Inflammation-based Glasgow prognostic score as an independent prognostic factor in patients with angioimmunoblastic T-cell lymphoma

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Angioimmunoblastic T-cell lymphoma (AITL) is an aggressive form of peripheral T-cell lymphoma (PIT) associated with poor prognosis. It is characterized by lymph node enlargement, B symptoms (unexplained recurrent fevers (often above 38°C), night sweats, and unexplained weight loss of more than 10% within 6 months), polyclonal hypergammaglobulinemia, and autoimmune hemolysis.[1] C-reactive protein (CRP) synthesized by hepatocytes is an acute-phase protein and an important marker of systemic inflammation. Serum CRP level is not only an independent prognostic factor in Hodgkin lymphoma but also an important independent predictor of AITL. Meanwhile, albumin (ALB) is used for nutrition assessment and acts as an anti-acute phase protein. The plasma concentration of ALB decreases during inflammation and bacterial infection. The Glasgow prognostic score (GPS), consisting of ALB and CRP levels, has been studied in several common solid tumors, including hepatocellular carcinoma, colorectal cancer, and renal cell carcinoma.[2] However, the value of GPS in the realm of AITL is unclear. On the other hand, the prognosis index for PIT has been widely used to evaluate the prognosis of various types of T-cell non-Hodgkin lymphoma. Therefore, we conducted a retrospective cohort study to explore the prognostic value of GPS and to compare the prognostic significance of GPS and PIT models in patients with AITL.

A retrospective analysis was performed on 106 patients with AITL diagnosed during 2009 to 2019 at the Sun Yat-sen University Cancer Center and the First Affiliated Hospital of Hainan University. Organized clinical data including age, sex, B-symptoms, serum lactate dehydrogenase (LDH) level, hemoglobin (Hb) level, platelet (PLT) level, ALB level, CRP level, Ann Arbor stage, extranodal sites, bone marrow (BM) involvement, Eastern Cooperative Oncology Group (ECOG) performance status score, and PIT score were collected. Progression-free survival (PFS) and overall survival (OS) were the primary endpoints of this study. PFS was calculated from the date of diagnosis to the date of occurrence of progression, relapse, death due to any cause, or the last date of follow-up. OS was defined as the time between the date of diagnosis to death or the last date of follow-up. Treatment response was assessed by positron emission tomography/computed tomography imaging of nodal regions according to the International Workshop to Standardize Response Criteria. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee and the Institutional Review Board of the two hospitals (Sun Yat-sen University Cancer Center [No. B2019-052] and The First Affiliated Hospital of Hainan Medical College [No. 2019 (Research)-25]) and with the 1964 *Helsinki Declaration* and its later amendments or comparable ethical standards.

GPS was calculated from serum CRP and ALB values. In brief, patients with both elevated CRP (>10 mg/L) and hypoalbuminemia (<35 g/L) were rated with a score of 2; patients with only elevated CRP (>10 mg/L) or hypoalbuminemia (<35 g/L) were rated with a score of 1; patients with neither of these abnormalities were rated with a score of 0.[3] We defined GPS = 0 as a low-risk group, GPS = 1 as a medium-risk group, and GPS = 2 as a high-risk group. Categorical data were compared by Chi-square tests. Kaplan-Meier method and Cox regression

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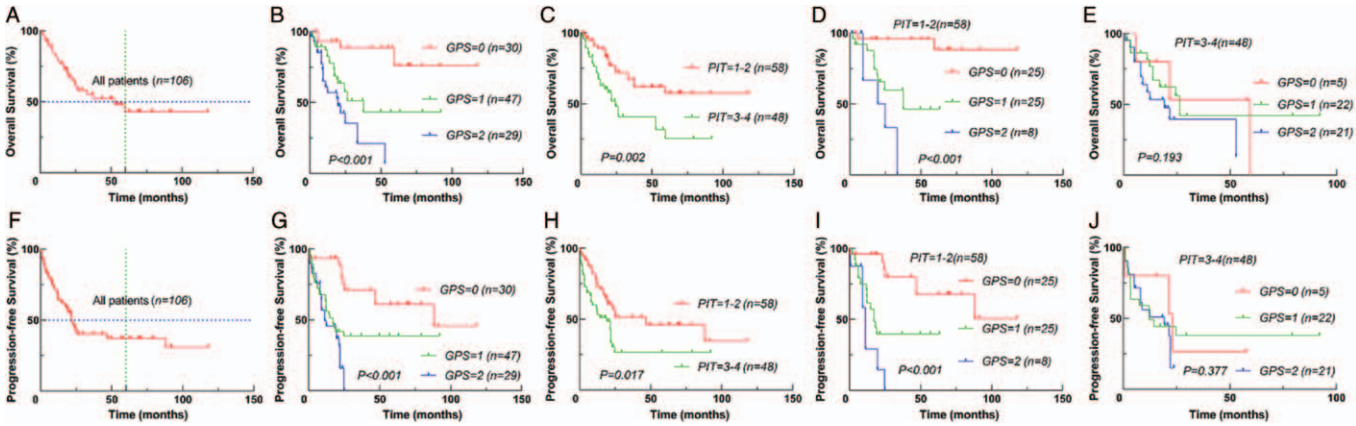

Figure 1: Kaplan-Meier curves for OS (A) and PFS (F) among 106 patients with AITL. Kaplan-Meier curves comparing OS (B) and PFS (G) among patients according to GPS. Kaplan-Meier curves comparing OS (C) and PFS (H) among patients according to PIT. Kaplan-Meier curves comparing OS (D) and PFS (I) among patients in the low-risk group by PIT score according to GPS. Kaplan-Meier curves comparing OS (E) and PFS (J) among patients in the high-risk group by PIT score according to GPS. AITL: Angioimmunoblastic T-cell lymphoma; GPS: Glasgow prognostic score; OS: Overall survival; PFS: Progression-free survival; PIT: Prognostic index for peripheral T-cell lymphoma unspecified.

model were used to estimate the survival rates with 95% confidence intervals (CIs). In all analyses, *P* values were bilateral and $P < 0.05$ was considered statistically significant. All statistical analyses were performed by SPSS Version 23.0 (IBM Corp., Armonk, NY, USA), and figures were drawn using the GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA, USA).

A homogeneity test was first conducted on the baseline data from the two hospitals and this demonstrated no significant difference [Supplementary Table 1, http://links.lww.com/CM9/A445]. Of the 106 patients included in this study, 65 were men with a male-to-female ratio of 1.59. The median age at the initial diagnosis was 63 years (range: 34–84 years). Fifty-eight patients (54.7%) were >60 years old, and 22 (20.8%) had high ECOG scores at the time of diagnosis. Only 19 (17.9%) patients had B symptoms. Overall, 61 (57.5%) patients had an elevated LDH level, 91 (85.8%) patients were at an advanced clinical stage, 42 (39.6%) patients had an extranodal disease, and 20 (18.9%) patients had BM invasion. There were 48 (45.3%) of the patients had a PIT score of >2, and 65 (61.3%) patients had anemia. For the GPS, 30 (28.3%), 47 (44.3%), and 29 (27.4%) patients were categorized into GPS = 0, GPS = 1, and GPS = 2, respectively. High GPS was significantly associated with older age ($P = 0.002$), elevated LDH level ($P = 0.003$), advanced clinical stage ($P < 0.001$), high PIT score ($P < 0.001$), low PLT ($P = 0.035$), and low Hb level ($P < 0.001$) compared with those with lower GPS. No significant difference was found in the other characteristics among patients with varying GPSs [Supplementary Table 2, http://links.lww.com/CM9/A445].

Of the 106 patients, 74 (69.8%) received cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP or CHOP like) regimen; 22 (20.8%) received etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisone (EPOCH); and 10 (9.4%) received gemcitabine and oxaliplatin (GEMOX) regimen. The proportion of patients with GPS = 2 (37.9% $n = 11$) receiving EPOCH or GEMOX regimens was higher than those with GPS = 0 (26.7% $n = 8$) and GPS = 1 (27.7% $n = 13$). After an initial treatment, 56 patients (52.8%) in the entire study cohort achieved a complete response (CR). The CR rate of patients with GPS = 1 (46.8%) and GPS = 2 (41.4%) was significantly lower than those of patients with GPS = 0 (73.3%) ($P = 0.001$) [Supplementary Table 3, http://links.lww.com/CM9/A445].

Overall, the median follow-up duration was 50.5 months (95% CI: 41.2–59.8 months). The median OS and PFS were 52.7 and 22.0 months, respectively. The estimated 5-year OS rates and PFS rates were 43.0% (95% CI: 33.6–52.4%) [Figure 1A] and 37.0% (95% CI: 27.8–46.2%) [Figure 1F], respectively. Furthermore, patients with GPS = 0 had significantly higher rate of 5-year OS (76.0% *vs.* 43.4% *vs.* 0, $P < 0.001$) [Figure 1B] and 5-year PFS (61.0% *vs.* 38.7% *vs.* 0, $P < 0.001$) [Figure 1G] when comparing with GPS = 1 and GPS = 2, respectively. The 5-year OS rate (57.4% *vs.* 25.4%, $P = 0.002$) [Figure 1C] and 5-year PFS rate (46.1% *vs.* 26.5%, $P = 0.017$) [Figure 1H] were significantly higher among patients with PIT = 1–2 than those with PIT = 3–4. In the low-risk group by PIT score, patients with a GPS of 0 had higher 5-year OS rate (88.4% *vs.* 46.5% *vs.* 0, $P < 0.001$) [Figure 1D] and 5-year PFS rate (67.7% *vs.* 39.6% *vs.* 0, $P < 0.001$) [Figure 1I] than those with a GPS of 1 or 2. However, in the high-risk group by PIT score, no significant difference was observed in the OS and PFS among the different risk groups stratified by GPS ($P = 0.193$, Figure 1E, and $P = 0.377$, Figure 1J). This indicated that both GPS and PIT can stratify the prognosis of AITL patients, but GPS also allows the prognosis of patients to be delineated further in the low-risk PIT group. There were 74 patients treated with CHOP or CHOP-like regimen. Among these, patients with GPS = 1–2 had worse 5-year OS rate (48.8% *vs.* 0 *vs.* 72.7%, $P = 0.002$) and 5-year PFS rate (42.4% *vs.* 0 *vs.* 57.1%, $P = 0.017$) [Supplementary Figure 1A and 1C, http://links.lww.com/CM9/A445] than patients with GPS = 0. Elevated PIT was associated with lower 5-year OS rate (25.5% *vs.* 58.9%, $P = 0.013$) [Supplementary Figure 1B, http://links.lww.com/CM9/A445]. However, there was no significant difference in the PFS among different PIT groups ($P = 0.185$) [Supplementary Figure 1D, http://links.lww.com/CM9/A445]. Therefore, in the CHOP

or CHOP-like group, GPS has better prognostic significance than PIT.

In the univariate analysis, age >60 years, elevated serum LDH, and anemia were adverse prognostic factors for OS ($P = 0.017$, $P = 0.016$, and $P = 0.006$, respectively) [Supplementary Table 4, http://links.lww.com/CM9/A445]. High GPS ($P < 0.001$ and $P < 0.001$) and high PIT ($P = 0.002$ and $P = 0.017$) were significantly associated with both inferior OS and PFS, respectively [Supplementary Table 4, http://links.lww.com/CM9/A445]. In general, patients with low ALB were observed to have higher ECOG scores, but this did not reach statistical significance ($P = 0.510$). Multivariate analysis showed that only high GPS was a significant predictor of both poor OS (relative risk [RR]: 5.702, 95% CI: 2.214–14.686, $P < 0.001$) and PFS (RR: 3.324, 95% CI: 1.668–6.626, $P = 0.001$) [Supplementary Table 4, http://links.lww.com/CM9/A445].

In summary, our study revealed that age >60 years, elevated serum LDH, anemia, and high PIT were adverse prognostic factors for OS in the univariate model. These findings are consistent with a previous study.[4] In multivariate analysis, the GPS, independent of PIT and other factors, was a powerful predictor for patients with AITL. The risk stratification of patients using the GPS appears superior and better in the distribution for prognostic significance compared with PIT in the low-risk group. The biological mechanism of the relationship between an elevated GPS and the poor prognosis of AITL remains unknown. Given that CRP and ALB have been used to develop the GPS system that correlates with tumor prognosis, some explanations in this regard are introduced here. First, bioactive molecules such as cytokines, growth factors, and chemokines are produced by tumor-infiltrating cells during inflammation to promote the growth and invasive behavior of tumor cells. Hence, the concentration of circulating CRP levels is raised, which may reflect the phenotype or aggressiveness of the tumor.[5] Second, the presence of hypoalbuminemia before treatment may suggest malnutrition or unfavorable general health status of patients, which results in patients lacking the ability to tolerate intensive chemotherapy. Third, elevated CRP levels may indicate impaired T-lymphocytic response to the tumor, and lymphocyte depletion is likely a reflection of an impaired T-lymphocyte-mediated anti-tumor response that represents an adverse prognostic trait. Furthermore, elevated GPS is associated with elevated LDH, advanced Ann Arbor stage, and frequent extranodal invasion, which are all indicators of high tumor burden. Further studies are required to delineate the underlying mechanisms of the relationship between high GPS and low survival outcomes in AITL patients.

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Conflicts of interest

None.

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