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ORIGINAL ARTICLE

# The prognostic potential of pretreatment C-reactive protein to albumin ratio in stage IE/IIE extranodal natural killer/T-cell lymphoma*

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## Abstract

**Objective** The aim of this study was to determine the prognostic significance of the C-reactive protein-to-albumin ratio (CRP/Alb) for stage IE/IIE upper aerodigestive tract extranodal NK/T cell lymphoma patients.

**Methods** One hundred and fourteen patients diagnosed with extranodal NK/T cell lymphoma at Sichuan Cancer Hospital from September 2011 to November 2016 were retrospectively reviewed. An optimal cutoff value of CRP/Alb for overall survival rate as an endpoint was obtained using the receiver operating curve (ROC).

**Results** The optimal cutoff value of CRP/Alb was 0.15. For the low CRP/Alb group, the 3-year progression-free survival (PFS) was 78.6% and the 3-year overall survival (OS) was 80.7%. The 3-year PFS and OS values for the high CRP/Alb group were 41.6% and 45.2%, respectively. Differences for PFS ($P < 0.001$) and OS ($P < 0.001$) between the two groups were statistically significant. Univariate analysis showed that ECOG, IPI, CRP, GPS, and CRP/Alb were significantly associated with PFS. Similarly, all five were also significantly associated with OS. Multivariate analysis further confirmed that ECOG and CRP/Alb were independent prognostic factors for both PFS and OS. Moreover, the cutoff value of CRP/Alb showed superior prognostic ability in discriminating between patients with different outcomes in low-risk group based on GPS, IPI, and KPI scores.

**Conclusion** CRP/Alb is a promising prognostic marker for early-stage extranodal NK/T cell lymphoma.

**Key words:** C-reactive protein to albumin ratio (CRP/Alb); extranodal NK/T cell lymphoma; prognosis introduction

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Extranodal natural killer/T cell lymphoma, nasal-type (ENKTL) is a rare type of non-Hodgkin's lymphoma (NHL) characterized by highly aggressive and heterogeneous clinical features [1]. It occurs much more frequently in Asia than in Western countries (5.3% *vs* 0.3%) [2–3]. Most ENKTL tumors (about 80%) are localized to the upper aerodigestive tract, including the nasal cavity, paranasal sinus, nasopharynx, and oropharynx. It was previously known as lethal midline granuloma. Less common tumor sites (20%) are the gastrointestinal tract, skin, testis, lung, muscle, and salivary glands [4]. The vast majority of patients are diagnosed at stage IE/IIE and are sensitive to radiotherapy; however, a significant fraction of patients exhibit recurrence [5]. An International Prognostic Index (IPI) has been established for many subtypes of NHL, but its prognostic value has remained controversial for ENKTL because of the imbalanced patient distributions [6]. Given the limitations of the IPI, the Korean Prognostic Index (KPI) has been shown to have better prognostic performance than the IPI, but the KPI has not been stratified for early-stage patients [7] These prognostic models are based mainly on clinical characteristics that fail to account for our increasing understanding of the mechanisms underlying ENKTL. Therefore, a novel prognostic biomarker for these patients is urgently needed.

Recently, multiple studies have shown that inflammation plays an important role in th tumor microenvironment, with inflammation mediators (such as chemokines, cytokines, free radical) affecting tumor proliferation, progression, and metastasis [8–10]. So far, multiple investigators have reported that prognostic scores

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based on inflammatory factors, including the C-reactive protein (CRP) [11] and the Glasgow Prognostic Score (GPS) [12], have significant prognostic value for ENKTL patients. However, the prognostic value of the CRP/Alb ratio for ENKTL has not yet been examined. Therefore, we tested whether the CRP/Alb ratio could serve as a predictor of survival in early-stage ENKTL patients.

## Materials and methods

### Patients

One hundred and fourteen patients with newly-diagnosed upper aerodigestive tract ENKTL were identified at Sichuan Cancer Hospital from September 2011 to November 2016, using the 2016 World Health Organization criteria [13] and clinical staging according to the Ann Arbor system [14]. All study subjects met the following inclusion criteria: (1) pathologically and immunohistochemically confirmed ENKTL [1]; (2) newly diagnosed as stage I/IIE patients; (3) no antitumor therapy had been performed; (4) neither active infections nor symptoms of inflammation; and (5) follow-up data were available. Exclusion criteria for subjects in this study were as follows: (1) advanced, recurrent, or refractory ENKTL; (2) previous chemotherapy or radiotherapy; (3) obvious cardiopulmonary insufficiency.

We collected pretreatment data, including age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), B symptoms, serum lactate dehydrogenase (LDH) levels, serum C-reactive protein (CRP) levels, and serum albumin (Alb) levels. CRP was measured with a kit of Nephstar equipment (Goldsite Diagnostics Inc., China). Alb was measured with an ALB Kit (Medicalsystem Biotechnology Co. China) on a Mindray BS-820 Chemistry Analyzer (Mindray, China). To confirm tumor staging, bone marrow examination, computed tomography (CT) of the chest, abdomen, and pelvis, and/or magnetic resonance imaging (MRI) of the head and neck were performed. The IPI [6] and KPI [7] scores were calculated as previously described. The GPS score [12] was calculated from CRP and Alb measurements using standard thresholds (>10 mg/L for CRP and < 35 g/L for Alb). Patients with CRP levels above 10 mg/L or Alb levels below 35 g/L were assigned a score of 1.

### Treatments

The treatment regimans were radiotherapy alone (21 patients); CHOP or CHOP-like combined with radiotherapy (26); and asparaginase combined with radiotherapy (67). Chemotherapy regimens were CHOP or CHOP-like (cyclophosphamide, doxorubicin, vincristine, prednisone or etoposide) and P-GEMOX (Peg-asparaginase, gemcitabine, oxaliplatin). Intensity-modulated radiotherapy (IMRT) was delivered using a 6-MeV linear accelerator, with a dose range of 50–62 Gy in daily fractions of 1.8-2.0 Gy, 5 d/week.

### Follow-up

Overall survival (OS) was defined as the time of diagnosis until death from any cause ,or until the time of the most recent follow-up visit for surviving patients. Progression-free survival (PFS) was defined as the interval from the time of diagnosis to the time of first documented disease progression, relapse, death, or most recent follow-up visit.

### Statistical analysis

The receiver operating curve (ROC) and the Youden index [maximum (sensitivity + specificity - 1)] [15] were used to determine the optimal cutoff value for CRP/Alb. Patients were divided into low and high CRP/Alb groups according to the calculated CRP/Alb cutoff value. The chi-square test was used to test for the statistical significance of correlations between CRP/Alb values and clinicopathological parameters. Survival analysis was performed using the Kaplan–Meier method and differences were evaluated using the log-rank test. Multivariate analysis was conducted by stepwise Cox regression. All data were analyzed using SPSS 17.0 software. $P < 0.05$ was considered statistically significant and all $P$ values presented here correspond to two-sided significance tests.

## Results

### Patient characteristics

This study cohort included 74 males and 40 females (ratio 1.9). Median age was 45 years (range 15-84), with 19% older than 60. A majority of patients (54%) were in stage IE. LDH levels were elevated in only 28% of patients. A minority of patients (40%) presented with systemic B symptoms. The majority of patients (84%) exhibited good performance status according to ECOG scores. CRP levels over 10 mg/L were observed in 21% of patients, and 13% presented with hypoalbuminemia.

The majority of patients (75%) were classified as GPS score 0. According to IPI scores, 74% were low-risk (score 0–1). According to KPI scores, 67% were classified as low-risk (score 0–1). For the CRP/Alb score, 73% were classified as low-risk, with the remaining 27% classified as high-risk. The CRP/Alb high-risk classification was significantly correlated with elevated CRP, low Alb levels, GPS score ≥ 1, and KPI score ≥ 2 (all $P < 0.05$). The relationships between the CRP/Alb and clinical characteristics are summarized in Table 1.

## Optimal cutoff value for CRP/Alb

Using overall survival rate as an endpoint, ROC analysis revealed that the optimal cutoff value of CRP/Alb ratio was 0.15 and the area under curve (AUC) was 0.712 (sensitivity = 57.1%, specificity = 84.9%) (Fig. 1a). In contrast, ROC analysis showed that GPS, IPI, and KPI were inferior predictors of OS CRP/Alb; (GPS: AUC = 0.659, sensitivity = 47.2%, specificity = 84.6%; IPI: AUC = 0.592, sensitivity = 38.9%, specificity =7 9.5%; and KPI: AUC = 0.561, sensitivity = 41.7%, specificity = 70.5%) (Fig. 1b).

## Survival analysis

Follow-ups have been performed through March 2019. The overall median survival was 37.5 months (range 3–82). For all subjects, 3-year PFS was 68.1% (Fig. 2a) and 3-year OS was 70.6% (Fig. 2b). For the low-risk CRP/Alb group, the 3-year PFS was 78.6% and 3-year OS was 80.7%. For the high-risk CRP/Alb group, 3-year PFS and OS were 41.4%, and 45.2%, respectively. The result revealed that ENKTL patients in the high CRP/Alb group had significantly poorer PFS ($\chi^2$ = 24.183, $P$ < 0.001, Fig. 2c), and overall survival ($\chi^2$ = 22.514, $P$ < 0.001, Fig. 2d).

## Prognostic factors for progression-free survival

Univariate analysis showed that ECOG ($P$ = 0.002), IPI ($P$ = 0.035), CRP ($P$ < 0.001), GPS ($P$ < 0.001), and CRP/Alb ($P$ < 0.001) were significantly associated with PFS. Multivariate analysis further demonstrated that both ECOG ($P$ = 0.033) and CRP/Alb ($P$ = 0.018) were independent prognostic factors for PFS. The results of univariate and multivariate analysis were presented in Table 2.

## Prognostic factors for overall survival

Similarly, univariate analysis revealed that ECOG ($P$ = 0.001), LDH ($P$ = 0.046), IPI ($P$ = 0.022), CRP ($P$ < 0.001), GPS ($P$ < 0.001), and CRP/Alb ($P$ < 0.001) were

**Table 1** Relationship between the CRP/Alb and patient parameters (*n*, %)

| Characteristics | Total | CRP/Alb ≤ 0.15 | CRP/Alb > 0.15 | $\chi^2$ | *P* |
|---|---|---|---|---|---|
| Age (years) | | | | | |
| ≤ 60 | 92 (80.7) | 68 (81.9) | 24 (77.4) | 0.295 | 0.587 |
| > 60 | 22 (19.3) | 15 (18.1) | 7 (22.6) | | |
| Gender | | | | | |
| Female | 40 (35.1) | 30 (36.1) | 10 (32.3) | 0.150 | 0.699 |
| Male | 74 (64.9) | 53 (63.9) | 21 (67.7) | | |
| ECOG | | | | | |
| 0–1 | 96 (84.2) | 72 (86.7) | 24 (77.4) | 0.859 | 0.354 |
| ≥ 2 | 18 (15.8) | 11 (13.3) | 7 (22.6) | | |
| B symptoms | | | | | |
| No | 68 (59.6) | 55 (66.3) | 13 (41.9) | 5.551 | 0.018 |
| Yes | 46 (40.4) | 28 (33.7) | 18 (58.1) | | |
| LDH (U/L) | | | | | |
| ≤ 240 | 82 (71.9) | 67 (80.7) | 15 (48.4) | 11.688 | 0.001 |
| > 240 | 32 (28.1) | 16 (19.3) | 16 (51.5) | | |
| Clinical stage | | | | | |
| I | 61 (53.5) | 47 (56.6) | 14 (45.2) | 1.193 | 0.275 |
| II | 53 (46.5) | 36 (43.4) | 17 (54.8) | | |
| CRP (mg/L) | | | | | |
| ≤ 10 | 90 (78.9) | 83 (100) | 7 (22.6) | 81.394 | < 0.001 |
| > 10 | 24 (21.1) | 0 (0) | 24 (77.4) | | |
| ALB (g/L) | | | | | |
| < 35 | 15 (13.2) | 5 (6.0) | 10 (32.3) | 11.395 | 0.001 |
| ≥ 35 | 99 (86.8) | 78 (94.0) | 21 (67.7) | | |
| GPS score | | | | | |
| 0 | 85 (74.6) | 78 (94.0) | 7 (22.6) | 60.655 | < 0.001 |
| ≥ 1 | 29 (25.4) | 5 (6.0) | 24 (77.4) | | |
| IPI score | | | | | |
| 0–1 | 84 (73.7) | 65 (78.3) | 19 (61.3) | 3.373 | 0.066 |
| ≥ 2 | 30 (26.3) | 18 (21.7) | 12 (38.7) | | |
| KPI score | | | | | |
| 0–1 | 76 (66.7) | 62 (74.7) | 14 (45.2) | 8.861 | 0.003 |
| ≥ 2 | 38 (33.3) | 21 (25.3) | 17 (54.8) | | |

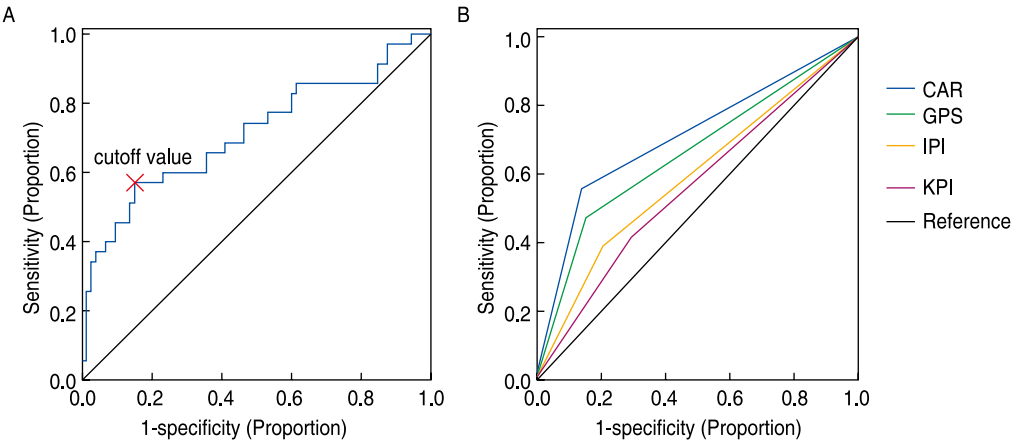


**Fig. 1** The receiver operating curves analysis: (a) the optimal cut-off value for CRP/Alb determined by ROC; (b) The comparison among CRP/Alb, Glasgow Prognostic Score (GPS), International Prognostic Index (IPI), and Korean Prognostic Index (KPI) by ROC

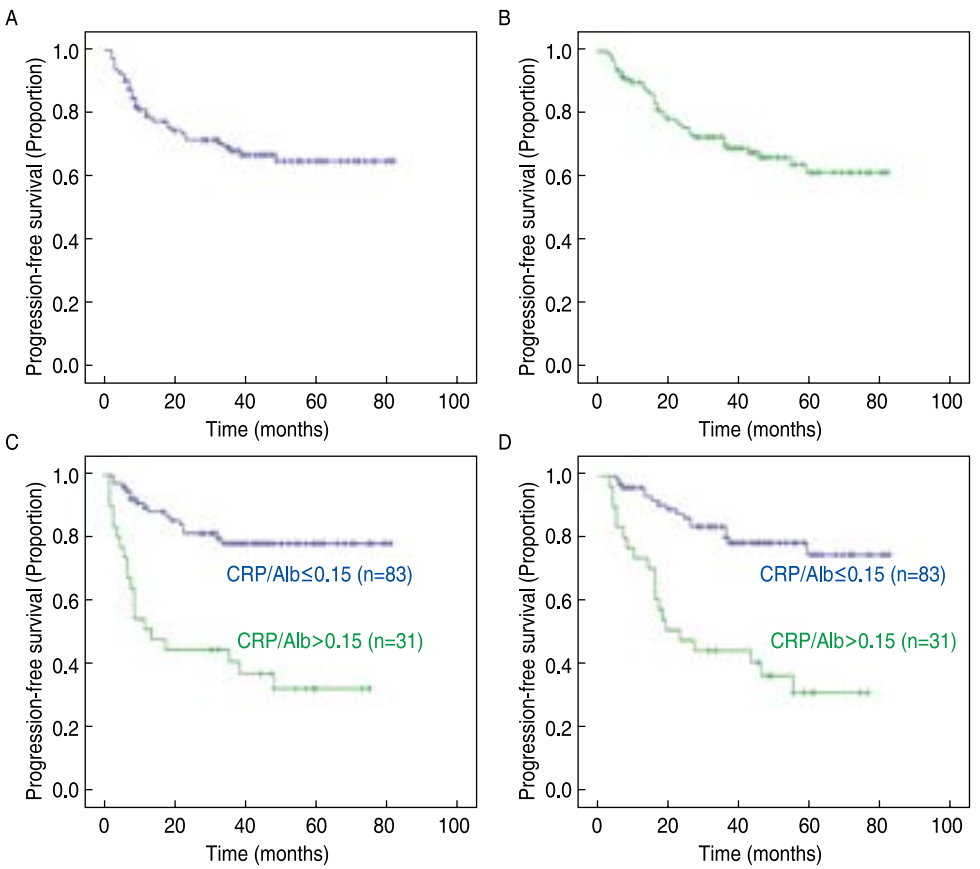


**Fig. 2** Kaplan-Meier curves depicting the difference in survival: (a) The whole patients for PFS; (b) The whole patients for OS; (c) PFS of patients CRP/Alb ≤ 0.15 vs CRP/Alb > 0.15; (d) OS of patients CRP/Alb ≤ 0.15 vs CRP/Alb > 0.15

significantly related to OS. Multivariate analysis further revealed that ECOG ($P = 0.027$) and CRP/Alb ($P = 0.025$) were independent prognostic factors for OS. These results were shown in Table 3.

## Prognostic value of combining CRP/Alb with GPS, IPI, and KPI

Based on GPS scores, 75% of cases were placed in the low-risk group (score 0), which could not be further

**Table 2** Prognostic factors for progression-free survival (PFS)

| Clinical characteristics | | Univariate analysis (PFS) | | Multivariate analysis (PFS) | | |
|---|---|---|---|---|---|---|
| | | $\chi^2$ | *P* | HR | 95% CI | *P* |
| Age (years) | ≤ 60 *vs* > 60 | 0.215 | 0.643 | | | |
| Gender | Male *vs* Female | 0.728 | 0.393 | | | |
| ECOG score | 0-1 *vs* ≥ 2 | 9.714 | 0.002 | 4.150 | 1.124–15.318 | 0.033 |
| B symptoms | No *vs* Yes | 0.483 | 0.487 | | | |
| Clinical stage | IE *vs* IIE | 2.596 | 0.107 | | | |
| LDH (U/L) | ≤ 240 *vs* > 240 | 3.275 | 0.070 | | | |
| IPI score | 0–1 *vs* ≥ 2 | 4.451 | 0.035 | 0.596 | 0.171–2.079 | 0.417 |
| KPI score | 0–1 *vs* ≥ 2 | 1.388 | 0.239 | | | |
| CRP (mg/L) | ≤10 *vs* > 10 | 19.210 | < 0.001 | 1.010 | 0.101–10.132 | 0.993 |
| GPS score | 0 *vs* ≥ 1 | 13.713 | < 0.001 | 1.244 | 0.161–9.623 | 0.834 |
| CRP/Alb | ≤ 0.15 *vs* > 0.15 | 24.183 | < 0.001 | 3.818 | 1.262–11.549 | 0.018 |

**Table 3** Prognostic factors for overall survival

| Clinical characteristics | | Univariate analysis (PFS) | | Multivariate analysis (PFS) | | |
|---|---|---|---|---|---|---|
| | | $\chi^2$ | *P* | HR | 95% CI | *P* |
| Age (years) | ≤ 60 *vs* > 60 | 0.241 | 0.624 | | | |
| Gender | Male *vs* Female | 0.668 | 0.414 | | | |
| ECOG score | 0–1 *vs* ≥ 2 | 10.478 | 0.001 | 4.482 | 1.184–16.970 | 0.027 |
| B symptoms | No *vs* Yes | 0.391 | 0.532 | | | |
| Clinical stage | IE *vs* IIE | 2.772 | 0.096 | | | |
| LDH (U/L) | ≤ 240 *vs* > 240 | 3.995 | 0.046 | 1.159 | 0.490–2.741 | 0.736 |
| IPI score | 0–1 *vs* ≥ 2 | 5.270 | 0.022 | 0.597 | 0.159–2.247 | 0.446 |
| KPI score | 0–1 *vs* ≥ 2 | 1.614 | 0.204 | | | |
| CRP (mg/L) | ≤ 10 *vs* > 10 | 18.048 | < 0.001 | 0.983 | 0.095–10.198 | 0.988 |
| GPS score | 0 *vs* ≥ 1 | 13.265 | < 0.001 | 1.234 | 0.147–10.356 | 0.847 |
| CRP/Alb | ≤ 0.15 *vs* > 0.15 | 22.514 | < 0.001 | 3.623 | 1.176–11.165 | 0.025 |

distinguished differences low-risk group. According to the IPI score, 74% of patients were classified as low-risk (score 0–1), which also failed to discriminate between patients with different outcomes. Similarly, by KPI score 67% were placed in the group (score 0–1), which also was unsatisfactory. However, when CRP/Alb was added to all three of the aforementioned three models, we obtained significantly better discrimination: GPS score 0 (PFS: $\chi^2$ = 7.932, $P$ = 0.005, Fig. 3a; OS: $\chi^2$ = 7.326, $P$ =0.007, Fig. 3b); IPI score 0–1 (PFS: $\chi^2$ = 19.743, $P$ < 0.001, Fig. 3c; OS: $\chi^2$ = 17.210, $P$ < 0.001, Fig. 3d); and KPI score 0-1 (PFS: $\chi^2$ = 24.971, $P$ < 0.001, Fig. 3e; OS: $\chi^2$ = 20.495, $P$ < 0.001, Fig. 3f).

## Discussion

ENKTL is a distinct subtype of NHL characterized by prominent vascular destruction, tissue necrosis, and inflammatory cell infiltration [1]. Despite recent improvements resulting from combining asparaginase with radiotherapy for early-stage ENKTL patients, there remain patients with poor prognoses [16–17]. Therefore, a novel, powerful predictor for those patients is needed. A diverse set of studies have been devoted to elucidating the link between inflammation and cancer, evidence to support inflammatory cells, proinflammatory cytokines, and chemokines in the tumor microenvironment promoted tumor cell growth, proliferation, development and metastasis, resistance to treatment, leading to worse survival and prognosis [8–10]. A previous study introduced the CRP/Alb ratio as an inflammation-based prognostic ratio for patients with acute medical admissions and sepsis [18]. A recent meta-analysis demonstrated that pretreatment CRP/Alb was correlated with poor survival in multiple types of solid tumors [19]. Some studies have shown that C-reactive protein and GPS scores are independent prognostic factors for ENKTL patients [11–12]. However, the mechanisms by which the CRP/Alb ratio might be related to survival have remained unclear. Several potential explanations might account for this.

CRP, an important acute-phase response protein, is produced mainly by hepatocytes. Elevated CRP level

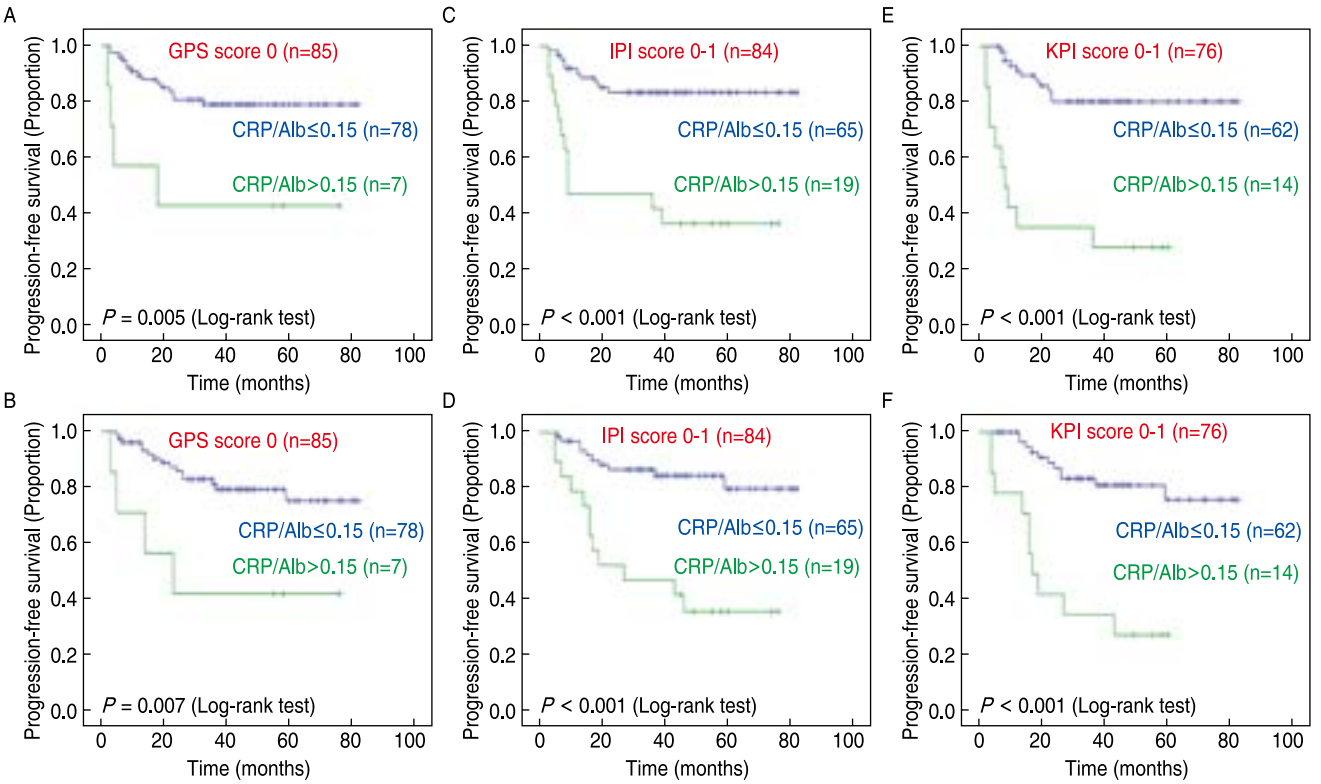


**Fig. 3** Subgroup survival analysis for prognostic value of combing CRP/Alb with GPS, IPI, and KPI: (A) PFS of GPS score 0 patients for CRP/Alb ≤ 0.15 vs CRP/Alb > 0.15. (B) OS of GPS score 0 patients for CRP/Alb ≤ 0.15 versus CRP/Alb > 0.15. (C) PFS of IPI score 0–1 patients for CRP/Alb ≤ 0.15 vs CRP/Alb > 0.15. (D) OS of IPI score 0–1 patients for CRP/Alb ≤ 0.15 vs CRP/Alb > 0.15. (E) PFS of KPI score 0–1 patients for CRP/Alb ≤ 0.15 vs CRP/Alb > 0.15. (F) OS of KPI score 0–1 patients for CRP/Alb ≤ 0.15 vs CRP/Alb > 0.15

is a marker for an inflammatory response secondary to infection, cell injury, tissue destruction, and/or tumor necrosis. It is regulated by proinflammatory cytokines, especially interleukin-6, secreted by innate immune cells. In addition, increases in CRP levels result in activation of inflammatory pathways that might trigger DNA mutation and inhibit apoptosis, leading to tumor development and progression. Previous studies have demonstrated that persistent inflammation often exists in the tumor microenvironment, inducing increases in the levels of multiple cytokines, including interleukin-6, tumor growth factors, and CRP. These cytokines in turn promote tumor cell proliferation, invasiveness, metastasis, suppression of the antitumor immune response, all of which have large effects on the response to treatment [22–23]. Studies have shown that serum elevated CRP was positively associated with the solid cancer [24–26], including ENKTL [11]. Therefore, the underlying mechanisms of the relationship between elevated CRP and poor prognosis need to be better understood.

Albumin is also produced by the liver, which helps to maintain intravascular oncotic pressure, facilitate the transport of substances, and scavenge free radicals. Hypoalbuminemia is not merely a consequence of inflammation, but also can reflect a patient's nutritional state [27]. There are several possible mechanisms that could underlie the association between decreased albumin and cancer. First, hypoalbuminemia may reflect a systemic inflammatory response triggered by production of proinflammatory cytokines from the tumor itself, restraining the ability of the liver to generate albumin and promoting acute-phase protein synthesis [28]. Second, the release of cytokines from inflammatory cells increases microvascular permeability, increasing the flow of serum albumin toward the extravascular compartment [29]. Third, serum albumin may provide an indication that mirrors some other unfavorable status of the host, such as functional impairment or immunosuppression. There is evidence that supplement of some trophic factors improves immune function in cancer patients [30]. The presence of a systemic inflammatory response and a concomitant nutritional decline may make hard for patients to bear treatment toxicity. If that is the case, serum albumin level may be an appropriate index for evaluation and prediction of nutritional improvements for cancer patients in clinical practice. Recently, accumulating evidence have shown that hypoalbuminemia was correlated with poor survival in many cancer patients [31–34].

By the chi-square test, we found that the CRP/Alb ratio was strongly associated with important clinical factors including B symptoms, elevated LDH, and the KPI score (Table 1), suggesting that high CRP/Alb is correlated with more aggressive tumor behaviors or high tumor burden. There also were positive correlations between high CRP/Alb ratios and elevated CRP, low serum albumin levels, and the GPS score. Univariate analysis showed that LDH, ECOG, and IPI scores were associated with PFS or OS in ENKTL patients (Table 2, Table 3), consistent with previous studies [6–7, 11–12].

In accordance with previous studies [11–12], CRP and GPS scores were significantly associated with poor survival in ENKTL patients in univariate analyses. However, in the our study, CRP and GPS scores were not independent prognostic factors in multivariate analysis. Two possible explanations for this difference might be that CRP and GPS both use the same two biomarkers, or that using the ratio of CRP/Alb better captures the interplay between the two markers than the simple category assignment method. By contrast to a previous report [12], no significant correlation was observed between clinical stage and B symptoms by univariate analysis. The reason for this might be that all patients had localized lesions that were sensitive to radiotherapy, which is very effective in treating in early stage ENKTL patients. Li *et al* [11–12] demonstrated that age was an independent prognostic factor for survival. By contrast, we observed no significant correlation between age and survival. The explanation might be that our older patients could tolerate treatment better, because of progress in the optimization of chemotherapy and radiotherapy technology.

Finally, we analyzed whether our new prognostic model was equivalent or superior to other validated prognostic models. The GPS score [12] is one of the best-demonstrated inflammation-based prognostic scores for ENKTL, so it was our primary benchmark. Most surprising was that when classified by the GPS, 75% of our patients were in the score 0 group (Table 1), meaning that GPS had no prognostic power for the majority of our patients. Similar to GPS score, the CRP/Alb ratio is calculated with the same values (CRP and albumin). Thus, when we categorized patients into two groups and explored their survival differences, we found that CRP/Alb identified a group of patients with a GPS score of 0 (Fig. 3a–3b). Therefore, the CRP/Alb ratio could be used in combination with the GPS score to better predict survival. The IPI score is an important prognostic score in patients with NHL, but its predictive value was not perfect in ENKTL [6] because of the imbalanced distribution of patients in risk groups. Consistent with previous studies [6–7], we found that 74% of our patients were in the IPI score 0–1 group (low to low-intermediate risk) and 67% were in the KPI score 0–1 group. In this way, both IPI and KPI failed to further discriminate among patients within these groups. However, when the CRP/Alb ratio was added to IPI or KPI, the low- to low-intermediate risk group patients were separated into two groups with significantly different survival outcomes (Fig. 3c–3f). In summary, the CRP/Alb ratio had better prognostic ability in discriminating among lower-risk patients than did the GPS, IPI, or KPI scores.

## Conclusions

The CRP/Alb ratio is a simple, feasible and inexpensive prognostic biomarker for ENKTL. This ratio showed superior prognostic ability in discriminating between patients with different outcomes in the low-risk group than the more established prognostic scores, GPS, IPI and KPI. The limitations of our study were its small sample size, its retrospective nature, and heterogeneity in treatment regimens. Therefore, larger, multicenter prospective studies are needed to confirm the prognostic value of the CRP/Alb ratio and to provide a better understanding of the mechanisms underlying it.

## Conflicts of interest

The authors declare that they have no competing interests.

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