio (PLR) [5, 11], Lymphocyte-to-Monocyte Ratio (LMR) [12, 13], Neutrophil-Platelet Score (NPS) [14] and Systemic Immune-Inflammation Index (SII) [15]. These scores not only reflect systemic inflammation, but also the patient's anti-tumour response and immunosurveillance status. Increased neutrophil counts or neutrophilia in cancer occur due to the secretion of myeloid growth factors by tumour cells triggering neutrophil production, or due to cancer-related inflammation secondary to tissue destruction or hypercytokinaemia. On the other hand, lymphocytes are important anti-tumour cells, and their reduction may indicate immunosuppression or weakened anti-tumour response [5, 10, 16]. Both the Prognostic Nutrition Index (PNI) [17] and Glasgow Prognostic Score (GPS) [5, 7] take into account serum albumin levels (Table 1), and they reflect the nutritional and immunological status of the patient [5, 7, 16, 18].

In general, increased NLR, PLR, NPS, SII and GPS, as well as low LMR and low PNI are associated with poor clinical outcomes in cancer (Table 1) [5, 7, 9, 13]. Several lines of research support the role of pre-operative FBC and serum inflammation-based scores in predicting surgical outcomes and prognosis in oncological patients [5, 16], including in non-metastatic tumours, such as meningiomas [19] and gliomas [15, 18, 20]. Endocrine neoplasms have also been studied for serum inflammatory scores including thyroid cancer [21, 22], neuroendocrine tumours [23–26], and craniopharyngiomas [8, 27]. To our knowledge, there is only one study describing FBC and serum inflammation-based scores in PA patients, comparing these with data from patients with craniopharyngiomas and Rathke's cleft cysts and healthy subjects; however, details on PA subtypes or their correlation with clinical features and outcomes were not assessed [8].

Identifying any of these pre-operative serum inflammation-based scores as predictors of invasiveness, challenging disease course and/or clinical outcomes in PA patients would provide added value to risk stratification and management algorithms for these patients. Hence, in this study, we aimed to characterise the FBC and serum inflammation-based scores in patients with PAs, as well as to investigate the applicability of such biochemical parameters in predicting

Table 1 Serum inflammation-based scores considered in this study and their association with clinical outcomes in cancer patients

Serum inflammation-based score	Abbreviation	Calculation formula/Score thresholds	Association with poorer clinical outcomes if
Glasgow Prognostic Score	GPS	Score of 0 if C-reactive protein $\leq$ 10 mg/dL and albumin $\geq$ 35 g/L Score of 1 if C-reactive protein > 10 mg/dL or albumin < 35 g/L Score of 2 if C-reactive protein > 10 mg/dL and albumin < 35 g/L	Higher score
Lymphocyte-to-Monocyte Ratio	LMR	Lymphocyte count: monocyte count	Decreased
Neutrophil-Platelet Score	NPS	Score 0 if neutrophils $\leq 7.5 \times 10^9$/L and platelets $\leq 400 \times 10^9$/L Score 1 if neutrophils $> 7.5 \times 10^9$/L or platelets $> 400 \times 10^9$/L Score 2 if neutrophils $> 7.5 \times 10^9$/L and platelets $> 400 \times 10^9$/L	Higher score
Neutrophil-to-Lymphocyte Ratio	NLR	Neutrophil count: lymphocyte count	Increased
Platelet-to-Lymphocyte Ratio	PLR	Platelet count: lymphocyte count	Increased
Prognostic Nutrition Index	PNI	Serum albumin (g/L) + (5 × lymphocyte count)	Decreased
Systemic Immune-Inflammation Index	SII	Platelet count x Neutrophil-to-Lymphocyte Ratio	Increased

invasive, challenging disease course or treatment refractory disease.

Materials and methods

Study population

Clinical records of 424 patients with PAs (68 prolactinomas, 72 acromegaly, 70 Cushing's disease, 208 non-functioning PAs (NFPAs) and 6 thyrotrophinomas) who underwent first operation at the Center for Endocrine Tumors at Leiden University Medical Center were retrospectively analysed. Patients who had first pituitary operation at our centre between 2006 and 2019 and with pre-operative FBC, differential leucocyte count, CRP and albumin data were included in our study (Supplementary Table 1). For the clinical and treatment outcome analyses only patients with a minimum of 1 year post-operative follow-up were considered. Patients with infection, malignancies, autoimmune, haematological conditions, serious cardiac, hepatic or renal disease, and patients on supraphysiological doses of glucocorticoids or on immunosuppressives at time of the pre-operative blood test were excluded. Data were obtained after waiver of medical ethical review approved by our institutional ethical board (G19.011).

Clinical and outcome data and study definitions

Patients' demographic, clinical, radiological, treatment and outcome data were retrieved from medical records. Based on their clinical and histological diagnoses, PA patients were grouped as follows: patients with acromegaly (GHomas), prolactinomas (PRLomas), clinically NFPAs, Cushing's disease (ACTHomas) and thyrotrophinomas (TSHomas). "Functioning non-Cushing PAs" subgroup included patients with GHomas, PRLomas and TSHomas. Invasiveness was evaluated using the Knosp classification [28], with grades 3 and 4 considered as presence of cavernous sinus invasion [28]. Hypopituitarism was defined as the presence of at least 1 pituitary deficiency documented biochemically through basal pituitary function tests, and when necessary dynamic tests were performed as appropriate [29]. The number of treatments corresponded to the number of individual treatments received (each medication, surgery and radiotherapy) including the first operation at our centre. Multimodal treatment was defined as the employment of 2 or more distinct forms of treatment in patient's management including the first operation at our centre. Multiple treatment was defined as the employment of 3 or more treatments received by the patient including the first operation at our centre. Re-operation subgroup involved patients who had at least 1 additional surgery following their first operation at our centre. Active disease at last follow-up was considered in case of persistent or recurrent progressive tumour remnants in both functioning PAs and NFPAs; small persistent tumour remnants after operation, stable over time and requiring no further intervention, were regarded as not active at last follow-up. For functioning PAs, biochemical remission at the last follow-up assessment was interpreted according to current guidelines: normalisation of IGF-I and nadir GH levels < 0.4 ng/L during oral glucose suppression test for acromegaly [30, 31], normalisation of prolactin (< 23.3 µg/L for women and < 15.2 µg/L for men) for prolactinoma patients [32, 33], and for Cushing's disease a post-operative cortisol < 50 nmol/L, a cortisol < 138 nmol/L measured 3 months after surgery, a normal 24 h-urinary free cortisol (UFC) on two consecutive samples and/or a 1 mg dexamethasone suppression to cortisol < 50 nmol/L, as clinically appropriate [34, 35]. The mean follow-up duration of our study was calculated from the date of the first pituitary operation at our centre until the last clinical follow-up observation.

The occurrence of apoplexy as well as the presence of large, compressive and invading tumours at the pre-operative evaluation, e.g. macroadenoma, visual field defects, suprasellar extension and cavernous sinus invasion, were regarded as potentially indicative of challenging disease course (i.e. PAs with challenging or more eventful disease course). During follow-up, the presence of tumour remnant, tumour regrowth or persistent hormone excess requiring any additional treatment after first operation at our centre, were regarded as suggestive of poorer clinical outcome and/or more refractory pituitary disease (i.e. PAs more difficult to treat).

Pre-operative biochemical data collection and serum inflammation-based scores definitions

Blood samples from each patient with confirmed diagnosis of a PA were taken before the first pituitary surgery at our centre, as part of the pre-operative work-up, which included also a baseline pituitary hormones assessment performed in our center. Serum FBC, albumin and CRP were performed in certified health service laboratories in a standardised manner on automated counters. From these retrospectively available pre-operative biochemical data, the following scores were calculated (Table 1): NLR by dividing the absolute neutrophil count by the absolute lymphocyte count; PLR by dividing the absolute platelet count by the absolute lymphocyte count; LMR by dividing the absolute lymphocyte count by the absolute monocyte count [5]; SII by multiplying the absolute platelet count and NLR [15]; NPS giving a score of 0 if neutrophils $\leq 7.5 \times 10^9$/L and platelets $\leq 400 \times 10^9$/L, a score of 1 if neutrophils $> 7.5 \times 10^9$/L or platelets $> 400 \times 10^9$/L, or a score of 2 if neutrophils $> 7.5 \times 10^9$/L and

platelets > 400×10^9/L [14]; PNI by applying the formula albumin level (g/L) + (5 × total lymphocyte count) [17]; and GPS giving a score of 0 if CRP ≤ 10 mg/dL and albumin ≥ 35 g/L, a score of 1 if CRP > 10 mg/dL or albumin < 35 g/L, and a score of 2 if CRP > 10 mg/dL and albumin < 35 g/L [7].

Statistical analysis

Data are presented as mean and standard deviation for continuous variables, and as absolute number or percentages for categorical variables. Qualitative variables were analysed with the χ^2 test to compare two or more groups. Quantitative or continuous variables were tested for Gaussian distribution with the Shapiro–Wilk test, and non-parametric and parametric data were further analysed with Mann–Whitney U and Student's T-tests, respectively. Correlations between continuous variables (r) were determined by Pearson correlation coefficient for two variables with normal distribution or Spearman's correlation coefficient for abnormally distributed variables. Logistic regression was performed to assess predictive performance of continuous variables on dichotomous outcomes, data shown as odds ratio (OR) with 95% confidence interval (95%CI). For variables that showed a significant predictive value (defined as P < 0.05), Receiver Operator Characteristics (ROC)-curves were prepared. The ROC analysis was used to evaluate a cut-off point for these predictive markers and to calculate the sensitivity and specificity of these cut-offs. An arbitrary optimal cut-off point was chosen with a high sensitivity and a specificity > 50%. To assess the effect of length of follow-up on outcomes, Cox-regression was performed, with data shown as hazard ratio (HR) with 95%CI. As length of follow-up and HRs differed between subgroups, the performance of the inflammation-based scores was only assess within these subgroups. Statistical analyses were carried out using the SPSS software version 20 (IBM, USA) and GraphPad version 6 (Prism, USA). The α for statistical significance was set at 0.05. Correction for multiple testing was applied using family-wise Benjamini–Hochberg procedure, with an accepted false discovery rate of 10%, which means we accept that 10% of reported significant associations are false-positive (data shown in Supplementary Table 2). Families of tests were based on performed statistical test and type of variables, e.g. all correlation analyses between inflammation-based scores and serum or urinary hormone levels. Because this is an exploratory study, all factors with a crude (i.e. before multiple testing correction) *p*-value < 0.05 are reported, so they may be explored in further cohorts. However, factors that lost significance after correction for multiple testing are marked with (ns), while those factors that remained significant are marked with an asterisk (*).

Results

General characterisation of pre-operative biochemical parameters and serum inflammation-based scores in patients with PAs

Pre-operative FBC data, albumin and CRP (when available) and the respective serum inflammation-based scores from our cohort of 424 patients with PAs are shown in Table 2, while patients' demographic, clinical and outcome data are presented in Supplementary Table 1. Sixty out of 68 prolactinoma patients received dopamine agonists at any point before the pituitary surgery, 13 of whom were refractory to this medical therapy, while 40 were intolerant for medication. Two prolactinoma patients suffered from apoplexy, 2 had a cerebrospinal fluid leak, 7 optic chiasm compression, 3 preferred surgical management and 1 patient underwent a biopsy. The mean follow-up duration of the whole cohort of PA patients was 5.0 ± 3.6 years, and longer (6.5 ± 4.2 years) for the subgroup of Cushing's disease (Supplementary Table 1). Hazard for recurrence and multimodal and multiple treatment were higher in prolactinoma, acromegaly and Cushing's disease as compared to NFPAs. Additionally, Cushing's disease patients had an increased hazard for additional surgery and radiotherapy (Supplementary Table 1).

In general, the different FBC parameters among PA patients were within the normal reference range, with only a few patients displaying thrombocytosis (0.6%), thrombocytopenia (3.0%) and leucopenia (2.1%). Leucocytosis was seen in 15.1% of cases (30 of 64 cases with leucocytosis had Cushing's disease), and a CRP > 10 mg/dL was observed in 11.5% of the patients (Table 2).

Pre-operative FBC data and serum inflammation-based scores among the different PA subtypes are shown in Figs. 1 and 2 (and in more detail in Supplementary Table 3). Cushing's disease patients had significantly higher leucocyte and neutrophil counts than other PA subtypes, and subsequently also higher NLR, SII and NPS (Figs. 1 and 2). Cushing's disease patients had higher platelet and monocyte counts than acromegaly (284.21 ± 81.71 vs 237.22 ± 63.90; p = 0.001*, and 0.77 ± 0.31 vs 0.48 ± 0.24; p = 0.001*) and higher monocyte counts than NFPA (0.58 ± 0.18; p < 0.001*) patients (Fig. 1). Apart from Cushing's disease, FBC parameters and serum inflammation-based scores did not differ among the other PA subtypes (Figs. 1 and 2).

Table 2 Pre-operative biochemical parameters and serum inflammation-based scores in the study population

	Whole cohort PA patients [n = 424]
Red cell count ($\times 10^{12}$/L) *(NR: M 4.5 -5.5; F 4.0–5.0)*	4.61 ± 0.43 *[n = 384]*
Platelet count ($\times 10^{9}$/L) *(NR: 150—450)*	258.58 ± 67.31 *[n = 361]*
White cell count ($\times 10^{9}$/L) *(NR: 4.5 – 10.0)*	7.76 ± 2.66 *[n = 424]*
Neutrophils ($\times 10^{9}$/L) *(NR: 1.5 – 7.5)*	5.36 ± 2.97 *[n = 147]*
Lymphocytes ($\times 10^{9}$/L) *(NR: 1.0 – 3.5)*	2.03 ± 0.73 *[n = 143]*
Monocytes ($\times 10^{9}$/L) *(NR: 0.1 – 1.0)*	0.62 ± 0.25 *[n = 143]*
Eosinophils ($\times 10^{9}$/L) *(NR: < 0.5)*	0.17 ± 0.23 *[n = 146]*
Basophils ($\times 10^{9}$/L) *(NR: < 0.2)*	0.04 ± 0.03 *[n = 143]*
NLR	3.05 ± 2.21 *[n = 143]*
LMR	3.82 ± 2.39 *[n = 143]*
PLR	137.37 ± 64.14 *[n = 140]*
Thrombocytosis ($> 450 \times 10^{9}$/L)	2 (0.6%) *[n = 361]*
Thrombocytopenia ($< 150 \times 10^{9}$/L)	11 (3.0%) *[n = 361]*
Leucocytosis ($> 10 \times 10^{9}$/L)	64 (15.1%) *[n = 423]*
Leucopenia ($< 4 \times 10^{9}$/L)	9 (2.1%) *[n = 423]*
SII	769.11 ± 601.53 *[n = 140]*
NPS score 0	237 (86.5%)
Score 1	35 (12.8%)
Score 2	2 (0.7%) *[n = 274]*
C-reactive protein < 5 mg/dL 5-10 mg/dL > 10 mg/dL	134 (70.2%) 35 (18.3%) 22 (11.5%) *[n = 191]*
Elevated C-reactive protein (> 10 mg/dL)	22 (11.5%) *[n = 191]*
Albumin < 40 g/L	27 (13.8%) *[n = 196]*
GPS score 0	118 (84.9%)
score 1	20 (14.4%)
score 2	1 (0.7%) *[n = 139]*
PNI	51.54 ± 10.82 *[n = 103]*

Data from continuous variables for pre-operative biochemical parameters and serum inflammation-based scores are shown for the whole cohort of PA patients as a mean ± standard deviation, while categorical data as n (%). *F* females, *GPS* Glasgow Prognostic Score, *LMR* lymphocyte-to-monocyte ratio, *M* males, *NLR* neutrophil-to-lymphocyte ratio, *NPS* Neutrophil-Platelet Score, *NR* normal range, *ns* non-significant, *PA* pituitary adenoma, *PLR* platelet-to-lymphocyte ratio, *PNI* Prognostic Nutrition Index, *SII* Systemic Immune-Inflammation Index

Serum inflammation-based scores and their correlation with the extent of pre-operative pituitary hormone excess in patients with functioning PAs

Within Cushing's disease cohort, there was a negative correlation between 24 h-UFC levels and eosinophil (r = − 0.574; p < 0.001*) counts. There was a crude negative correlation between 24 h-UFC and platelet (r = -0.362; p = 0.006 (ns)) and basophil (r = − 0.425; p = 0.006 (ns)) counts (Fig. 3 and Supplementary Table 4). In addition, 24 h-UFC levels had a crude positive association with elevated CRP and GPS, and Cushing's disease patients with GPS ≥ 1 also had a crude positive association with ACTH levels (p = 0.014 (ns)) (Fig. 4). In patients with an elevated CRP (> 10 mg/dL) random serum cortisol was higher than in patients with CRP < 5 mg/dL and than those with CRP comprised between 5 and 10 mg/dL (0.997 ± 0.367 vs 0.641 ± 0.195 µmol/L; p = 0.006*, and 0.997 ± 0.367 vs 0.681 ± 0.278 µmol/L; p = 0.050*, respectively). Finally, there was a crude positive correlation between leucocyte counts and random serum cortisol (r = 0.244; p = 0.047 (ns)) (Fig. 3).

Among acromegaly patients, a crude negative correlation between platelet count and IGF-1 xULN (r = -0.280; p = 0.033 (ns)) (Fig. 3) was observed, while in prolactinoma patients there was no correlation between serum prolactin and pre-operative FBC or serum inflammation-based scores (Supplementary Table 4). There were no associations between prolactin and GH or IGF-1 levels and elevated CRP, GPS or NPS among acromegaly or prolactinoma patients (data not shown).

Pre-operative serum inflammation-based scores and their relation with clinical features at presentation and follow-up and outcomes in patients with PAs

Functioning non-Cushing PAs (prolactinoma, acromegaly and thyrotrophinoma)

Functioning non-Cushing PA patients with pre-operative GPS ≥ 1 had a crude association with higher rates of pre-operative hypopituitarism (25.0% vs 3.8%; p = 0.048 (ns)) and suprasellar extension (25.0% vs 4.0%; p = 0.048 (ns)) than those with GPS = 0. Pre-operative NPS ≥ 1 had a crude association with higher rates of suprasellar extension (14.8% vs 2.9%; p = 0.028 (ns)), and lower PLR in patients with functioning non-Cushing macroadenomas (p = 0.039 (ns)) (Fig. 5-A and Supplementary Table 5).

Functioning non-Cushing PA females had significantly lower platelet count and higher red cell and leucocyte counts than males (Supplementary Table 5). However, the distribution of males and females did not differ within the

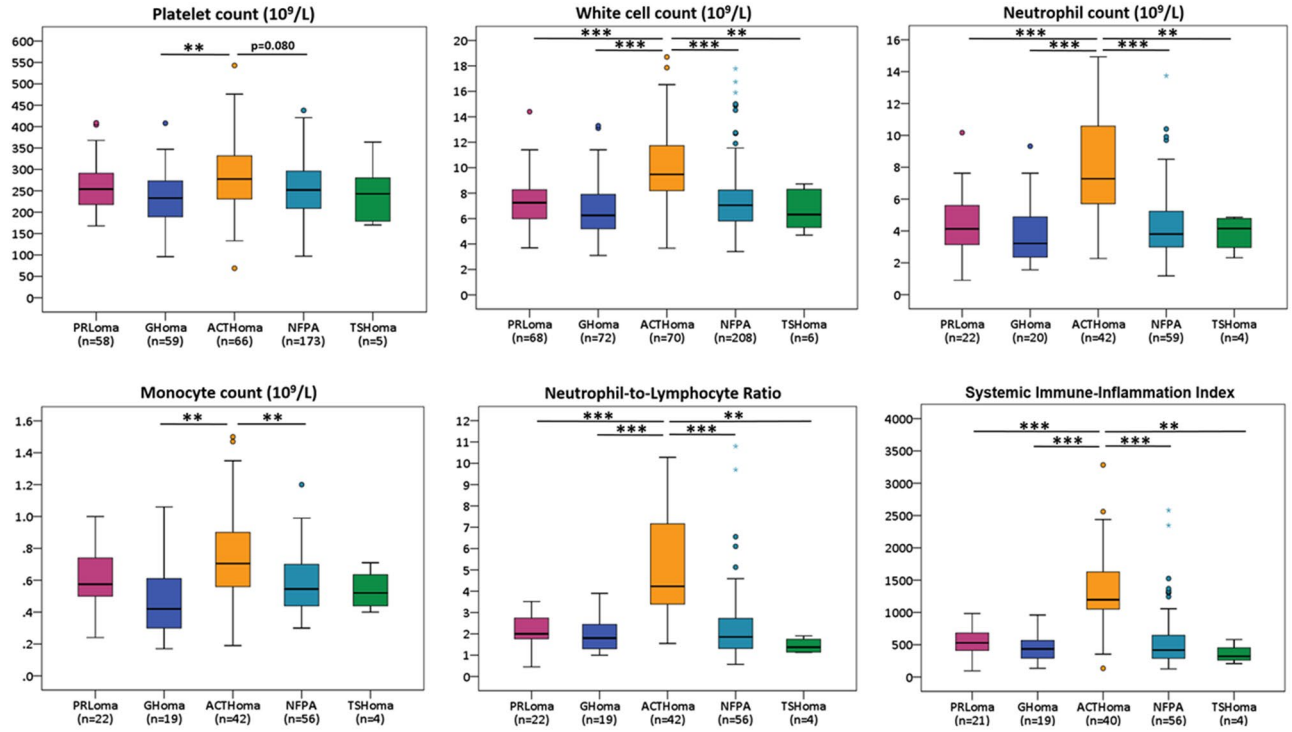


Fig. 1 Continuous pre-operative biochemical parameters and serum inflammation-based scores in patients with different subtypes of pituitary adenomas. Data are shown as mean ± standard deviation for the biochemical parameters that showed crude significant differences, which also remained significant after Benjamini–Hochberg correction. *, < 0.05, **, < 0.01, ***, < 0.001 (One-way ANOVA test with post-hoc Bonferroni multiple comparison test). *ACTHoma* Cushing's disease, *GHoma* acromegaly, *NFPA* non-functioning pituitary adenoma, *PRLoma* prolactinoma, *TSHoma* thyrotrophinoma

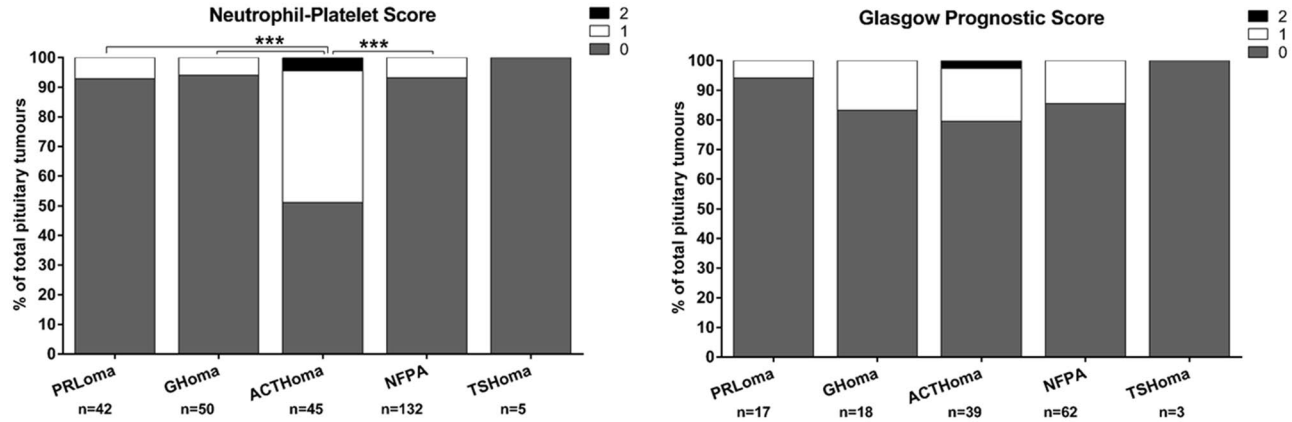


Fig. 2 Categorical serum inflammation-based scores in patients with different subtypes of pituitary adenomas. Data are shown as percentage of total pituitary adenomas within each subtype and per categorical biochemical variable. The crude statistical differences observed regarding the Neutrophil-Platelet Score remained significant after Benjamini–Hochberg. ***, < 0.001 (Chi-squared test with post-hoc multiple comparison tests). *ACTHoma* Cushing's disease, *GHoma* acromegaly, *NFPA* non-functioning pituitary adenoma, *PRLoma* prolactinoma, *TSHoma* thyrotrophinoma

functioning non-Cushing PAs subgroup as well as within prolactinoma, acromegaly and thyrotrophinoma subgroups (Supplementary Table 1), therefore excluding a gender-related effect on the observed associations.

PNI seemed to be lower in functioning non-Cushing PA patients who required multiple treatments (35.85 ± 23.10 vs 55.42 ± 5.07; p = 0.048 (ns)) including post-operative radiotherapy (39.68 ± 20.58 vs 54.08 ± 9.71; p = 0.024 (ns)) (Fig. 5-A and Supplementary Table 6).

Cushing's disease Cushing's disease patients with tumours invading the cavernous sinus had lower platelet counts (233.30 ± 46.19 vs 293.30 ± 83.58; p = 0.012 (ns)) (Fig. 5b and Supplementary Table 5).

Cushing's disease patients who required multimodal treatment had a lower platelet count (242.14 ± 50.00 vs 304.03 ± 86.54; p = 0.001*). Pre-operative lower platelet count was also observed in Cushing's disease patients who had multiple treatments (239.81 ± 49.94 vs 296.07 ± 84.51; p = 0.006 (ns)), including post-operative medical therapy (245.50 ± 54.85 vs 297.14 ± 83.77; p = 0.031 (ns)), radiotherapy (249.53 ± 41.75 vs 291.37 ± 87.70; p = 0.032 (ns)) (Fig. 5-B and Supplementary Table 6).

None of the studied serum inflammation-based scores correlated with clinico-pathological features or outcomes in patients with Cushing's disease (Supplementary Tables 5 and 6).

NFPAs NFPA patients who suffered apoplexy more often had a GPS ≥ 1 (40.0% vs 6.4%; p = 0.001*), and showed a crude association with more neutrophils (6.17 ± 3.23 vs 3.94 ± 1.70; p = 0.004 (ns)), monocytes (0.70 ± 0.19 vs 0.54 ± 0.16; p = 0.005 (ns)), leucocytes (8.65 ± 3.30 vs 7.22 ± 2.14; p = 0.013 (ns)) and elevated CRP (30.4% vs 8.5%; p = 0.008 (ns)) (Fig. 6 and Supplementary Table 5). NFPA patients with visual field defects at presentation showed a crude association with lower lymphocyte count (2.02 ± 0.80 vs 2.90 ± 0.39; p = 0.014 (ns)), higher NLR (2.61 ± 2.11 vs 1.20 ± 0.30; p = 0.024 (ns)) and lower LMR (3.84 ± 1.87 vs 5.45 ± 1.09; p = 0.031 (ns)) (Fig. 6 and Supplementary Table 5).

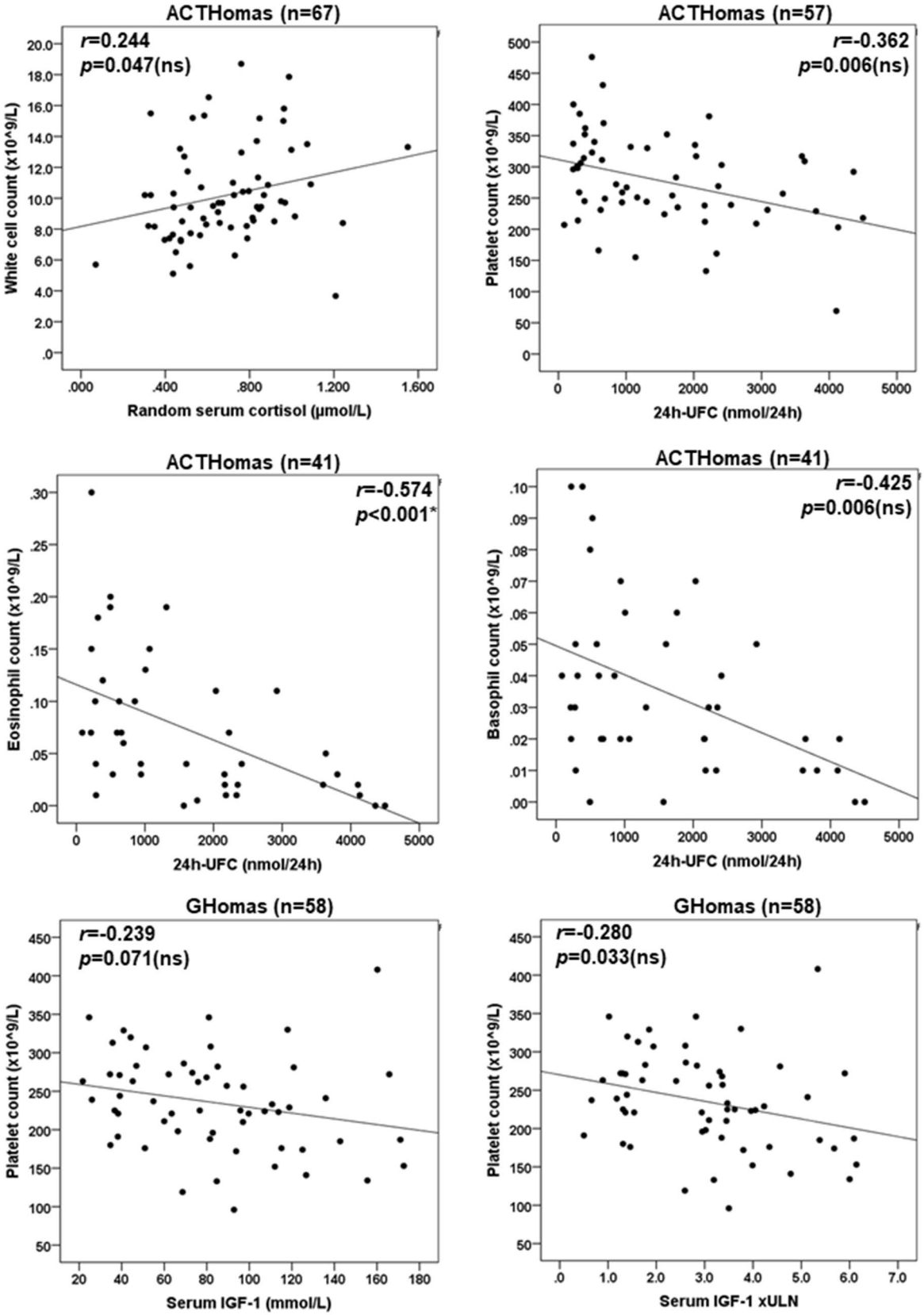
NFPA patients with a tumour remnant within 1-year after operation had fewer lymphocytes (1.83 ± 0.57 vs 2.58 ± 0.75; p < 0.001*), and a crude association with fewer leucocytes (6.90 ± 2.16 vs 7.68 ± 2.42; p = 0.010 (ns)) and higher PLR (131.07 ± 45.65 vs 109.33 ± 64.70; p = 0.021 (ns)). Patients who were reoperated had a crude association with fewer leucocytes (6.29 ± 2.27 vs 7.48 ± 2.42; p = 0.029 (ns)), lymphocytes (1.46 ± 0.36 vs 2.26 ± 0.74; p = 0.005 (ns)) and higher NLR (3.15 ± 0.96 vs 2.15 ± 1.34; p = 0.017 (ns)) than those requiring no further surgeries. NFPAs managed with multiple treatments had a crude association with lower lymphocyte count (1.56 ± 0.40 vs 2.21 ± 0.76; p = 0.047 (ns)) and higher NLR (3.12 ± 0.99 vs 2.20 ± 1.34; p = 0.049 (ns)), and NFPA patients with active disease at last follow-up with lower PNI (25.88 ± 22.32 vs 54.69 ± 6.10; p = 0.021 (ns)) (Fig. 6 and Supplementary Table 6).

Assessment of the diagnosis efficacy and usefulness of pre-operative biochemical parameters and inflammation-based scores in predicting challenging disease course

The value of pre-operative biochemical parameters and serum inflammation-based scores in predicting challenging disease course in patients with PAs were tested within each PA subgroup for those parameters with significant associations or trends with clinical features and outcomes. Platelet count showed the highest accuracy and was the best biochemical tool in predicting refractory disease in patients with Cushing's disease. Univariate logistic regression showed an OR of 0.987 (95%CI: 0.978–0.997; p = 0.008*) for multimodal treatment, and an OR of 0.989 (95%CI: 0.980–0.998; p = 0.023*) for multiple treatment per 1×10^9 platelets. ROC-analysis showed an AUC of 0.758 (95%CI: 0.634–0.882) for multimodal treatment and an AUC of 0.735 (95%CI: 0.604–0.867) for multiple treatment, with an optimal platelet cut-off of 299.5×10^9/L for both. This cut-off of 299.5×10^9 corresponded with a 90.9% sensitivity (95%CI: 74.5–98.4%) and a 58.3% specificity (95%CI: 42.1–73.4%) in predicting multimodal treatment in Cushing's disease (Fig. 7a), and with a 93.8% sensitivity and a 52.4% specificity in predicting multiple treatment in Cushing's disease (Fig. 7b). No other specific cut-offs regarding other biochemical parameters were identified as useful or reliable in predicting invasive or refractory disease in the different PA subtypes (data not shown).

Discussion

FBC data and serum inflammation-based scores are widely used in cancer to predict outcomes and prognosis [5, 9, 10, 12, 13, 16], including in endocrine neoplasms [8, 21–27]; however, up until this study, there were no data in PAs. In this study, we characterised the FBC, CRP, albumin and several serum inflammation-based scores in patients with PAs, and we investigated the usefulness of such parameters in predicting challenging disease course or refractory disease


ACTHomas (n=67)
r=0.244
p=0.047(ns)
White cell count (x10^9/L)
Random serum cortisol (µmol/L)
ACTHomas (n=57)
r=-0.362
p=0.006(ns)
Platelet count (x10^9/L)
24h-UFC (nmol/24h)
ACTHomas (n=41)
r=-0.574
p<0.001*
Eosinophil count (x10^9/L)
24h-UFC (nmol/24h)
ACTHomas (n=41)
r=-0.425
p=0.006(ns)
Basophil count (x10^9/L)
24h-UFC (nmol/24h)
GHomas (n=58)
r=-0.239
p=0.071(ns)
Platelet count (x10^9/L)
Serum IGF-1 (mmol/L)
GHomas (n=58)
r=-0.280
p=0.033(ns)
Platelet count (x10^9/L)
Serum IGF-1 xULN

◂**Fig. 3** Correlation between biochemical parameters and inflammation-based scores and serum pituitary hormone levels within the different hormone-secreting pituitary adenoma subtypes. Data are shown for correlations where a crude significant correlation was observed before correction; significant correlations after correction with Benjamini–Hochberg procedure are marked with an asterisk (*) while correlations that lost significance after correction are marked with (ns). *P*-values were determined by the Spearman's correlation coefficient for variables without normal distribution and with Pearson correlation coefficient for correlations between two normally distributed variables. *ACTHomas* Cushing's disease, *GHomas* acromegaly, *IGF-1* insulin-like growth factor 1, *ns* non-significant after correction, *UFC* urinary free cortisol, *ULN* upper limit of the normal range

aiming to provide advances in risk stratification and management of PA patients.

In our cohort of PA patients, FBC parameters were overall within normal range and the inflammation-based scores were rather unimpressive, with mean NLR and PLR being relatively low compared to those usually seen in highly malignant neoplasms [5, 12, 13], where NLR > 5 (> 4 in craniopharyngiomas [27]) and PLR > 300 are frequent and indicative of poor prognosis [5, 16]. On the other hand, the mean LMR in our PA cohort (3.82) was relatively high when compared to other neoplasms, where LMR < 2.18–2.71 indicate aggressive disease and poor outcomes [12, 36]. The proportion of PA patients with GPS ≥ 1 we observed (15.1%) was in general lower to what is often described in other cancers [7]. Chen et al. observed more leucocytes, lymphocytes and platelets as well as higher LMR and PNI in craniopharyngioma patients in comparison to PA patients with no differences regarding NLR or PLR individually, however the combinations NLR + PLR and dNLR + PLR were able to differentially diagnose papillary craniopharyngiomas, PAs and Rathke's cleft cysts [8]. Overall, these data are not surprising considering that PAs are usually benign and lack metastatic properties, and despite the fact that pituitary tumour cells secrete factors such as cytokines and growth factors [4, 37] their release into the circulation and/or systemic repercussions may be less prominent than in other malignancies [5, 12, 13], or even than in craniopharyngiomas [8]. Nevertheless, the systemic inflammation appears to be higher in PA patients than healthy individuals, as suggested by the observations of higher NLR, lower PNI, more leucocytes, neutrophils, monocytes, and fewer platelets in PA patients in comparison to healthy controls [8].

PA secretome also includes hormones which are released in the circulation and may remarkably influence the haematopoiesis and circulating immune cells, as well as the degree of systemic inflammation (Fig. 8). This is well-known for Cushing's disease, in which excessive glucocorticoid levels increase leucocyte and neutrophil counts [38, 39]. In fact, about 40–52% of Cushing's disease patients present with leucocytosis (42.9% in our cohort), and in most cases (including those with normal baseline counts) the leucocyte and neutrophil counts decrease 20–30% after treatment, demonstrating the direct effect of hypercortisolism on these blood cells [38, 39]. We also observed higher platelet count in Cushing's disease patients compared to other subtypes, particularly than acromegaly and NFPA patients. The effect of hypercortisolism on coagulation results in a hypercoagulability state in Cushing's syndrome [40], as excessive glucocorticoid levels increase several plasma clotting factors and lead to defective fibrinolysis [41, 42]. The effects of cortisol on platelet count and function are less known, but higher numbers of platelets in patients with Cushing's syndrome than in obese non-Cushingoid [43] and than in healthy controls [44] have been reported. Additionally, oxidative injury and platelet aggregation were enhanced in Cushing's syndrome [45–47], processes that may further contribute to hypercoagulability, thromboembolic events, and cardiovascular disease recognised in this condition [41, 42]. When compared to other subtypes, our Cushing's disease cohort had the highest absolute monocyte count and the lowest eosinophil count, consistent with previous reports [38, 48]. Cushing's disease patients also had the lowest lymphocyte count (non-significant) and their serum inflammation-based scores differed from other subtypes, particularly those incorporating leucocyte and neutrophil counts (NLR, NPS and SII, all higher in Cushing's disease), which is consistent with the Cushing's disease-related inflammation and immunosuppression [49].

The extent of glucocorticoid excess appears to influence, at least in part, the degree of systemic inflammation in Cushing's disease, as we noted a crude positive correlation between leucocytes and serum cortisol and ACTH levels; 24 h-UFC negatively correlated with eosinophil, platelet and basophil counts, and was higher in patients with elevated CRP and GPS. Other studies failed to find an association between pre-treatment leucocyte counts and UFC or other parameters of hypothalamic–pituitary–adrenal axis activity [38, 39]. However, Masri-Iraqi et al. reported a positive correlation between decrease in UFC and reduction in leucocyte counts following treatment for Cushing's disease [39]. In another study, CRP did not differ between Cushing's syndrome patients and healthy controls, however, interleukin-6 and soluble tumour necrosis factor-α receptor were more elevated in Cushing's syndrome [49]. To determine whether our findings are purely due to hormone excess and its extent, a comparison between patients with Cushing's syndrome of pituitary versus adrenal origin could be performed in future studies.

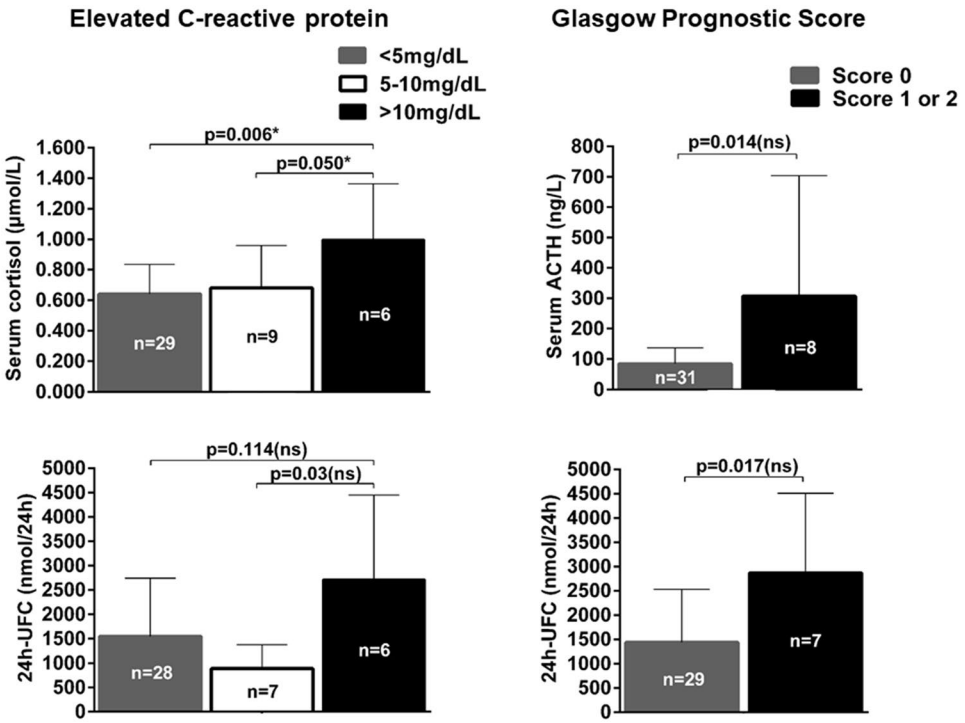


Fig. 4 Categorical biochemical parameters and inflammation-based scores and degree of hormone excess within patients with Cushing's disease. Data are shown for the correlations within the subgroup of Cushing's disease where a crude significant association was observed prior to correction with Benjamini–Hochberg method; significant factors after correction are marked with an asterisk (*), and comparisons where significance was lost after correction are marked with (ns). *ACTH* adrenocorticotropic hormone, *ns* non-significant, *UFC* urinary free cortisol

Excessive levels of GH/IGF-1 or prolactin in acromegaly and prolactinoma patients do not seem to have similar effects as to those observed for glucocorticoid excess in Cushing's disease, considering that FBC parameters and inflammation-based scores did not differ among other non-Cushing PA subtypes. Moreover, there were no correlations between GH, IGF-1 or prolactin and FBC parameters neither with serum inflammation-based scores among acromegaly or prolactinoma patients, except the negative crude correlation between IGF-1 and platelets in acromegaly, which was somewhat unexpected considering the thrombopoietic effects of GH [50]. Despite the fact that GH/IGF-1 or prolactin can influence haematopoiesis [51–53], these pituitary hormones may not be crucial for haematopoiesis, at least in comparison to other conventional immune-stimulating cytokines and myeloid factors [53–55]. Hence, our data suggest that PA-related hormone status may not be relevant in determining the haematopoiesis and systemic inflammation in patients with functioning non-Cushing PAs.

On the other hand, pituitary hormone deficiencies may not be significant in determining the haematopoiesis or the degree of systemic inflammation in PA patients, as we found no statistical associations between the presence of pre-operative hypopituitarism and the different FBC and serum inflammation-based scores, except within functioning non-Cushing PA patients in whom a GPS ≥ 1 had a crude association with higher rates of pre-operative hypopituitarism.

Our exploratory study suggests that some FBC parameters and serum inflammation-based scores may have a role in predicting invasive or refractory disease depending on the PA subtype (Fig. 8). GPS, NPS and PNI may be relevant for the subgroup of functioning non-Cushing PAs, but no value was noted for individual FBC elements. Consistently, Tam et al. reported no differences regarding leucocyte and platelet counts between prolactinoma patients and healthy controls, neither before or 6 months after cabergoline treatment among prolactinoma patients [56]. However, in our Cushing's disease cohort, the pre-operative platelet count emerged as the most relevant biochemical parameter in predicting refractory disease, with an optimal cut-off of 299.5×10^9/L below which multimodal treatment is more likely required. In our Cushing's disease cohort, lower platelet counts were noted for patients with invasive and multi-treated tumours, however thrombocytopenia was in general uncommon (only 3%). In cancer, platelet counts are often decreased as a result of thrombopoiesis impairment, platelet consumption or platelet aggregation [57]. Low platelet counts, regarded as "sentinels" of the tumour disease state, have been associated with more aggressive

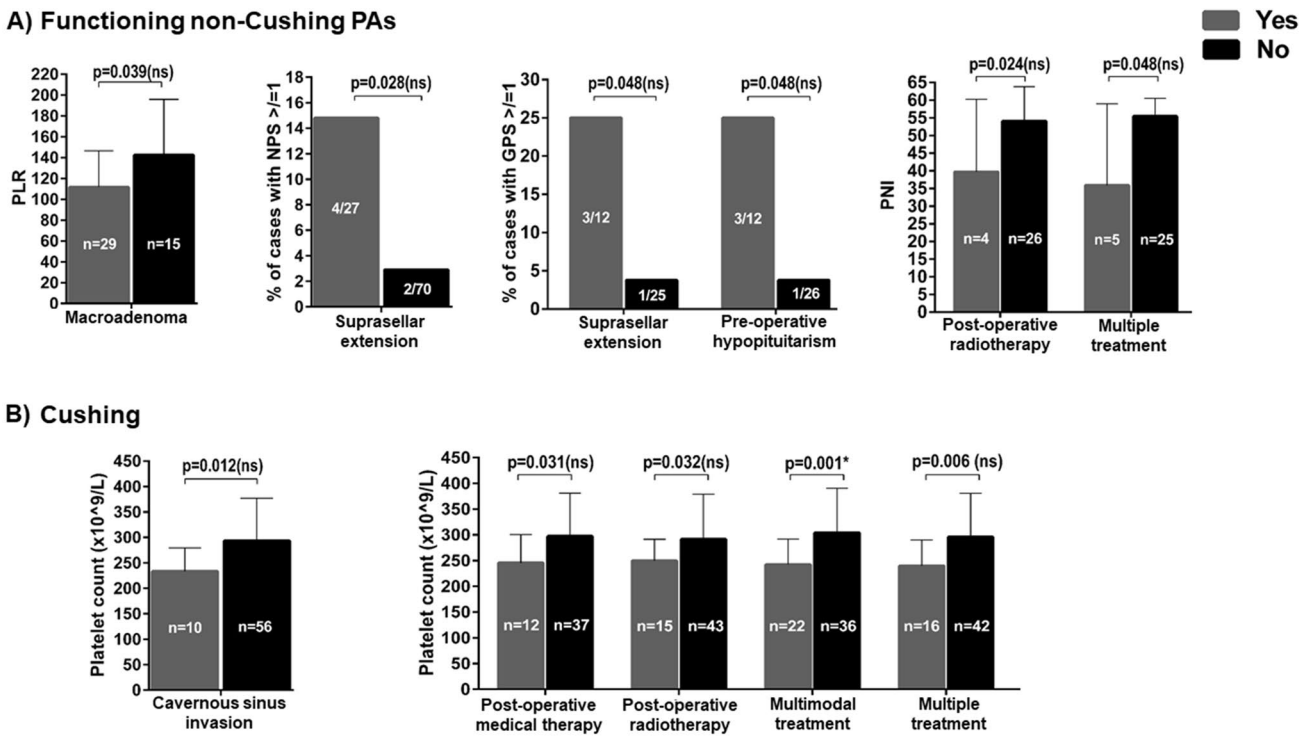
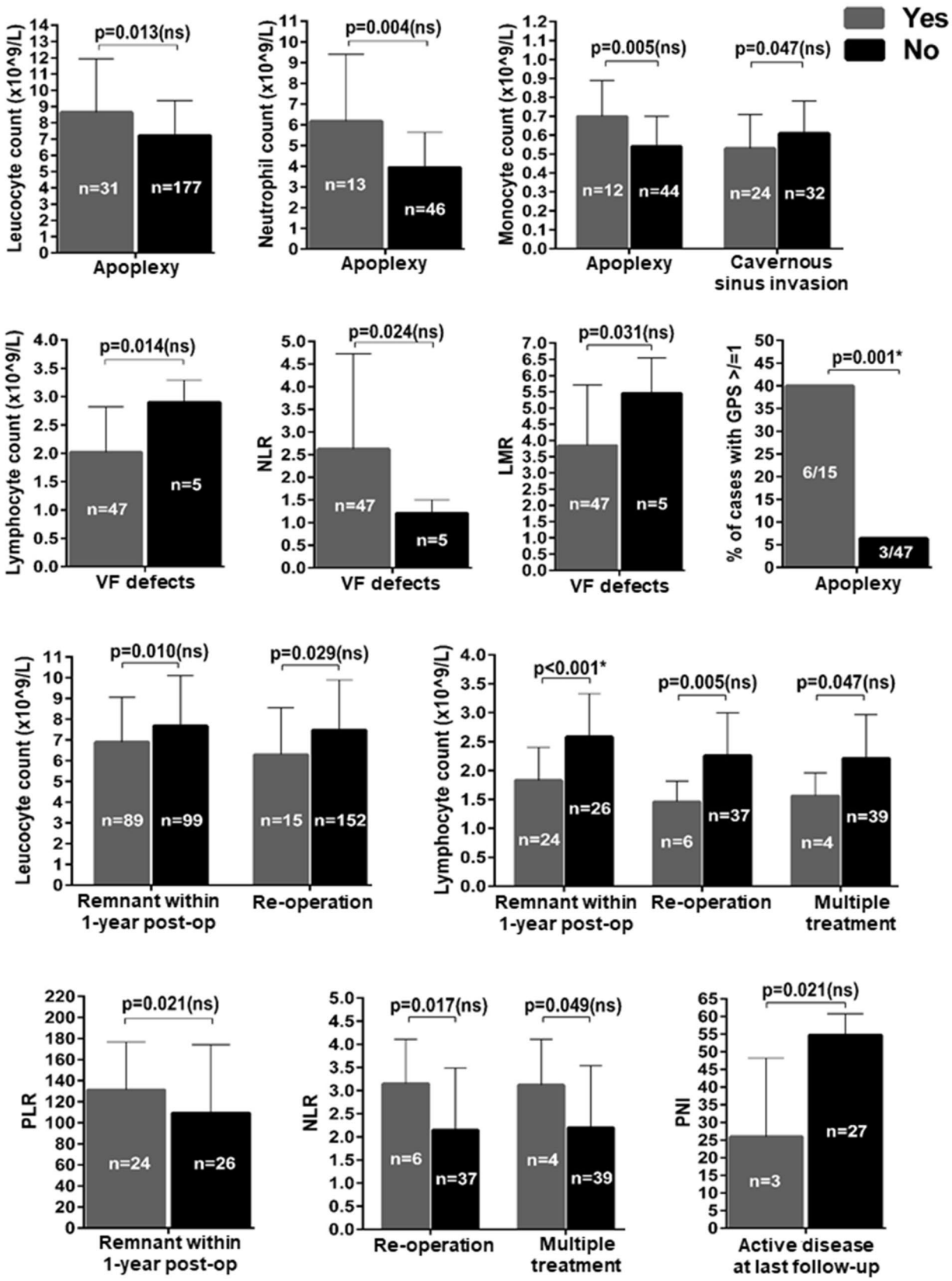


Fig. 5 Significant associations between biochemical parameters and serum inflammation-based scores data and clinical features and outcomes within functioning non-Cushing pituitary adenomas (**a**) and Cushing's disease (**b**). For a certain clinical feature or outcome, the presence/absence are depicted in grey (for Yes) and in black (for No), respectively. In the bars is represented the number of cases with presence or absence of a certain feature or outcome versus the total number of cases with available data for categorical biochemical data, or simply the number of cases with available data for continuous biochemical data. Data are shown as percentage of cases with GPS ≥ 1 and NPS ≥ 1 regarding different clinical features. Continuous biochemical parameters/scores data are shown as mean ± standard deviation. Chi-squared and Mann Whitney U test were used as appropriate, and significant crude *p*-values (< 0.05) are shown. Significant factors after Benjamini–Hochberg correction are marked with an asterisk (*), and comparisons where significance was lost after correction are marked with (ns). *GPS* Glasgow Prognostic Score, *NPS* Neutrophil-Platelet Score, *ns* non-significant, *PA* pituitary adenoma, *PLR* Platelet-to-Lymphocyte Ratio, *PNI* Prognostic Nutrition Index

disease and worse outcomes [58], including bleeding or thrombotic events [59], however, to our knowledge, this has not been shown in Cushing's disease. We found no association between leucocytes or neutrophil counts, or related inflammation-based scores, and features suggestive of invasive or refractory Cushing's disease. These data suggest that leucocytosis and neutrophilia are probably a direct consequence of hypercortisolism but do not necessarily imply deleterious systemic inflammation or poorer outcomes in Cushing's disease, despite the fact that leucocytes and NLR may be valuable in predicting outcomes in non-neoplastic cardiometabolic diseases [60, 61].

Regarding NFPAs, patients with more treatment refractory disease had fewer leucocytes and lymphocytes, higher NLR and PLR, and lower PNI pre-operatively. From a clinical perspective, the identification of such biochemical parameters in predicting challenging disease course may be relevant for decision-making and management of NFPA patients, and our observations here reported require confirmation in other cohorts. As this study included only NFPA patients who underwent surgery, our findings should be validated in a series involving NFPAs who had either surgery or only surveillance aiming to assess whether there is a value for leucocyte count (or any other parameter) in predicting which NFPAs will grow or require surgery, and thus contribute for the decision of advising early operation (or monitor instead) in NFPAs with no or borderline indication for surgery when first presented. More leucocytes, neutrophils, monocytes, as well as fewer lymphocytes, GPS ≥ 1 and higher NLR, and CRP levels were observed in NFPA patients who suffered apoplexy, which might be a consequence of the local inflammation, haemorrhage or infarction


Yes
No
Leucocyte count (x10^9/L)
p=0.013(ns)
n=31
n=177
Apoplexy
Neutrophil count (x10^9/L)
p=0.004(ns)
n=13
n=46
Apoplexy
Monocyte count (x10^9/L)
p=0.005(ns)
p=0.047(ns)
n=12
n=44
n=24
n=32
Apoplexy
Cavernous sinus invasion
Lymphocyte count (x10^9/L)
p=0.014(ns)
n=47
n=5
VF defects
NLR
p=0.024(ns)
n=47
n=5
VF defects
LMR
p=0.031(ns)
n=47
n=5
VF defects
% of cases with GPS >/=1
p=0.001*
6/15
3/47
Apoplexy
Leucocyte count (x10^9/L)
p=0.010(ns)
p=0.029(ns)
n=89
n=99
n=15
n=152
Remnant within 1-year post-op
Re-operation
Lymphocyte count (x10^9/L)
p<0.001*
p=0.005(ns)
p=0.047(ns)
n=24
n=26
n=6
n=37
n=4
n=39
Remnant within 1-year post-op
Re-operation
Multiple treatment
PLR
p=0.021(ns)
n=24
n=26
Remnant within 1-year post-op
NLR
p=0.017(ns)
p=0.049(ns)
n=6
n=37
n=4
n=39
Re-operation
Multiple treatment
PNI
p=0.021(ns)
n=3
n=27
Active disease at last follow-up

◂**Fig. 6** Significant associations between biochemical parameters and serum inflammation-based scores data and clinical features and clinical outcomes within non-functioning pituitary adenomas. For a certain clinical feature or clinical outcome, the presence/absence are depicted in grey (for Yes) and in black (for No), respectively. In the bars is represented the number of cases with presence or absence of a certain feature or outcome versus the total number of cases with available data for categorical biochemical data, or simply the number of cases with available data for continuous biochemical data. Continuous biochemical parameters/scores data are shown as mean ± standard deviation. Mann Whitney U tests were used as appropriate, and significant crude *p*-values (<0.05) are shown. Significant factors after Benjamini–Hochberg correction are marked with an asterisk (*), and comparisons where significance was lost after correction are marked with (ns). *NLR* Neutrophil-to-Lymphocyte Ratio, *ns* non-significant, *PLR* Platelet-to-Lymphocyte Ratio, *PNI* Prognostic Nutrition Index, *post-op* post-operatively, *VF* visual fields

within the tumoural tissue, and/or a result of the patient being clinically unwell or critically unstable during an apoplexy episode [62], rather than depending on the PA characteristics or predicting clinical outcomes per se.

As this is the first study investigating the role of FBC and serum inflammation-based scores in patients with PAs, we explored several biochemical parameters and clinical/outcome variables. This inexorably resulted in a high amount of analyses, which makes our study very comprehensive and exploratory in nature, but also constitutes a limitation on its own. Therefore, to minimise the type I-errors associated with multiple testing, we applied Benjamini–Hochberg correction when reporting on significance (shown in Supplementary Table 2). As this is an exploratory study, we reported crude *p*-values up to 0.05 before correction worth being investigated in future studies. Another limitation of our study is that we have relatively small number of cases with available clinical and biochemical data for some subgroups, as some patients had missing clinical and/or biochemical data. In fact, this relatively small size of some subgroups limited the assessment of some serum inflammation-based scores we studied, and provides insufficient statistical power to detect significant differences after correction, particularly if we take into consideration that such biochemical parameters have substantial inter- and intra-individual variability. Hence, some of our negative findings may not reflect the lack of association but instead insufficient sample size for some comparative subanalyses performed. Thus, the positive and negative data from our exploratory study require further validation in larger series. Other limitations of our study include: i) single-centre study, mainly including a population of Dutch patients, hence limiting the generalizability of our findings to other populations or ethnicities; ii) retrospective study, iii) absence of healthy controls as comparator or other specific subgroups of (ultra-rare) cases, such as pituitary carcinomas; iv) our cohort does not reflect the usual prevalence distribution of the different PA subtypes, particularly the hyperfunctioning ones, due to its surgical nature; v) we cannot exclude that some patients would have unknown/unreported concomitant diseases capable of influencing haematopoiesis or systemic inflammation; vi) the specific effects of the hormonal excess (or the pre-operative medical therapies) in each serum inflammation-based score per PA subtype were not comprehensively assessed in our study, as the serum inflammation-based scores calculation and their usefulness were considered before the first operation at our centre, and not by the time of the PA diagnosis or prior any

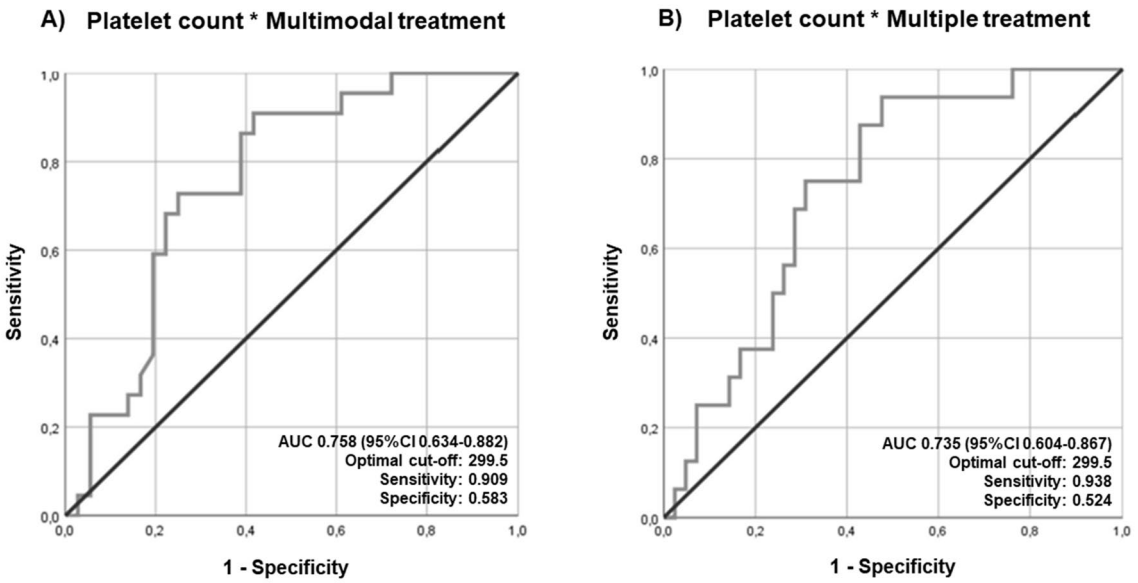


Fig. 7 Receiver operator characteristics curve of platelet count to predict need for multimodal treatment (**a**) and multiple treatment (**b**) in patients with Cushing's disease. *AUC* area under the curve, *CI* confidence interval

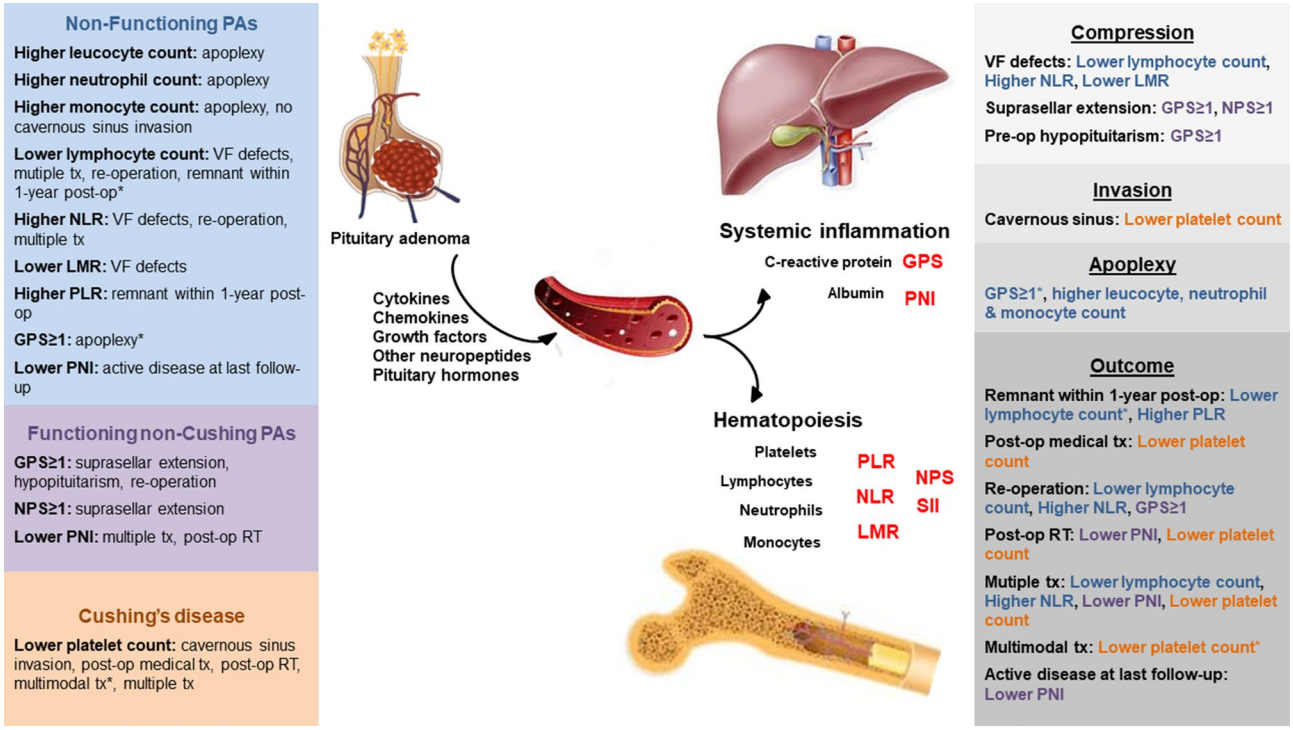


Fig. 8 Overview of the interactions between pituitary tumour secreted factors and biological processes such as haematopoiesis and systemic inflammation, determining challenging disease course and clinical outcomes in patients with pituitary adenomas. Cytokines, chemokines, growth factors, hormones and other neuropeptides are secreted by a PA into the circulation, where they exert systemic effects such as modulation of haematopoiesis or systemic inflammation by altering the liver production of acute-phase proteins such as C-reactive protein or albumin. Relevant biochemical parameters and serum inflammation-based scores that showed a crude association (crude p-value < 0.05) with clinical features and outcomes within the subgroups of functioning non-Cushing PAs, Cushing's disease and non-functioning PAs are shown in the colour boxes in the left side of the figure. In the right side is shown the clinical features at presentation and outcomes that were found significantly associated to biochemical full or serum inflammation-based scores, coloured as the respective PA subgroup where such significance was observed (blue corresponding to non-functioning PAs; purple corresponding to functioning non-Cushing PAs; and orange corresponding to Cushing's disease). *denotes the parameters that remained significantly different after correction with Benjamini–Hochberg method (corrected p-value < 0.05). *GPS* Glasgow Prognostic Score, *LMR* lymphocyte-to-monocyte ratio, *NLR* neutrophil-to-lymphocyte ratio, *NPS* neutrophil-platelet score, *PA* pituitary adenoma, *PLR* platelet-to-lymphocyte ratio, *PNI* Prognostic Nutrition Index, *post-op* post-operatively, *RT* radiotherapy, *SII* Systemic Immune-Inflammation Index, *tx* treatment, *VF* visual fields

therapeutical intervention. Worth noting that most studies regarding serum inflammation-based scores have been conducted in aggressive cancers, hence clinical outcomes such as overall survival, progression-free survival and mortality rates are often reported in those studies, making difficult to contrast our results with those reported in the literature as such clinical variables are not applicable to a cohort of patients with benign and often non-aggressive PAs.

Conclusions

FBC and serum inflammation-based scores remarkably differ in Cushing's disease comparing to other PA subtypes. The extent of pituitary hormone excess may influence, at least in part, the systemic inflammation in Cushing's disease. Platelet count below 299.5×10^9/L predicts multimodal treatment in patients with Cushing's disease. Some serum inflammation-based scores may have a role in predicting invasive, challenging disease course or treatment refractory disease, namely GPS and PNI in NFPAs and functioning non-Cushing PAs; NPS in functioning non-Cushing PAs; NLR or PLR in NFPAs. Further studies involving larger cohorts of patients are needed to confirm some of the observations from our exploratory study.

Author contributions PM and FdV designed and performed the study, collected and analysed the data and wrote the manuscript; OMD helped with the statistical analysis and provided critical input to the design of the study; WRvF, MK and NRB provided critical input; AMP designed the study, provided critical input and wrote the manuscript.

Funding P.M. was supported by the Fellowship Program Grant ´3E´, the Exchange in Endocrinology Expertise, Board of Endocrinology of the UEMS and Novo Nordisk A/S and Novartis (2019).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This study was approved by our institutional ethical board (G19.011).

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