Decreased peripheral blood lymphocyte-monocyte ratio and platelet-monocyte ratio and the Peripheral Blood Score model predict poor survival in peripheral T-cell lymphoma patients

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Abstract

Background Peripheral T-cell lymphoma(PTCL) is a group of lymphoproliferative tumors originated from post-thymic T cells or mature natural killer (NK) cells. It shows highly aggressive clinical behaviour, resistance to conventional chemotherapy, and a poor prognosis. Its incidence rate in China is 1 to 2 times higher than in western countries. Therefore, optimal strategies for identifying high-risk patients are urgently needed.

Materials and Methods We retrospectively studied 347 newly diagnosed PTCL patients from January 2011 to October 2019 and analyzed the relationship between peripheral blood lymphocyte-monocyte ratio (LMR) and platelet-monocyte ratio (PMR) and prognosis. The model of Peripheral Blood Score was established to screen out high-risk patients.

Results The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off value based on survival rate. It was found that patients with PTCL with LMR ≤ 1.68 and PMR ≤ 300 had inferior overall survival (OS) and the difference was significant in both low-risk (P<0.001) and medium high-risk (P<0.001) groups of IPI score. In multivariate analysis, LMR ≤ 1.68 (HR=1.751, 95% CI 1.158-2.647, p=0.006), PMR ≤ 300 (HR=1.762, 95% CI 1.201-2.586, p=0.002), stage III-IV (HR=3.276, 95% CI 1.512-7.099, p=0.003), Eastern Cooperative Oncology Group (ECOG) score 3-5 (HR=2.351, 95% CI 1.647-3.356, p<0.001) and extra-nodal invasion more than one site (HR=1.659, 95% CI 1.125-2.445, p=0.039) were independently associated with short survival. LMR and PMR were integrated into "Peripheral Blood Score (PBS)" model. PTCL patients were divided into three risk groups: low-risk group, medium risk group and high-risk group. The 1-year OS was 86%, 55.3% and 22.6%, and the 3-year OS was 43.4%, 20% and 13.1%, respectively.

Conclusion Overall, LMR and PMR can be used as early prognostic indicators in PTCL patients. Moreover, we can easily detect the complete blood cell count (CBC), and use PBS model to preliminarily screen and stratify patients. It is simple, convenient and accurate to screen out patients with short lives, and formulate personalized treatment strategies.

Introduction

Peripheral T-cell lymphoma(PTCL) is a group of rare hematological malignancies with heterogeneous morphological and biological characteristics. The overall manifestations are high invasiveness, short survival and poor prognosis. The total incidence rate is 0.5-2, per 100000 persons per year, and account for about 10% of all non-Hodgkin's lymphomas (NHL) in Western countries[1]. However, the incidence of PTCL in Asia is higher, accounting for 25%-30% of NHL in China[2]. Nowadays, the internationally recommended first line therapy is still anthracycline-based chemotherapy. But the complete response (CR) rate after chemotherapy is only 40%-60% , with overall survival (OS) of 30-40% . Most patients face the problem of short-term recurrence [3]. And the recurrence or progression of the lack of effective treatment measures [4-5].

According to the WHO classification, PTCL can be further divided into many pathological subtypes. The most common subtypes include PTCL-not otherwise specified (PTCL-NOS), extra-nodal natural killer (NK)/T cell lymphoma, nasal type (ENKTL), angioimmunoblastic T-cell lymphoma (AITL), anaplastic lymphoma kinase positive anaplastic large cell lymphoma (ALK+ ALCL) and anaplastic lymphoma kinase negative anaplastic large cell lymphoma (ALK- ALCL) [6]. In addition, there are some rare subtypes, such as monomorphic epitheliotropic intestinal T-cell lymphoma(MEITL), subcutaneous panniculitis like T-cell lymphoma(SPTCL), mycosisfungoides/Sezary's syndrome(MF/SS), Hepatosplenic T-cell lymphoma (HSTCL) and so on. Due to its rarity and heterogeneity, the prognosis of PTCL are less studied.

International Prognostic Index (IPI) confirmed its usefulness for PTCL including age, Eastern Cooperative Oncology Group (ECOG), Ann Arbor staging, lactic dehydrogenase (LDH) and extra-nodal invasion [3]. The Intergruppo Italiano Linfomi (now Fondazione Italiana linfomi, FIL) performed a large study in the 1990s on 385 patients diagnosed and treated. Based on this study, they identified a prognostic model, the Prognostic Index for PTCL-unspecified (PIT). The results showed that age, ECOG, LDH and bone-marrow involvement were independent predictors of OS and they confirmed that the PIT was slightly more effective than the IPI in PTCL-NOS patients[7]. But even so, these scoring systems are relatively complex and need to be evaluated from multiple aspects. Therefore, our study found that through the determination of peripheral blood lymphocyte-monocyte count ratio and platelet-monocyte count ratio could be simple and effective to screen out high-risk patients.

Tumor micro-environment, host immunity and systemic inflammatory response are the key factors that determine the clinical course and prognosis of tumor patients. More and more studies found tumor-associated macrophages (TAMs) are associated with poor clinical prognosis of a variety of tumors, including colon cancer, thyroid cancer and Burkitt's lymphoma by promoting angiogenesis, local invasion and metastasis[8-10]. Moreover, it has been confirmed that the growth and survival of malignant T cells depend on alternatively activated (M2) macrophages in micro-environment, and the growth of alternatively activated (M2) macrophages are affected by TAMs [11-12]. Yingming Zhu et al. found that serum monocytes were locally absorbed and differentiated into macrophages after tumor invasion, and reacted to a wide range of chemokines and growth or differentiation factors such as CCL-2 and CSF-1 produced by tumor and stromal cells, and further confirmed the correlation between LMR and TILs / TAMs ratio[13].

Increasing evidence indicates that platelets play several roles in the progression of malignancies and in cancer-associated thrombosis. A notable cross-communication exists between platelets and cancer cells[14]. CXCL12 promoted monocytes and M1-M2 macrophages to phagocytic apoptosis platelets, and promoted their differentiation into foam cells through CXCR4 and CXCR7. Therefore, platelet derived CXCL12 could regulate monocyte macrophage functions through the different binding of CXCR4 and CXCR7, which indicated that they played an important role in the inflammatory reaction of platelet aggregation site[15]. Our study is the first time to discuss the relationship between PMR, LMR and prognosis of PTCL. We found that the decreased of PMR and LMR were closely related to the low survival

of PTCL. On this basis, we established a peripheral blood score (PBS) model to identify high-risk patients early.

Materials And Methods

2.1 Patients and characteristics

This is a single center retrospective study. A total of 347 patients with PTCL newly diagnosed in the First Affiliated Hospital of Zhejiang University School of Medicine from January 2011 to October 2019 were included. The final observation time was January 2020, and the median follow-up time was 18 months (rang: 0-108 months). The inclusion criteria were as follows: (1) Age ≥15 years; (2) The pathological diagnosis was consistent with PTCL; (3) Newly diagnosed and no chemotherapy before clinical data were collected; (4) Complete clinical data; (5) At least two cycles of treatment were given. Although the treatment plan were not completely unified, all the patients in our study received cyclophosphamide-doxorubicin-vincristine-prednisone (CHOP) or CHOP-like chemotherapy regimen, and all ENKTL patients were treated with chemotherapy combined with Pegaspargase. All procedures involving human participants in our study were conducted in accordance with the Helsinki declaration.

We collected the medical records, physical examinations, laboratory results, pathological reports and radiological results of these patients through electronic medical records, and re analyzed the clinical data of them. All baseline data are presented in Table 1. Follow-up was performed by making phone calls. The absolute counts of lymphocytes, monocytes and platelets were obtained from a standard complete blood count (CBC) performed at diagnosis. LMR was the absolute count of lymphocyte divided by the absolute count of monocyte. PMR was the ratio of platelet absolute count to monocyte absolute count. OS was defined as the time from diagnosis to death for any reasons or last follow-up.

2.2 Cut-off value for LMR/PMR

The optimal cut-off of LMR and PMR were obtained by calculating the area under the curve by receiver operating characteristic (ROC) curve analysis.

2.3 Statistical analysis

Post hoc power analyses were conducted with GPOWER (Faul, Erdfelder, Lang, & Buchner, 2007) in order to estimate the probability of occurrence of effects in the sample. Through the normal distribution test, the continuous variables included in this study all conform to the normal distribution. The continuous variables such as lymphocyte count, monocyte count and platelet count were shown as median with range and were compared by Mann-Whitney U-test. Other continuous variables were grouped according to the usual clinical threshold and were presented as frequencies and percentages (n, %) in company with categorical variables. All hierarchical and categorical variables were compared by Pearson's chi-square test. Among them, histological subtypes were performed bonferroni-post-hoc-correction. Kaplan-Meier curve was used to analyze OS and log-rank test was used for comparison. Univariate and multivariate

logistic regression models were used to evaluate the correlation between clinical variables and complete remission (CR). Cox proportional hazard regression model was used to analyze univariate and multivariate of OS. Statistical analysis was performed by spss23.0 software package. In all comparisons, the results were considered to be statistically significant when the p value was < 0.05, and 95% confidence interval (CI) was given.

Results

3.1 Patients Characteristics

According to the admission conditions, we enrolled 347 patients with newly diagnosed PTCL for analysis. The clinical characteristics and laboratory data were listed in Table 1. The four most common subtypes of PTCL-NOS, ENKTL, AITL and ALCL accounted for 32.0%, 32.5%, 20.2% and 11.8%, respectively. Other rare subtypes including MEITL, SPTCL, HSTCL and MF/SS accounted for 3.5% totally. However, the different subtypes of PTCL did not show statistical significance in the stratification of LMR in our study, either by Pearson's chi square test (P=0.330) or performing bonferroni-post-hoc-correction (P=0.570). Although the difference of case typing in PMR was statistically significant through Pearson's chi square test (P=0.018), the difference was not statistically significant in bonferroni-post-hoc-correction (P=0.139). The median age at diagnosis was 55 years (rang: 15-84 years), and among them, 36% of the elderly patients were over 60 years old. The ratio of male to female was close to 2:1. About 81.3% of patients were in stage III-IV and 58.5% of them had B symptoms. At the first diagnosis, 32.3% of patients had albumin below 35 g/L, and 64.6% of them were infected with Epstein-Barr virus (EBV). In addition, 163 patients had more than one extra-nodal site involved. The serum lactic dehydrogenase (LDH) and beta-2 microglobulin (β2-MG) levels were increased in 64% of the patients, respectively.

All patients received at least two cycles of chemotherapy. Except for all ENKTL patients received the protocol containing Pegaspargase. The rest of patients included in this study were treated with CHOP (cyclophosphamide-doxorubicin-vincristine-prednisone) or CHOP-like chemotherapy. Furthermore, 36 patients proceeded to hemopoietic stem cell transplantation, in which 24 of them accepted autologous stem cell transplantation.

3.2 The cut-off values and the association of LMR/PMR with clinical parameters and complete response (CR)

The ROC curve was generated to select the appropriate cutoff values for LMR and PMR based on the survival analysis (Figure 1). For LMR, the area under curve (AUC) was 0.734 (95% CI: 0.682-0.786), with a generated maximum joint sensitivity and specificity at the value of 1.68. In addition, for PMR the AUC was calculated to be 0.718 (95% CI: 0.664-0.772), with a generated maximum joint sensitivity and specificity at the value of 300. Table 1 compared the clinical characteristics of patients with LMR and PMR at different levels and the high group and low group were defined as being greater than the cutoff value and less or equal to than the cutoff value, respectively. Post hoc analysis demonstrated sufficient power to distinguish the significant differences (power = 0.996). Patients with LMR≤1.68 or PMR≤300,

only 14.2% and 14.3% of them achieved complete response (CR) after treatment. Therefore, it is not difficult to speculate that patients with LMR≤1.68 or PMR≤300 may have poor therapeutic effect. Moreover, we found that in the low LMR and PMR groups, the proportion of patients with IPI at 3-5 points is higher. Whether in the low-risk group (IPI = 0-2) or the high-risk group of IPI (IPI = 3-5), the OS of PTCL patients with low LMR group and low PMR group were significantly lower than those of patients in the high LMR group and high PMR group (Figure 3).

In univariate logistic regression analysis, lower CR rate was related to first diagnosis older than 60 years, IPI≥3, ECOG≥3, stage III-IV, B symptoms, bone marrow involvement, Albumin≤35g/L, EBV infection, Extra-nodal≥1, lymphocyte (LY)(×10^9/L)≤0.8, monocyte (MONO)(×10^9/L)≥1, platelet (PLT)(×10^9/L)≤83, elevated LDH and elevated β2-MG, LMR≤1.68 and PMR≤300 (Table 2). Nevertheless, in the multivariate logistic regression analysis, only first diagnosis older than 60 years(OR=4.031, 95% CI 2.021-8.041, p≤0.001), ECOG≥3(OR=3.610, 95% CI 1.572-8.290, p=0.002), stage III-IV(OR=2.737, 95% CI 1.255-5.969, p=0.011), bone marrow involvement(OR=2.581, 95% CI 1.173-5.683, p=0.018) and EBV infection(OR=2.090, 95% CI 1.170-3.734, p=0.013) were statistically significant(Table 2).

3.3 The association of LMR/PMR with OS

In our study, we analyzed the survival of low and high groups of LMR and PMR patients, and found that there were significant differences in OS between all the two groups (P≤0.001)(Figure 2). The median survival time in the groups with LMR≤1.68 and LMR≥1.68 and PMR≤300 and PMR≥300 were 5 months and 28.5 months, 6 months and 28 months, respectively. The univariate analysis showed that first diagnosis older than 60 years, IPI≥3, ECOG≥3, stage III-IV, B symptoms, bone marrow involvement, decreased albumin, EBV infection, Extra-nodal≥1, LY(×10^9/L)≤0.8, MONO(×10^9/L)≥1, PLT(×10^9/L)≤83, elevated LDH, elevated β2-MG, LMR≤1.68 and PMR≤300 were prognostic indicators of OS(Table 3). Then, multivariate analysis was showed that patients with poor OS had ECOG≥3 (HR=2.351, 95% CI 1.647-3.356, p≤0.001), stage III-IV (HR=3.276, 95% CI 1.512-7.099, p=0.003), Extra-nodal≥1 (HR=1.659, 95% CI 1.125-2.445, p=0.039), LMR≤1.68 (HR=1.751, 95% CI 1.158-2.647, p=0.006), and PMR≤300 (HR=1.762, 95% CI 1.201-2.586, p=0.002).

Considering the heterogeneity of PTCL, we analyzed the five common pathological subtypes separately, and found that the decrease of LMR and PMR was significantly correlated with OS except ALCL, ALK+ (Table 4, 5). May be related to the small number of this subtypes in this study.

3.4 Establishment of PBS model and its correlation with OS

We compared the peripheral blood cell count of the patients at the initial stage, and scored 1 point for LMR≤1.68 and PMR≤300 respectively. The patients were divided into PBS 0, 1 and 2. 0 was divided into low-risk group, 1 was medium risk group, and 2 was high-risk group. The OS of the three groups was statistically analyzed by Kaplan Meier curve and log-rank test. It was found that the OS of low-risk, medium risk and high-risk patients was significantly different. The median OS of the three groups were 32.5 months, 13 months and 5 months respectively (P≤0.001)(Figure 4). Not only that, in the PBS high-

risk group, 77.4% of the patients survived for less than 1 year, and only 13.1% survived for more than 3 years. In the low-risk group with PBS 0 score, 86% of the patients survived more than 1 year, and 43.4% of the patients survived for more than 3 years, nearly half of them.

Discussion

The prognosis of PTCL is poor, either in first-and second-line therapy or salvage therapy. There is an urgent need to use accurate predictive models to classify patients at risk. Among all the previously reported indices, IPI and PIT are the most commonly used. It is worth noting that there is considerable overlap in the parameters used to establish the various models and that the patients need to be evaluated by imaging, examination, bone marrow, etc. . The operations are complex, and the establishments of these scoring models are not entirely based on PTCL, so their accuracy are questionable.

With the development of medical science in recent years, more and more attention had been paid to the study of tumor molecular mechanisms, especially in tumor micro-environment. Therefore, the research on PTCL has opened a new chapter.

Recently, a growing body of research has consistently shown that tumor-associated inflammatory response is a key determinant of prognosis in cancer patients [16]. In previous retrospective studies, we found an association between increased serum Interleukin-10 levels and low survival and early recurrence in patients with PTCL [17]. Interleukin-10 is involved in the body's inflammatory and immune responses and plays an important role in tumors and infections. It is mainly secreted by monocytes, activated T-cells, macrophages, certain tumor cells and so on. Thus, monocyte and macrophage systems are closely related to the prognosis of PTCL. About 2-9% of peripheral leukocytes are peripheral blood monocytes (PBMC), but only 40% of them are used for monocyte circulation, while 60% of monocytes migrate [18]. However, some immature PBMC can differentiate into specialized, tissue-specific macrophages and Antigen-presenting cells (APC). Their differentiation directly determines their functions. The differentiated monocytes/macrophages (Mphi) plays a specific role in the cell mediated innate immunity against infection, immunoregulation, morphogenetic remodelling and malignancy or tissue repair [19-20]. Subsequently, macrophages respond to a wide range of chemokines and growth or differentiation factors such as CCL-2 and CSF-1 produced by tumors and stromal cells. VEGFA and EGF produced by Tumor-associated macrophages (TAMs) promote angiogenesis and tumor growth, respectively, which is consistent with the positive correlation between CD68 expression, vascular invasion and tumor length [21]. Macrophages are remarkably plastic. Depending on the stimulus that activates them, they can polarize to either type M1(causing an anti-tumor response) or type M2(causing tumor growth and progression). It had been demonstrated that the growth and survival of malignant T-cells depend on alternatively activated (M2) macrophages in the micro-environment and that the growth of alternatively activated (M2) macrophages were influenced by TAMs [22]. Yingming Zhu et al. found that LMR was associated with TILs/TAMs ratio, and that low LMR had worse OS in patients with esophageal squamous cell carcinoma [13]. It suggests that a systemic inflammatory response may reflect concurrent focal inflammation in the tumor.

D.Iacono et al. retrospectively analyzed 165 patients with advanced melanoma. The severity and prognosis of the disease were assessed. The decrease of LMR suggests short OS and more distant metastatic sites in malignant melanoma [23]. Wang et al. reported 355 cases of diffuse large B-cell lymphoma (DLBCL). In the low LMR group, PFS and OS were shorter and M2-TAM content was higher. These results suggested that weak anti-tumor immunity may be an adverse prognostic factor for aggressive lymphoma, identified in high-risk patients [24]. Thus, lymphocyte counts, monocyte counts, and LMR surrogate markers of tumor micro-environment had been reported as prognostic factors for B cell lymphoma[24-26]. Similarly, recent studies had shown that both lymphocyte counts and monocyte counts could predict the clinical outcome of T-cell lymphomas[27-28]. And patients with T-cell lymphomas after autologous peripheral hematopoietic stem cell transplantation had longer OS and PFS with autograft lymphocyte-to-monocyte ratio(A-LMR) greater than or equal to 1. Compared with patients with A-LMR less than 1, the five years OS rate was 87% to 26% , and the five years PFS rate was 72% to 16% , significant difference [29]. But in our study, patients with LMR less than or equal to 1.68 had a median OS and significantly worse CR rate for treatment than patients with LMR greater than 1.68 (5 months vs. 28.5 months; 14.2% vs. 45%) . The main reasons for this difference include: first, in Luis F et al.'s study, they examined autograft lymphocyte-to-monocyte ratio(A-LMR), whereas our study examined LMR in patients'peripheral blood at the time of initial diagnosis; second, they included only 109 patients, we included 347 patients; third, they chose patients with T- cell lymphomas, and we included peripheral T-cell lymphomas, with different baseline characteristics.

Megakaryocytogenesis is a process in which megakaryocytes (MK) proliferate, differentiate and mature from pluripotent hematopoietic stem cells (HSC), while platelets are formed from mature MK fragments. The average platelet count in humans is between $150×10^9$ and $400×10^9$ per liter, but over time, the number of individual platelets remains the same[30]. Platelets mainly participates in the organism haemostasis and the thrombosis. In recent years, there are increasing evidences that platelets and tumor cells have significant cross-communication, suggesting that they play an important role in the progression of malignant tumors, the occurrence of tumor-associated local inflammation, and cancer-associated thrombosis. On the one hand, tumors can affect the RNA profile of platelets, the number of circulating platelets and their activation status. On the other hand, tumor-induced platelets contain a large number of active biomolecules, including platelet-specific and circularly ingested biomolecules that are released upon activation of platelets and are involved in the development of malignant tumors[31]. Tissue factor (TF) has a direct pro-inflammatory effect by inducing the production of reactive oxygen species [32]. Thus, platelets are directly involved in the initiation of inflammatory responses (clotting, monocyte recruitment, activation, and matrix remodeling) by inducing additional adhesion molecules, MMPs, tissue-type plasminogen activators, and cytokines (such as MCP-1) in endothelial cells [33]. Platelets store and release CXCL12 (SDF-1), which controls the differentiation of hematopoietic progenitors into endothelial cells or macrophage-foam cells. CXCL12 binds CXCR4 and CXCR7 and regulates the functions of monocyte/macrophages. M Chatterjee et al. found that platelets and platelet-macrophage aggregates increased in peritoneal fluid following peritonitis induction in mice in vivo. Compared with peripheral blood, the relative surface expressions of CXCL12, CXCR4 and CXCR7 in

infiltrated monocytes were also enhanced. Moreover, platelet CXCL12 and recombinant CXCL12 participate in the enhancement of specific induction of monocyte chemotaxis through CXCR4. Under static and dynamic arterial flow conditions, the adhesion of monocytes to the surface of immobilized CXCL12 and activated platelets rich in CXCL12 is mediated mainly through CXCR7, and is counter-regulated by neutralizing platelet-derived CXCL12. In the co-culture experiment with platelets, monocytes were mainly differentiated to CD163+ macrophages, and CD163+ macrophages weakened after blocking antibodies to CXCL12 and CXCR4/CXCR7. Therefore, platelets-derived CXCL12 can regulate mononuclear-macrophage functions through different combinations of CXCR4 and CXCR7, suggesting that it plays an important role in platelet aggregation in local inflammatory responses [34].

Platelet activation plays an important role in tumor-associated immune thrombosis and multiple metastasis. Activated platelets were known to secrete a range of inflammatory chemokines that activate inflammatory signaling pathways in white blood cells, including PAF, RANTES, CCL3, CXCL1, CXCL4 (platelet factor 4), and CXCL7 [35, 36]. Serotonin (5-hydroxytryptamine) is another platelet-releasing product that may affect monocyte function. Monocytes exposed to 5-hydroxytryptamine showed increased NF-κB activation, increased cytokine production induced by LPS, and decreased apoptosis, possibly due to changes in BCL-2 or MCL-1 expression [37]. In the past few decades, a large number of clinical studies have shown that daily aspirin can reduce the incidence, metastasis and mortality of tumors, especially for colorectal cancer [38]. Recently, Guillem Lobat P and his collaborators demonstrated in an immunodeficiency mouse model that low-dose aspirin reduces the metastasis of lung cancer by avoiding the enhanced pro-aggregation effect caused by platelet-tumor cell interaction [39]. These clinical studies have fully confirmed that platelets are closely related to the occurrence and development of tumors.

In conclusion, since both host immunity and tumor micro-environment are closely related to the occurrence, development and metastasis of tumor, the combination of lymphocyte count, monocyte count and platelet count can better reflect the prognosis of tumor. LMR had been studied in many different disease settings, had been widely discussed, and had been found to predict esophageal cancer, melanoma, Hodgkin's lymphoma, multiple myeloma, and DLBCL [13,23,40-42]. However, it has never been discussed in PTCL. Platelet counts and monocyte counts had been shown to be associated with sepsis, pulmonary embolism [43-44], and so on, but no correlation between platelet counts and monocyte count ratios and tumors has been previously reported. We analyzed 347 patients with primary PTCL and found that the patients with low LMR ratio and low PMR ratio had worse response to treatment and shorter survival time. The difference were significant in low-to-moderate-risk patients with an IPI score of 0-2 and in high-to-moderate-risk patients with an IPI score of 3-5. In multivariate tests, LMR ≤ 1.68 and PMR ≤ 300 were independent risk factors for OS shortening. By integrating reduced LMR and PMR to produce a "PBS" model, newly diagnosed PTCL patients can be divided into three risk groups. Specifically, patients in the low-risk group had no abnormal blood cells and had a 3-year survival rate of 43.4% , while those in the high-risk group had a 3-year survival rate of 13.1% .

Our study still has some limitations. Firstly, the retrospective study may be biased in the selection of patients. Secondly, the dynamic changes of patients during treatment did not taken into account during analysis. Third, our sample size is relatively small and lack of cytogenetic data. Another issue is the cut-off value of LMR/PMR used in clinical practice. In the past and in our study, the ROC curve based on survival was used to determine the optimal cut-off value, indicating that there was inconsistency between the centers. Therefore, further exploration and prospective trials with larger samples are needed in the future and the PBS model we established also needs further verification.

Conclusions

All in all, decreased LMR and PMR can be used as early prognostic indicators in PTCL patients. Moreover, we can easily detect the complete blood cell count (CBC), and use PBS model to preliminarily screen and stratify patients. It is simple, convenient and accurate to screen out patients with short lives, and formulate personalized treatment strategies. More large-sample prospective clinical trials are needed to confirm these findings in future research directions.

List Of Abbreviations

Abbreviations	Definitions
PTCL	peripheral T-cell lymphoma
NHL	non-Hodgkin's lymphoma
CR	complete response
OS	overall survival
ECOG	eastern cooperative oncology group
LMR	lymphocyte-monocyte ratio
PMR	platelet-monocyte ratio
PBS	peripheral blood score
CBC	blood cell count
PTCL-NOS	peripheral T-cell lymphoma, not otherwise specified
ENKTL	extra-nodal natural killer (NK)/T cell lymphoma, nasal type
AITL	angioimmunoblastic T-cell lymphoma
ALK+ ALCL	anaplastic lymphoma kinase positive anaplastic large cell lymphoma
ALK- ALCL	anaplastic lymphoma kinase negative anaplastic large cell lymphoma
MEITL	monomorphic epitheliotropic intestinal T-cell lymphoma
SPTCL	subcutaneous panniculitis like T-cell lymphoma
MF/SS	mycosisfungoides/Sezary's syndrome
HSTCL	hepatosplenic T-cell lymphoma
IPI	International Prognostic Index
LDH	lactic dehydrogenase
TAMs	tumor-associated macrophages
ROC	receiver operating characteristic
CI	confidence interval
EBV	epstein-Barr virus
β2-MG	beta-2 microglobulin
LY	lymphocyte
MONO	monocyte
PLT	platelet
PBMC	peripheral blood monocytes
APC	antigen-presenting cells

Mphi	monocytes/macrophages
DLBCL	diffuse large B-cell lymphoma
PFS	progression free survival
A-LMR	autograft lymphocyte-to-monocyte ratio
HSC	hematopoietic stem cells
TF	tissue factor

Declarations

7.1 Ethics approval and consent to participate

All procedures involving human participants in our study were conducted in accordance with the Helsinki declaration and all patients signed informed consents.

7.2 Consent for publication

All authors agreed to publish this manuscript. There is no copyright conflict.

7.3 Availability of data and materials

All data included in our manuscript were real clinical data. However, because this was a retrospective clinical study, the original blood samples have been unable to obtain, so the data used were all obtained from the previous patients' in-hospital tests, without repeated tests.

7.4 Competing interests

There is no conflict of interest between the authors.

7.5 Funding

Not applicable

7.6 Authors' contributions

Wanzhuo Xie designed the study. Yan Zhang, Yuanfei Shi, Xiaolong Zheng, Lihong Shou, Qiu Fang, Huafei Shen, Mingyu Zhu, Xin Huang, Jiansong Huang, Li Li, De Zhou, Lixia Zhu, Jingjing Zhu, Xiujin Ye and Jie Jin collected the patients' material. Yan Zhang and Yuanfei Shi analyzed data and wrote the paper.

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Tables

Table 1. Characteristics of 347 patients with PTCL based on the LMR and PMR.

cteristic	Total (n=347)	LMR≤1.68 (n=127)	LMR>1.68 (n=220)	p Value	PMR≤300 (n=126)	PMR>300 (n=221)	p Value
				0.063			0.202
s	222(64.0)	73(57.5)	149(67.7)		75(59.5)	147(66.5)	
rs	125(36.0)	54(42.5)	71(32.3)		51(40.5)	74(33.5)	
				0.482			0.289
	229(66.0)	87(68.5)	142(64.5)		88(69.8)	141(63.8)	
le	118(34.0)	40(31.5)	78(35.5)		38(30.2)	80(36.2)	
				<0.001*			<0.001*
	154(44.4)	29(22.8)	125(56.8)		27(21.4)	127(57.5)	
	193(55.6)	98(77.2)	95(43.2)		99(78.6)	94(42.5)	
				<0.001*			<0.001*
	241(69.5)	66(52.0)	175(79.5)		64(50.8)	44(19.9)	
	106(30.5)	61(48.0)	45(20.5)		62(49.2)	177(80.1)	
				<0.001*			<0.001*
	65(18.7)	1(0.8)	64(29.1)		6(4.8)	59(26.7)	
	282(81.3)	126(99.2)	156(70.9)		120(95.2)	162(73.3)	
oms				<0.001*			<0.001*
	203(58.5)	97(76.4)	106(48.2)		94(74.6)	109(49.3)	
	144(41.5)	30(23.6)	114(51.8)		32(25.4)	112(50.7)	
ical				0.330			0.018
IOS	111(32.0)	45(35.4)	66(30.0)		51(40.5)	60(27.1)	
	113(32.5)	32(25.2)	81(36.8)		31(24.6)	82(37.1)	
	70(20.2)	27(21.2)	43(19.5)		29(23.0)	41(18.6)	
LK+	20(5.8)	10(7.9)	10(4.5)		8(6.3)	12(5.4)	
LK-	21(6.0)	7(5.5)	14(6.3)		3(2.4)	18(8.1)	
	4(1.2)	3(2.4)	1(0.5)		1(0.8)	3(1.4)	
	5(1.4)	2(1.6)	3(1.4)		1(0.8)	4(1.8)	
	2(0.6)	1(0.8)	1(0.5)		2(1.6)	0(0.0)	
	1(0.3)	0(0.0)	1(0.5)		0(0.0)	1(0.5)	

arrow

| | | | | 0.005* | | | $\Box$0.001* |

hent

| | 119(34.3) | 56(44.1) | 63(28.6) | | 75(59.5) | 44(19.9) |
| | 228(65.7) | 71(55.9) | 157(71.4) | | 51(40.5) | 177(80.1) |

g/L$\Box$ $\Box$0.001* $\Box$0.001*

| | 112(32.3) | 66(52.0) | 46(20.9) | | 64(50.8) | 48(21.7) |
| | 235(67.7) | 61(48.0) | 174(79.1) | | 62(49.2) | 173(78.3) |

0.165 0.074

| e | 224(64.6) | 88(69.3) | 136(61.8) | | 89(70.6) | 135(61.1) |
| ve | 123(35.4) | 39(30.7) | 84(38.2) | | 37(29.4) | 86(38.9) |

dal $\Box$0.001* $\Box$0.001*

hent

| | 163(47.0) | 83(65.4) | 80(36.4) | | 82(65.1) | 81(36.7) |
| | 184(53.0) | 44(34.6) | 140(63.6) | | 44(34.9) | 140(63.3) |

l LDH $\Box$0.001* $\Box$0.001*

| | 222(64.0) | 99(78.0) | 123(55.9) | | 100(79.4) | 122(55.2) |
| | 125(36.0) | 28(22.0) | 97(44.1) | | 26(20.6) | 99(44.8) |

l $\Box$0.001* $\Box$0.001*

evel

| | 222(64.0) | 100(78.7) | 122(55.5) | | 97(77.0) | 125(56.6) |
| | 125(36.0) | 27(21.3) | 98(44.5) | | 29(23.0) | 96(43.4) |

/L)	1.06(0.1-7.24)	0.7(0.1-2.5)	1.3(0.1-7.24)	$\Box$0.001*	0.9(0.1-6.0)	1.2(0.1-7.24)	0.182
10^9/L)	0.49(0.04-1.83)	0.64(0.08-1.83)	0.45(0.04-1.34)	$\Box$0.001*	0.67(0.04-1.83)	0.42(0.04-1.19)	$\Box$0.001*
^{9}/L)	178(2-637)	147(14-557)	195.5(2-637)	0.003*	110(2-537)	213(44-637)	$\Box$0.001*

ent $\Box$0.001* $\Box$0.001*

| | 117(33.7) | 18(14.2) | 99(45.0) | | 18(14.3) | 99(44.8) |
| | 230(66.3) | 109(85.8) | 121(55.0) | | 108(85.7) | 122(55.2) |

IPI: International Prognostic Index; ECOG:Eastern Cooperative Oncology Group; PTCL: Peripheral T-cell lymphoma; PTCL-NOS: PTCL-not otherwise specifiied; ENKTL:extra-nodal NK/T-cell lymphoma, nasal type ; AITL: angioimmunoblastic T-cell lymphoma; ALCL,ALK+: anaplastic lymphoma kinase positive; ALCL,ALK—: anaplastic lymphoma kinase negative; MEITL: monomorphic epitheliotropic intestinal T-cell lymphoma; SPTCL: subcutaneous panniculitis-like T-cell lymphoma; HSTCL: hepatosplenic T-cell lymphoma; MF/SS: mycosisfungoides/Sezary's syndrome; EBV: Epstein-barr virus; LDH: lactic dehydrogenase; β2-MG: beta-2 micro-globulin; LY: lymphocyte; MONO: monocyte; PLT: platelet; CR: complete response.

*Significantly different.

Categorical variables are expressed in frequency and percentage (n, %); Continuous variables are expressed in median with range of minimum to maximum.

Table 2. Univariate and multivariate logistic regression models of complete response (CR) in PTCL patients.

	univariate analysis			multivariate analysis		
Covariate	OR	95%CI	p-value	OR	95%CI	p-value
Sex, Male	1.590	1.001-2.527	0.050			
Age,≥60years	3.257	1.927-5.505	$<0.001^*$	4.031	2.021-8.041	$<0.001^*$
IPI,3-5	5.818	3.561-9.506	$<0.001^*$			
ECOG,3-5	7.666	3.810-15.423	$<0.001^*$	3.610	1.572-8.290	0.002^*
Stage,III-IV	7.195	3.955-13.088	$<0.001^*$	2.737	1.255-5.969	0.011
B symptoms	2.389	1.516-3.766	$<0.001^*$			
Bone marrow Involvement	5.613	3.077-10.237	$<0.001^*$	2.581	1.173-5.683	0.018
Albumin,<35g/L	2.993	1.742-5.141	$<0.001^*$			
EBV,Positive	2.233	1.409-3.541	0.001^*	2.090	1.170-3.734	0.013
Extra-nodal,>1	3.118	1.936-5.021	$<0.001^*$			
LY($\times10^9$/L)<0.8	3.565	2.042-6.224	$<0.001^*$			
MONO($\times10^9$/L)<1	2.610	0.969-7.028	0.058			
PLT($\times10^9$/L)<83	7.847	2.759-22.318	$<0.001^*$			
Elevated LDH	2.263	1.429-3.585	0.001^*			
Elevated β2-MG	2.672	1.683-4.243	$<0.001^*$			
LMR≤1.68	4.955	2.816-8.717	$<0.001^*$	1.996	0.906-4.397	0.086
PMR≤300	4.869	2.767-8.567	$<0.001^*$	1.851	0.873-3.924	0.108

OR: odds ratio; CI: confidence interval.

*Significantly different.

Table 3. Univariate and multivariate Cox proportional hazard regression models for overall survival (OS) in PTCL patients.

	univariate analysis			multivariate analysis		
Covariate	HR	95%CI	p-value	HR	95%CI	p-value
Sex, Male	1.223	0.899-1.662	0.200			
Age,≥60years	1.379	1.032-1.843	0.030			
IPI,3-5	3.124	2.265-4.307	<0.001*			
ECOG,3-5	3.775	2.820-5.054	<0.001*	2.351	1.647-3.356	<0.001*
Stage,III-IV	7.859	3.862-15.993	<0.001*	3.276	1.512-7.099	0.003*
B symptoms	2.101	1.542-2.862	<0.001*			
Bone marrow Involvement	3.062	2.297-4.082	<0.001*			
Albumin,<35g/L	2.209	1.656-2.946	<0.001*			
EBV,Positive	1.390	1.024-1.887	0.035			
Extra-nodal,≥1	3.207	2.374-4.331	<0.001*	1.659	1.125-2.445	0.039
LY(×10^9/L)<0.8	2.279	1.706-3.045	<0.001*			
MONO(×10^9/L)≥1	2.292	1.492-3.523	<0.001*			
PLT(×10^9/L)<83	3.459	2.471-4.841	<0.001*			
Elevated LDH	1.613	1.182-2.200	0.003*			
Elevated β2-MG	2.159	1.560-2.986	<0.001*			
LMR≤1.68	3.496	2.617-4.669	<0.001*	1.751	1.158-2.647	0.006*
PMR≤300	3.947	2.947-5.287	<0.001*	1.762	1.201-2.586	0.002*

HR: hazard ratio; CI: confidence interval.

*Significantly different.

Table 4. The significance of LMR in univariate and multivariate analysis of OS in patients with five major subtypes of PTCL.

Histological Subtype-LMR	n	Univariable analysis			Multivariable analysis		
		HR	95%CI	p Value	HR	95%CI	p Value
PTCL,NOS	111	4.525	2.738-7.475	⏐0.001*	2.691	1.175-6.162	0.019
ENKTL	113	4.820	2.854-8.138	⏐0.001*	1.027	0.464-2.276	0.947
AITL	70	1.908	1.013-3.591	0.045	1.785	0.844-3.775	0.129
ALCL,ALK+	20	5.131	0.570-46.172	0.145	-	-	-
ALCL,ALK-	21	7.102	1.740-28.982	0.006*	1.415	0.120-16.636	0.782

HR: hazard ratio; CI: confidence interval.

*Significantly different.

Table 5. The significance of PMR in univariate and multivariate analysis of OS in patients with five major subtypes of PTCL.

Histological Subtype-PMR	n	Univariable analysis			Multivariable analysis		
		HR	95%CI	p Value	HR	95%CI	p Value
PTCL,NOS	111	4.106	2.468-6.830	⏐0.001*	2.010	0.941-4.293	0.071
ENKTL	113	4.732	2.777-8.064	⏐0.001*	2.260	1.062-4.812	0.034
AITL	70	3.807	1.986-7.297	⏐0.001*	2.962	1.313-6.684	0.009*
ALCL,ALK+	20	8.386	0.927-75.846	0.058	-	-	-
ALCL,ALK-	21	8.046	1.594-40.602	0.012	1.622	0.090-29.096	0.743

HR: hazard ratio; CI: confidence interval.
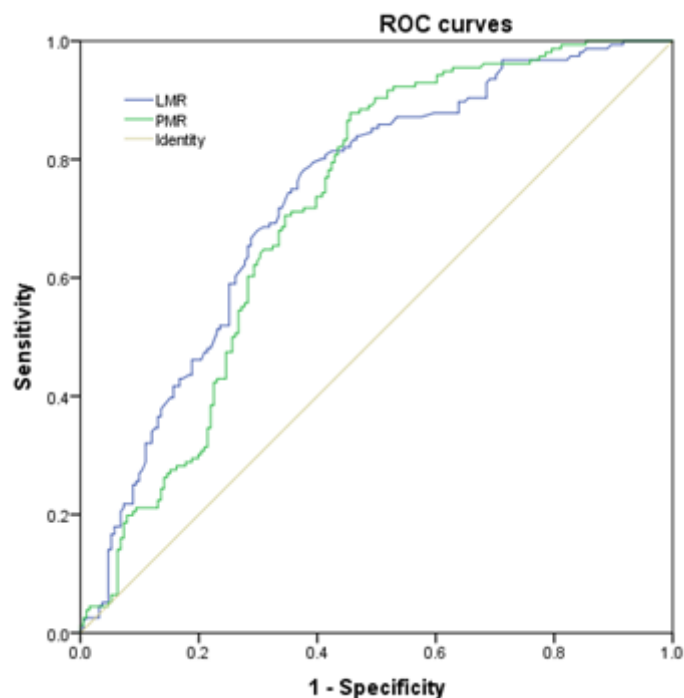
*Significantly different.

Figures

Figure 1

Receiver operating characteristic (ROC) curves of LMR and PMR of patients with PTCL. The AUC of LMR and PMR were 0.734 (95% CI: 0.682-0.786), 0.718(95% CI: 0.664-0.772).
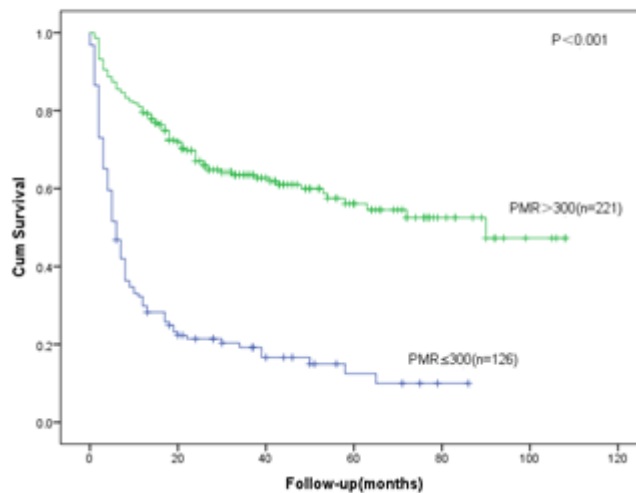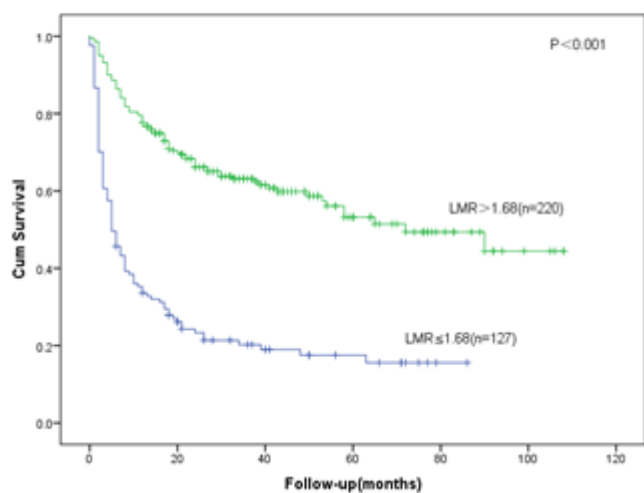
(A)   (B)

Figure 2

OS: Overall survival. (A) OS for different levels of LMR; (B) OS for different levels of PMR.
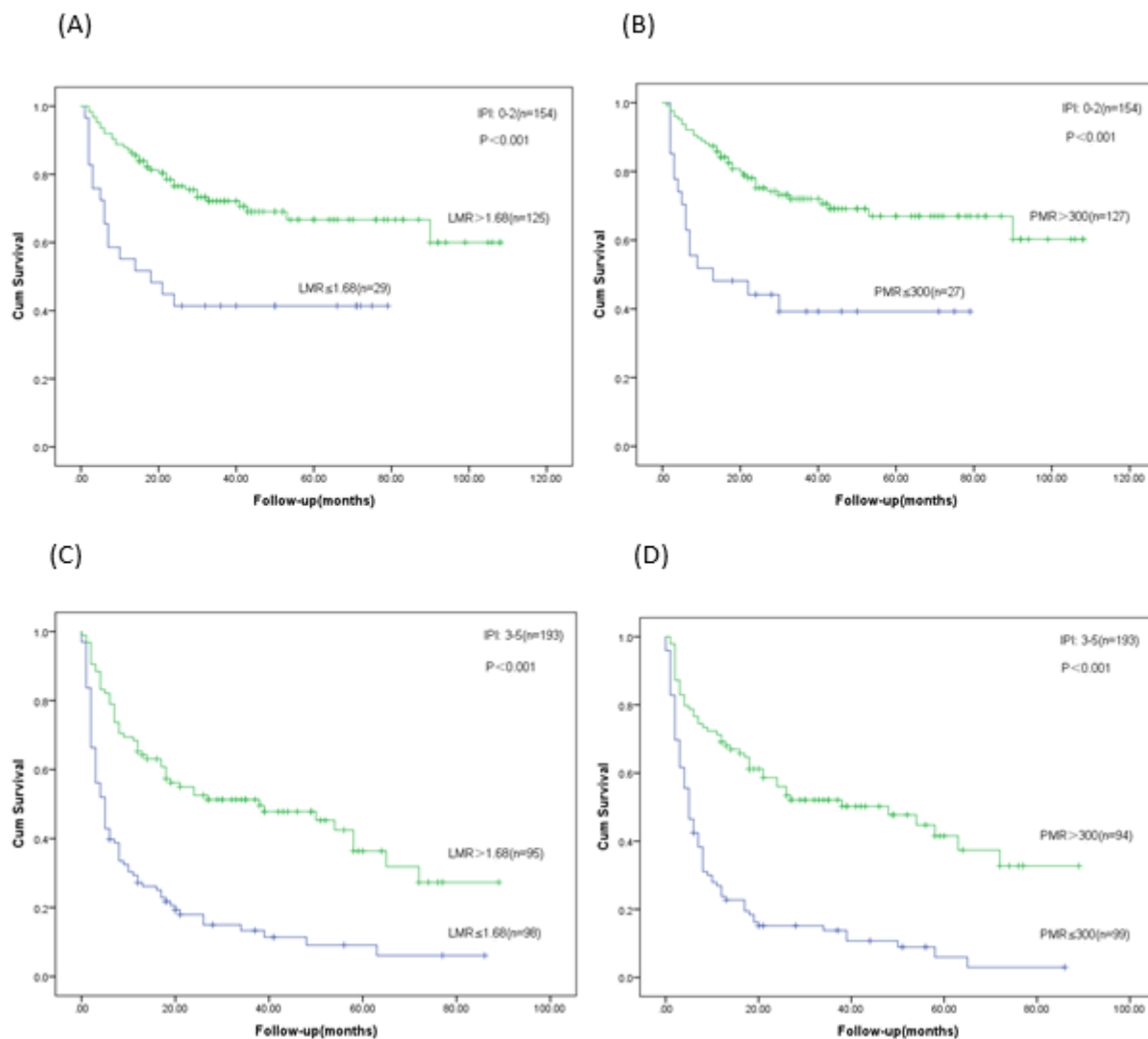
Figure 3

OS for different IPI risk stratification of PTCL patients. (A)OS of patients with different LMR levels in group of IPI score 0-2; (B)OS of patients with different PMR levels in group of IPI score 0-2; (C)OS of patients with different LMR levels in group of IPI score 3-5; (D)OS of patients with different PMR levels in group of IPI score 3-5.
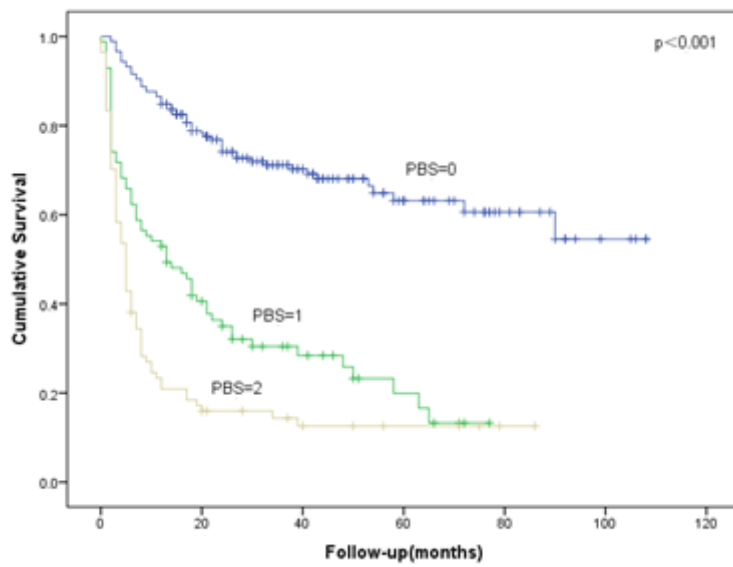
Figure 4

Prognostic PBS model in OS of Peripheral T-cell lymphoma. Abbreviation: PBS, Peripheral Blood Score.