



The diagnostic value of preoperative inflammatory markers in craniopharyngioma: a multicenter cohort study

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Abstract

To compare the different levels of preoperative inflammatory markers in peripheral blood samples between craniopharyngioma (CP) and other sellar region tumors so as to explore their differential diagnostic value. The level of white blood cell (WBC), neutrophil, lymphocyte, monocyte, platelet, albumin, neutrophil lymphocyte ratio (NLR), derived NLR (dNLR), platelet lymphocyte ratio (PLR), monocyte lymphocyte ratio (MLR) and prognostic nutritional index (PNI) were compared between the CP and other sellar region tumors. A receiver operating characteristics (ROC) curve analysis was performed to evaluate the diagnostic significance of the peripheral blood inflammatory markers and their paired combinations for CP including its pathological types. Patients with CP had higher levels of pre-operative WBC, lymphocyte and PNI. The papillary craniopharyngioma (PCP) group had higher neutrophil count and NLR than the adamantinomatous craniopharyngioma (ACP) and healthy control groups whereas the ACP group had higher platelet count and PNI than the PCP and healthy control groups. There were not any significant differences in preoperative inflammatory markers between the primary and recurrent CP groups. The AUC values of WBC, neutrophil, NLR + PLR and dNLR + PLR in PCP were all higher than 0.7. Inflammation seems to be closely correlated with CP's development. The preoperative inflammatory markers including WBC, neutrophil, NLR + PLR and dNLR + PLR may differentially diagnose PCP, pituitary tumor (PT) and Rathke cleft cyst (RCC). In addition, some statistical results in this study indirectly proved previous experimental conclusions and strictly matched CP's biological features.

Keywords Craniopharyngioma · Differential diagnosis · Inflammation · Peripheral blood · Recurrence

Abbreviations

| | | | |
|-----|------------------------------------|------|-----------------------------------------|
| CP | Craniopharyngioma | PT | Pituitary tumor |
| ACP | Adamantinomatous craniopharyngioma | RCC | Rathke cleft cyst |
| PCP | Papillary craniopharyngioma | GBM | Glioblastoma multiforme |
| | | CT | Computer tomography |
| | | MRI | Magnetic resonance imaging |
| | | WBC | White blood cell |
| | | NLR | Neutrophil lymphocyte ratio |
| | | dNLR | Derived neutrophil lymphocyte ratio |
| | | PLR | Platelet lymphocyte ratio |
| | | MLR | Monocyte lymphocyte ratio |
| | | PNI | Prognostic nutritional index |
| | | AUC | Area under curve |
| | | ROC | Receiver operating characteristic curve |
| | | CI | Confidence interval |

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Introduction

Craniopharyngioma (CP) is an epithelial tumor that arises along the craniopharyngeal duct. It accounts for 1.2–4.0% of all intracranial tumors and 6.0–9.0% of all pediatric brain tumors. CP is a pathologically benign tumor which is classified as a World Health Organization (WHO) grade I neoplasm. Its pathological types are composed of adamantinomatous craniopharyngioma (ACP) and squamous papillary craniopharyngioma (PCP). Although CP is a benign tumor, its aggressive behavior and tendency to adhere to critical parasellar structure are conducive to significant regrowth or recurrence even after total tumor removal, and its regrowth or recurrence make for unsatisfactory postoperative life qualities for patients [1–4]. Besides that, tumors in the sellar region such as CP, pituitary tumor (PT) and Rathke cleft cysts (RCC) are often difficult to be differentially diagnosed [5–7]. The traditional radiological examinations including computer tomography (CT) and magnetic resonance imaging (MRI) are insensitive. Unlike other tumors, CP does not have any sensitive and specific serum markers being clinically applied for differential diagnosis [8, 9]. Thus, there is an urgent unmet need for minimally invasive markers for CP.

Recently, some studies presented that inflammation is closely related to CP. The common inflammatory factors such as IL-6, CXCL1, CXCL8 and TREM-1 were reported to induce CP's development [5, 10–13]. It was remarkable that in some tumors, emerging studies have highlighted the crucial role of inflammatory response in tumor's differential diagnosis [14]. The inflammatory response could already be monitored by changes in the levels of white blood cells (WBC), neutrophils, lymphocytes, monocytes, platelets and albumin which were easy to measure by widely available and standardized assays. In addition to that, other markers based on traditional index including neutrophil lymphocyte ratio (NLR), derived NLR (dNLR), platelet lymphocyte ratio (PLR), monocyte lymphocyte ratio (MLR) and prognostic nutritional index (PNI) have also been proven to play the role of differential diagnosis in patients with tumors [15–18].

Therefore, the aims of this study were to describe differences in levels of several preoperative inflammatory markers among patients with CP, patients with other tumors in sellar region including PT and RCC, and healthy controls, and to assess their preoperative differential diagnostic values for CP. In addition, the research about inflammatory markers in peripheral blood could possibly provide evidence other than experiments at the molecular level for inflammation inducing CP's progression.

Methods

Patients and healthy controls

Medical records of patients diagnosed with CP, RCC, PT at three hospitals (Shanghai Xinhua Hospital, Fujian Provincial Hospital and Shanghai Renji Hospital) between January 2007 and 2017 were collected and retrospectively analyzed in this study. All patients included in the final analysis met the following criteria: (1) The primary and recurrent CPs in this study were both surgically totally resected, and this kind of total resection was judged by intraoperative observation under surgical microscope and postoperative images. The pathological types of CPs were histologically verified in surgical specimens according to WHO grade criteria. RCC and PT were also histologically proven in surgical specimens. (2) No preoperative hormone therapy including glucocorticoids, chemotherapy and radiotherapy. (3) No hematological diseases, current infectious diseases, hyperpyrexia, diabetes mellitus, metabolic syndrome, serious heart diseases, hypertension, severe renal or hepatic dysfunction, cancers, autoimmune diseases, inflammatory diseases and medication usage related to inflammatory conditions. (4) Complete data of preoperative routine blood test and serum albumin level test. (5) Informed consents were obtained from eligible patients. To choose a healthy control group, we reviewed the records of age-matched and gender-matched healthy individuals who performed their annual health check at the hospital. This study was approved by the institutional ethics committee.

Data collection

Patients' demographic and clinic pathological variables, including age, gender, pathological type and recurrence were retrieved from retrospective medical records. The time to recurrence was defined as the time span between first and second time's postoperative pathological diagnosis of CP. Preoperative blood samples were routinely taken for blood routine test and hepatic function test within 1 week of surgery as a part of the standard preoperative workup. All tests were performed by the staff at the department of clinical laboratory within 2 h of collection. The WBC, neutrophil, lymphocyte, monocyte and platelet counts were collected from blood routine test, and albumin levels were collected from hepatic function test. All the clinical inflammatory data mentioned above were collected by standardized automated counters. Moreover, preoperative NLR (quotient of neutrophil count to lymphocyte count), dNLR [quotient of neutrophil count to (WBC

count–neutrophil count)], PLR (quotient of platelet count to lymphocyte count), MLR (quotient of monocyte count to lymphocyte count), and PNI (albumin (g/L) + 5 × total lymphocyte count) were calculated.

Statistical analysis

Statistical analysis was carried out by SPSS 13.0. Initially, normal distribution of the variables was analyzed by the Kolmogorov–Smirnov test. Normally distributed data were analyzed by two-tailed Student's *t* test or One-way ANOVA. For non-parametric data, Mann–Whitney U test was used for comparisons between groups. Correlations between inflammatory markers including WBC, neutrophil, lymphocyte, monocyte, platelet, albumin, NLR, dNLR, PLR, MLR, PNI and time to recurrence were judged by the Pearson's correlation coefficient test for two variables with normal distribution or by Spearman's correlation coefficient test for abnormally distributed variables. The diagnostic performances of all the inflammatory markers mentioned before and their combinations were assessed by values of the area under curve (AUC) obtained from the receiver operating characteristic (ROC) curve. After post hoc analysis, the cutoff for abnormal score was determined by the value corresponding to maximal sum of sensitivity and specificity. A two-tailed *p* value of < 0.05 was considered statistically significant.

Results

Study population

A total of 312 patients with CP, 75 patients with RCC and 400 patients with PT were firstly enrolled in this study. After screen, a total of 197 patients with CP, 57 patients with RCC, 371 patients with PT and a control group of 682 healthy participants were enrolled in the final analysis. Detailed demographic information of the study participants are presented in Supplementary Tables 1–3. The CP patients ranged in age from 1 to 67 years old, and their median age was 25 years old. The CP cohort consisted of 134 male (68.02%) and 63 female (31.98%). The median age for patients with PT and RCC was 46 and 43 years old, respectively. As for healthy controls, median age was 42 years old, with 340 being males (49.85%) and 342 being females (50.15%). At the time of diagnosis, 157 (79.70%) of CP patients were classified as ACP and 40 (20.30%) as PCP according to the WHO 2007 criteria. 149 (75.63%) of CP were primary, and the other 48 (24.37%) were recurrent. The time to recurrence ranged from 0.17 to 15 years and its median was 3 years.

Comparison of preoperative inflammatory markers in patients with CP and healthy controls

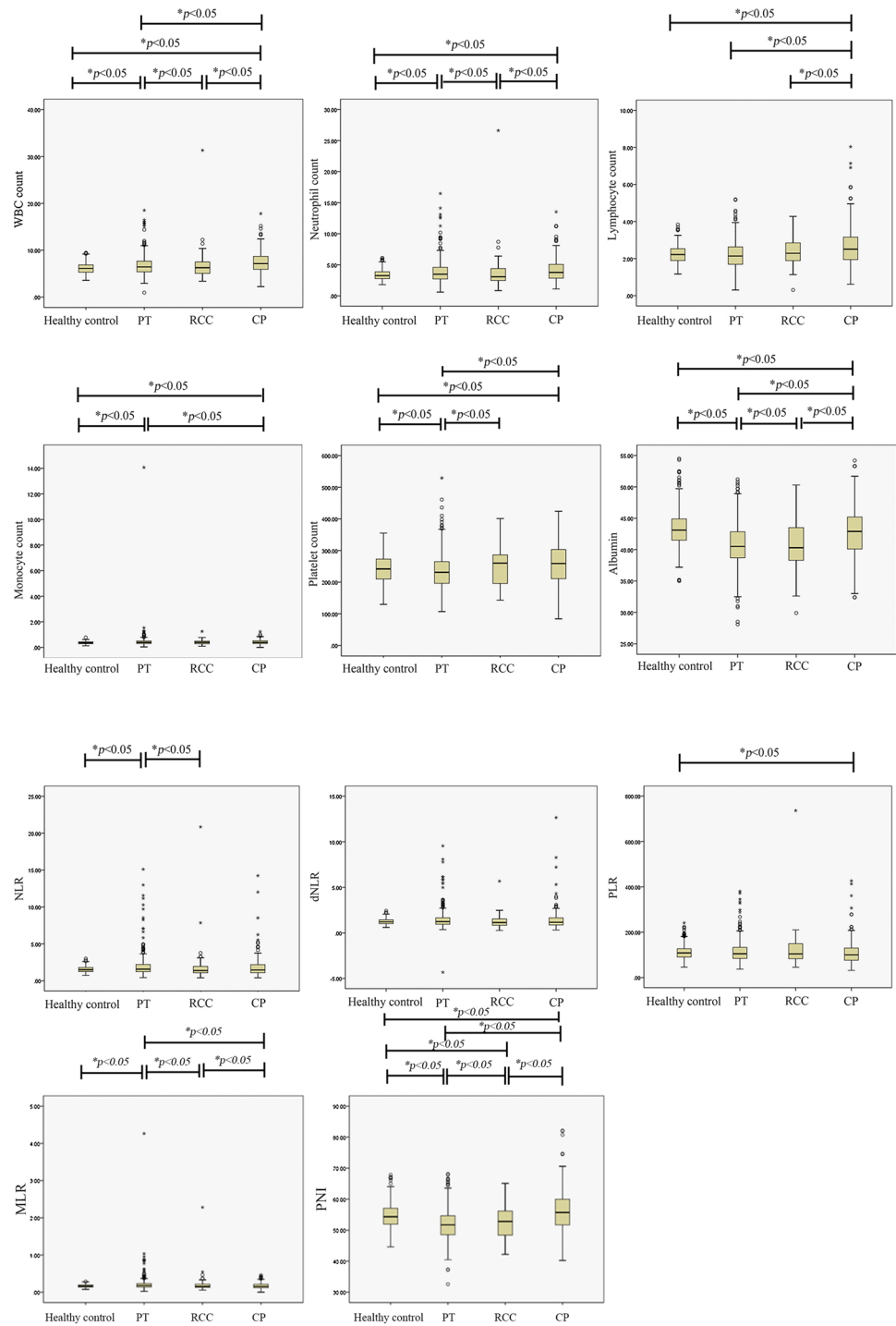
As shown in Fig. 1 and Supplementary Table 1, significantly higher WBC and lymphocyte counts were observed in preoperative patients with CP than in patients with PT, RCC and in the healthy control patients. The albumin level was observed to be higher in CP patients than in other groups except for healthy control. The platelet count was higher in the CP group than in the PT and RCC groups. The monocyte count was higher in the CP group than in the healthy control. As for calculated laboratory parameters, PNI was significantly higher in the CP group when compared to the other groups. PLR was elevated in CP patients relative to healthy controls. However, much lower values of MLR were noted in CP patients than in other groups except for the healthy control.

Inflammatory markers were further investigated according to CP's pathological type and recurrence (Fig. 2 and Supplementary Tables 2, 3). The neutrophil count of ACP and PCP were both significantly higher than in the healthy control, and the PCP group had the highest neutrophil count. The platelet count was obviously higher in the ACP group than in the PCP and healthy control groups. Among the ACP, PCP and healthy control groups, the PCP group had the highest NLR value, and the ACP group had the highest PNI value. Surprisingly, there were not any significant differences in inflammatory markers between primary and recurrent CP.

Evaluation of the diagnosis efficacy for inflammatory markers and their combinations in patients with CP as well as patients with other sellar region tumors

Figure 3 shows the diagnostic value (ROC curves) of WBC, neutrophil, lymphocyte, monocyte, platelet, albumin, NLR, dNLR, PLR, MLR, PNI and their paired combinations for CP patients. The corresponding AUC values appear in Supplementary Table 3. The AUC was 0.659 (0.614–0.704) for WBC, 0.592 (0.544–0.640) for neutrophil, 0.619 (0.570–0.668) for lymphocyte, 0.559 (0.513–0.605) for monocyte, 0.595 (0.547–0.642) for platelet, 0.531 (0.485–0.578) for albumin, 0.486 (0.436–0.537) for NLR, 0.477 (0.426–0.527) for dNLR, 0.446 (0.397–0.494) for PLR, 0.457 (0.408–0.506) for MLR, 0.616 (0.568–0.663) for PNI when patients with CP were tested against healthy participants, patients with PT and RCC. Significant correlations between these inflammatory markers were observed in CP (Fig. 4). WBC, lymphocyte and PNI demonstrated the highest accuracy in predicting CP (Fig. 3a, Supplementary Table 4). We also evaluated paired combinations of these markers for the diagnosis of CP. The best diagnostic

Fig. 1 Preoperative WBC, neutrophil, lymphocyte, monocyte, platelet, albumin, NLR, dNLR, PLR, MLR and PNI in patients with CP, PT, RCC and healthy controls. Initially, normal distribution of all the inflammatory markers in CP, PT, RCC and healthy controls was analyzed by the Kolmogorov–Smirnov test. The errors in the figure represented SEM. Normally distributed data were analyzed by two-tailed Student's *t* test or One-way ANOVA. For non-parametric data, Mann–Whitney U test was used for comparisons between groups. “*” represented the two-tailed *p* value < 0.05 which was considered statistically significant



value was obtained with the combination of NLR + PNI, dNLR + PNI and PLR + PNI with AUC of 0.635, 0.631 and 0.627 respectively (Fig. 3a, Supplementary Table 4).

The diagnostic value of inflammatory markers and their paired combinations were also assessed when patients with ACP or PCP when tested against healthy controls and patients with PT or RCC. As shown in Fig. 3b and Supplementary Table 4, ROC analysis indicated that WBC

(AUC: 0.638; 95% CI 0.587–0.688), lymphocyte (AUC: 0.623; 95% CI 0.569–0.677), platelet (AUC: 0.624; 95% CI 0.572–0.676), PNI (AUC: 0.616; 95% CI 0.562–0.669), NLR + PNI (AUC: 0.631; 95% CI 0.578–0.685), dNLR + PNI (AUC: 0.628; 95% CI 0.575–0.682), PLR + PNI (AUC: 0.638; 95% CI 0.585–0.692) and MLR + PNI (AUC: 0.617; 95% CI 0.564–0.670) had greater predictive value for predicting ACP than other groups. WBC

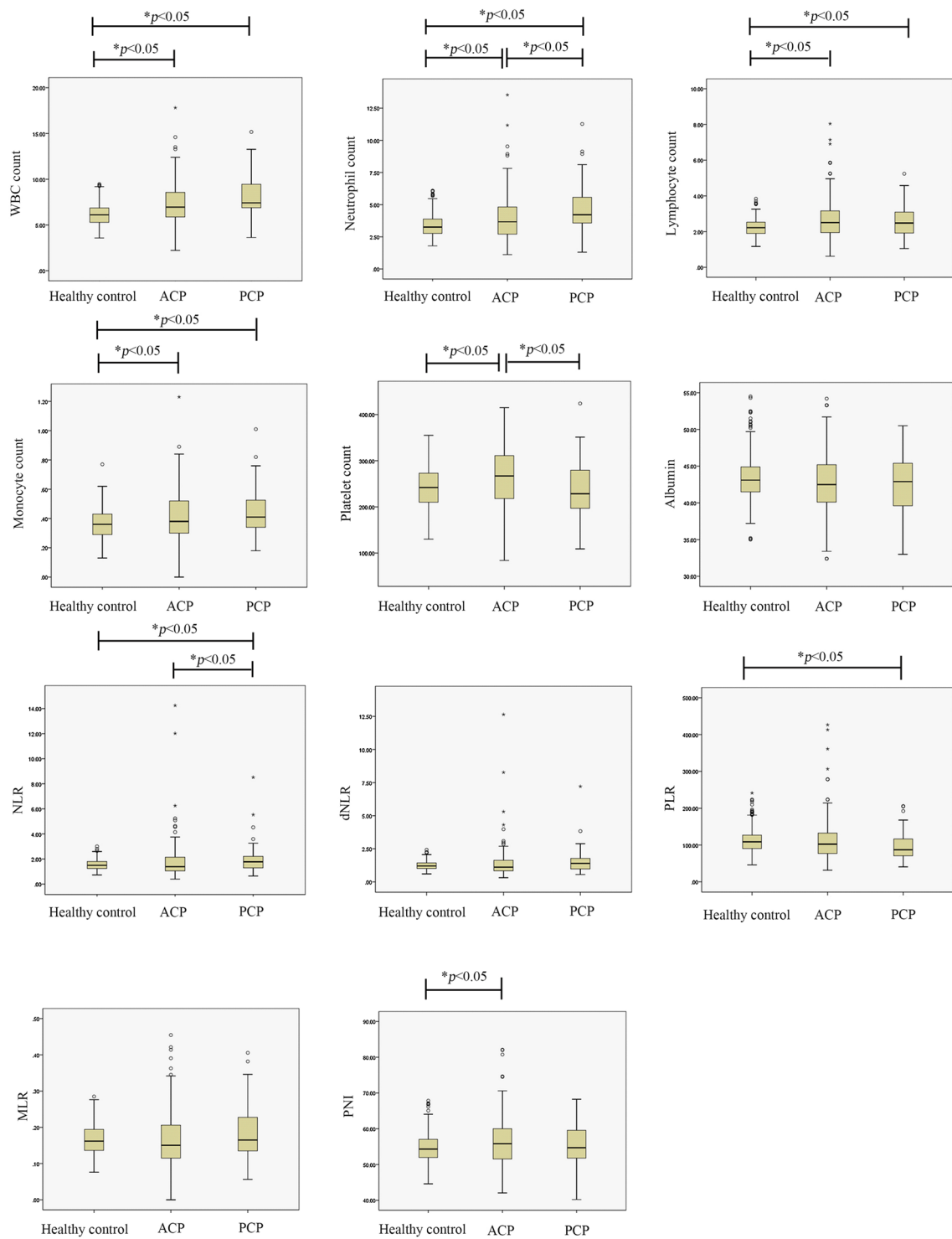


Fig. 2 Preoperative WBC, neutrophil, lymphocyte, monocyte, platelet, albumin, NLR, dNLR, PLR, MLR and PNI in patients with ACP, PCP and healthy controls. Initially, normal distribution of all the inflammatory markers in ACP, PCP and healthy controls was analyzed by the Kolmogorov–Smimov test. The errors in the figure

represented SEM. Normally distributed data were analyzed by two-tailed Student’s *t* test or One-way ANOVA. For non-parametric data, Mann–Whitney U test was used for comparisons between groups. “*” represented the two-tailed *p* value < 0.05 which was considered statistically significant

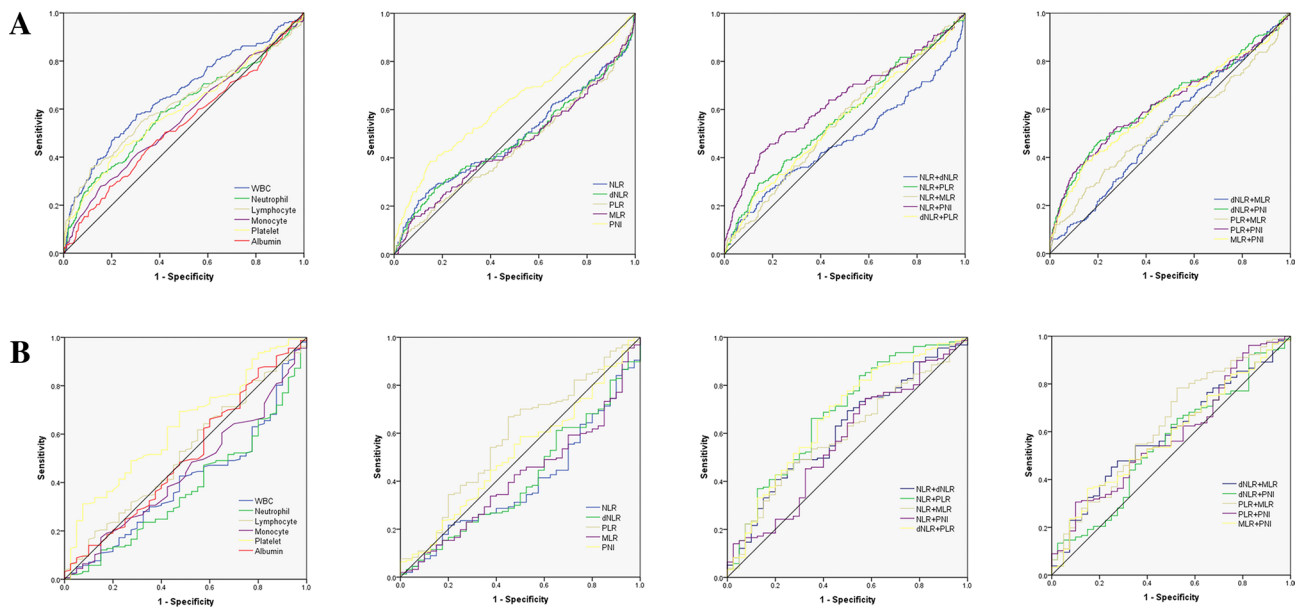


Fig. 3 The diagnostic value of preoperative WBC, neutrophil, lymphocyte, monocyte, platelet, albumin, NLR, dNLR, PLR, MLR, PNI and their combinations were evaluated by ROC analysis when patients with CP were tested against patients with PT, RCC and

healthy controls (a). The diagnostic value of preoperative WBC, neutrophil, lymphocyte, monocyte, platelet, albumin, NLR, dNLR, PLR, MLR, PNI and their combinations were evaluated by ROC analysis when patients with ACP were tested against patients with PCP (b)

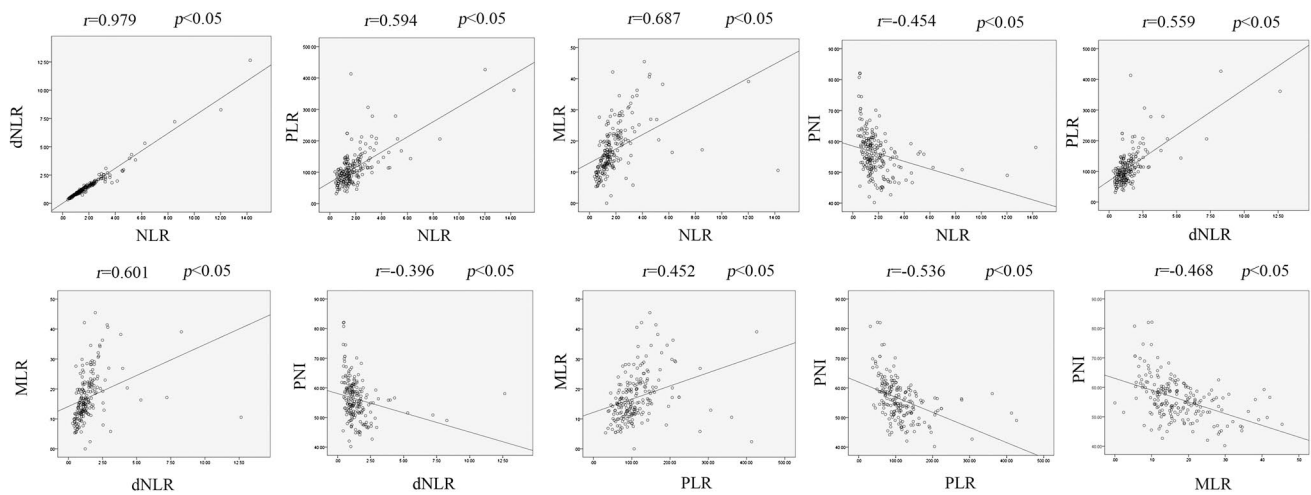


Fig. 4 Correlations between preoperative WBC, neutrophil, lymphocyte, monocyte, platelet, albumin, NLR, dNLR, PLR, MLR and PNI in patients with CP

(AUC: 0.744; 95% CI 0.658–0.829), neutrophil (AUC: 0.706; 95% CI 0.619–0.793), NLR + PLR (AUC: 0.713; 95% CI 0.621–0.805) and dNLR + PLR (AUC: 0.703; 95% CI 0.610–0.797) had significant predictive value for PCP when compared with other groups. When patients with ACP were tested against PCP, the AUC was 0.631 (95% CI 0.539–0.724) for platelet, 0.611 (95% CI 0.516–0.706) for NLR + dNLR, 0.680 (95% CI 0.583–0.777) for NLR + PLR, 0.699 (95% CI 0.573–0.766) for dNLR + PLR and 0.629 (95% CI 0.531–0.728) for PLR + MLR which had more

predictive and differential diagnosis value for two pathological types of CP (Fig. 3b and Supplementary Table 4). The sensitivity, specificity and cutoff of each marker were stated in Supplementary Table 5.

Correlations between the time to recurrence and inflammatory markers

The Supplementary Table 6 showed the correlations between the time to recurrence and inflammatory markers in CP, ACP

or PCP. In CP, the time to recurrence was correlated with monocyte count (correlation coefficient: -0.298). In ACP, the time to recurrence was also correlated with monocyte count (correlation coefficient: -0.350). In PCP, the time to recurrence was correlated with lymphocyte count (correlation coefficient: 0.776), PLR (correlation coefficient: -0.783), MLR (correlation coefficient: -0.674) and PNI (correlation coefficient: 0.577).

Discussion

Recent experimental studies have demonstrated that CP is tightly correlated with inflammation. Inflammatory factors such as IL-6, CXCL1, CXCL8 and TREM-1 were reported to induce the progression of CP cells [5, 10, 12, 13, 19, 20]. Preoperative inflammatory markers have been reported to be a useful diagnostic tool for various tumors. They have been identified as potential markers for early detection, disease staging and monitoring of tumors [21, 22]. However, little was known about the diagnostic value of inflammatory markers in patients with CP, and there was no research on direct evidence like inflammatory markers in peripheral blood for proving the relationship between CP and inflammation. In this study, we assessed the differential diagnostic values of several preoperative inflammatory markers in CP, explored their correlations with pathological types and recurrence.

In this research, the results of traditional inflammatory markers from peripheral blood samples indicated that the WBC and lymphocyte counts were higher in the CP group than in other groups. This meant that CP's progression could be associated with inflammation, and the lymphocyte could play an important role in CP's development. WBC was found to exist in different kinds of tumors, especially malignant ones. It was closely related to tumor's crucial biological characteristics such as proliferation, migration, immune escape and prognosis [14, 17]. As we all know, malignant tumor easily recurs or regrows even after being totally resected. This practical situation was similar to CP. Thus, in our opinion, the increase of WBC count in CP could similarly illustrate that inflammation was key to CP's proliferation. The lymphocyte was a vital component of WBC. It has been widely accepted that chronic inflammatory reaction induced lymphocyte's infiltration caused tumor's development. In the tumor's microenvironment, immune response from lymphocyte stimulated by local inflammatory was always reported to influence tumor cells' growth [23–27]. Previous studies have proven that GBM cells could reduce lymphocyte's infiltration by secreting immune-suppressor like IL-10 [28]. By coincidence, CP cells also secreted IL-10, so the lymphocyte count may be regulated by homologous or different mechanisms [29]. In addition, we always

observed some small round cells with nuclear hyperchromatism scattered or gathered in CP's pathological section, especially in CP's stroma part under microscope. We speculate that these cells could be lymphocytes, but this conjecture should be confirmed by additional evidence. Furthermore, the albumin level of CP was obviously higher than PT and RCC. From our point of view, this result may be affected by hypothalamic dysfunction because of the tight adhesion between CP and hypothalamus. The abnormal secretion of hormones may affect the metabolism and diet habit, eventually leading to the increase of albumin [30].

CP is pathologically composed of ACP and PCP. In this study, the neutrophil count of ACP and PCP were both significantly higher than in the healthy control. It was remarkable that PCP had the highest neutrophil count among these groups. This meant that PCP's biological performances could be more relative to neutrophil. It has been reported that the inflammatory response factor TREM-1, which is known as an activating receptor expressed on neutrophils, was more expressed in PCP than in ACP. In other words, it was only expressed in metaplastic squamous epithelium like PCP or part of ACP undergone metaplastic via inflammation [10]. Perhaps this experiment result could help to explain the reason why PCP had higher neutrophil count in this study. Moreover, the platelet count was obviously higher in ACP than in PCP and the healthy control. Former studies had shown that ACP overexpressed IL-6 which could accelerate platelet production [31, 32]. Therefore, we proposed that the increase of platelet and the release inflammatory factors of ACP cells may have mutually enhancing relationship.

The calculated preoperative inflammatory markers also had significant differences between CP and other groups. Currently, preoperative NLR has been recognized as a prognostic factor in GBM. Elevated NLR has been reported to be correlated with poorer survival and worse prognosis in GBM patients [33, 34]. In this study, there was no significant difference in NLR between CP and other groups, but among ACP, PCP and healthy control, PCP had the obviously highest NLR value. The increase in preoperative NLR may be resulted from an elevation of neutrophil count or a reduction of lymphocyte count. This result corresponded to the fact that neutrophil count was elevated in PCP. Unfortunately, the mechanism remained unknown. As for MLR, its increased level has also been identified as a poor prognostic index for several tumors [17, 35]. Our data suggested that MLR was significantly lower in CP than in PT and RCC. The increase of lymphocyte count mentioned before could be a reason to explain the decrease of MLR value. Besides that, in glioma, it was reported that macrophages could be recruited and induced to become M2 phenotypes by a wide variety of factors secreted by tumor cells including IL-6, IL-10, TGF beta and periostin [36, 37]. Similarly, IL-6 and periostin were also proven to be expressed in CP by experiments, and

they could have homologous or inverse mechanisms to down regulate CP's monocyte count [5, 38]. Compared with other groups, preoperative PNI level was significantly increased in patients with CP. PNI is now widely used as parameters for nutritional status and systemic inflammatory response, and low levels of them are reported to be associated with poor survival in malignant tumors. Our data revealed that ACP had the highest PNI level. This result agreed with the actual situation. Because of the chronic inflammation stimulation and the special relative position between CP and hypothalamus, the function of injured hypothalamus was often altered, leading to the problem of energy management, decreased exercise, drowsiness and eating disorder. These dysfunctions of hypothalamus consequently reflected in PNI level. Compared with PCP, ACP was more relative to hypothalamus, even always being adhesive to this vital area. This may also explain why PNI was higher in ACP.

It is worth mentioning that there were not any significant differences between primary and recurrent CP. This result may indicate that the role of inflammation in primary and recurrent CP is identical. The inflammatory microenvironment coexists with CP all the time, and the recurrence of CP is purely caused by the regrowth of postoperative residual CP cells. Besides that, the high monocyte count meant the possible short term recurrence both in CP and ACP. In PCP, the low lymphocyte count, low PNI, high PLR and high MLR meant possible short term recurrence. Hence, this hypothesis verified the importance of CP's totally resection and essential adjuvant therapies once again.

Because of the similar clinic manifestation and imaging features, it was difficult to differentially diagnose the sellar region tumors like CP, PT and RCC only from radiological images before operation. Furthermore, the preoperative biopsies for sellar region tumors were invasive and unnecessary. Unfortunately, unlike other tumors, none of circulating serum or plasma markers has been established for the routine clinical management for patients with CP [8, 39]. Here, we assessed the performance of preoperative WBC, neutrophil, lymphocyte, monocyte, platelet, albumin, NLR, dNLR, PLR, MLR, PNI and their combinations for CP by ROC curve analysis. Only the AUC values of PCP including WBC, neutrophil, NLR + PLR and dNLR + PLR were higher than 0.7. This result matched the statistical outcome and analyzation we mentioned before. In other words, compared with other sellar region tumors, the development of PCP was more closely related to neutrophil. The neutrophil-related preoperative inflammatory markers such as WBC, neutrophil, NLR + PLR and dNLR + PLR may help to differentially diagnose PCP. Besides that, unlike ACP's special performance of cystic change or calcification, PCP always performed as a solid tumor in radiological images, and this kind of performance which was similar to PT and RCC may further increase the difficulties of diagnosis. Therefore, the

preoperative inflammatory markers in peripheral blood for diagnosing PCP became more necessary.

There are still a few limitations in our study. First, our cohort consisted of a relatively small proportion of patients with CP; in particular, only a limited number of patients with PCP were included. Although we retrospectively acquired data from multicenter to minimize per definition the selection bias, larger studies are needed to confirm our preliminary results. Second, the change of preoperative inflammatory markers' values that were observed in our study may be a reflection of a nonspecific inflammatory response due to CP. Hence, there was a risk of generating false-positive test results in screening asymptomatic populations.

Conclusions

In this multicenter study, we found that inflammation is closely related to CP's development. The preoperative inflammatory markers including WBC, neutrophil, NLR + PLR and dNLR + PLR may differentially diagnose PCP, PT and RCC. In addition, some statistical results in this study match previous experimental conclusions or CP's biological features. This study may help us to better determine the mechanism of inflammation affecting CP.

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Compliance with ethical standards

Disclosure The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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