Clinica Chimica Acta 485 (2018) 316–322

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

The pretreatment albumin to globulin ratio as a significant predictor in patients with diffuse large B cell lymphoma

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ARTICLE INFO

Keywords:
Diffuse large B cell lymphoma
Albumin to globulin ratio
Survival predictor
Prognosis

ABSTRACT

Background: The pretreatment albumin to globulin ratio (AGR) has been used to predict survival in several types of tumors. However, whether AGR can predict outcomes in patients with diffuse large B-cell lymphoma (DLBCL) remains unclear. We evaluated the prognosis value of AGR in DLBCL patients.

Methods: We retrospectively analyzed the available serum biochemical results of 335 patients with newly diagnosed DLBCL before treatment. The AGR was calculated as: albumin (g/L)/globulin. X-tile program was used to generate an optimal cut-off value of 1.3 for AGR. And all patients were respectively divided into the low AGR and high AGR groups according to the cut-off value.

Results: The low AGR group displayed more adverse clinical chacteristics, including old age, sex (female), increased β2-microglobulinpoor (β2-MG), increased lactate dehydrogenase (LDH), B symptoms, poor performance status (PS), advanced stage, number of extranodal sites ≥ 2 and higher International Prognostic Index (IPI). AGR was negatively correlated with age, IPI score, ECOG score, Ann Arbor stage, B symptoms, β2-MG, LDH, and extranodal involvement, while positively correlated with gender. Patients with a low AGR presented with significantly poorer overall survival (OS, P = .001). Multivariate analysis further demonstrated that a low AGR was an independent adverse predictor for OS (HR = 0.613; 95% CI = 0.412–0.910, P = .015). In addition, AGR distinguished patients with different prognosis in stage III-IV and the non-germinal center B cell-like lymphoma (non-GCB) groups, a low AGR was also significantly associated with poor OS in 2 groups.

Conclusion: Pretreatment AGR was a simple and effective clinical marker of survival in patients with DLBCL, and may had an additional prognostic value based on Ann Arbor stage and cell of origin for DLBCL.

1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 30–40% of all non-Hodgkin lymphomas (NHLs) [1,2]. Although the majority of patients treated with the current standard-of-care rituximab (anti-CD20 monoclonal antibody) plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), 20–40% of patients are refractory to treatment or eventually relapse, and the majority of these patients ultimately have a poor outcome [3,4]. In the last decades, two major subtypes of DLBCL, the germinal center B cell-like subtype (GCB) and the non-germinal center B cell-like lymphoma (non-GCB) have been identified by gene expression profiling which correlate with outcomes after chemotherapy [5,6]. The international prognostic index (IPI) score based on clinical factors as a powerful tool for risk stratification was widely applied to predict therapeutic response and clinical outcome in patients with DLBCL [7–10]. However, the inherent different biological features of DLBCL patients not captured by the clinical-only IPI score. Thereafter, clinical risk stratification models such as the revised IPI (R-IPI)[10], the biological marker adjusted IPI (B-IPI) [11], the National Comprehensive Cancer Network IPI (NCCN-IPI)[12] were proposed to improve the clinical predictive capacity of IPI. Unfortunately, these were still insufficiently accurate to be applied in clinical practice. A variety of molecular biomarkers and gene signatures with prognostic value have also been identified in DLBCL patients [1,2,13,14]. However, most of molecular markers and genetic signatures are either expensive or unavailable before treatments. Therefore, identifying new and easily accessible prognostic markers are still

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https://doi.org/10.1016/j.cca.2018.07.015
Received 19 April 2018; Received in revised form 1 July 2018; Accepted 9 July 2018
Available online 11 July 2018

needed.

Albumin and globulin was two major components of human serum, which have attracted much attention as noninvasive prognostic factors in various malignancies. Furthermore, these 2 factors play a crucial role in immunity and inflammation [15], and serum albumin is also an objective parameter that reflects nutritional status. Several recent studies indicated that albumin and the Glasgow Prognostic Score (GPS) based on C-reactive protein (CRP) and albumin levels were stable predictor of prognosis in DLBCL patients [16]. Meanwhile, the pretreatment albumin to globulin ratio (AGR) based on combination of albumin and globulin has been widely reported to be an reliable prognostic predictor in many malignancies [15,17,18]. However, the significance of the AGR in DLBCL patients has never been reported. In this present study, we retrospectively analyzed in a large cohort of 335 patients with DLBCL and clarified the clinical significance of AGR in predicting overall survival (OS)) in patients with DLBCL. In addition, we also analyzed the correlation of AGR with common clinical features.

2. Methods

2.1. Patients and treatment

This study included 335 patients with newly diagnosed DLBCL between January 2010 and December 2015 admitted to Changhai Hospital, Shanghai, China. All patients who were diagnosed according to the 2008 World Health Organization (WHO) classification [19]. Basic clinical parameters were collected of 335 cases including age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS) (0–4), Ann Arbor stage (I–IV), cell of origin, B symptoms, serum lactate dehydrogenase (LDH) levels, serum Beta-2 microglobulin (β2-MG), The International Prognostic Index (IPI), number of extranodal sites, Ki-67, serum albumin and globulin, as well as Chemotherapy regimens. Patients were excluded in case of immunodeficiency virus infection, primary central nervous system (CNS) lymphoma or missing laboratory parameters at diagnosis (Fig. 1). For the study, all patients enrolled informed consent in accordance with requirements of the Declaration of Helsinki, and the study was approved by the Ethics Committee of the institute of Hematology, Changhai Hospital.

2.2. Follow-up

Overall survival (OS) was measured from the date of diagnosis until the date of death due to any cause or until the date of the last follow-up. The last date of follow-up until November 2017, and patients who were still alive at the end of the follow-up were treated with censored data for analysis. Follow up data were obtained from clinical records, or by telephone calls patients themselves or their relatives.

2.3. Statistical analysis

Intergroup comparisons between AGR and clinical parameters were performed using non-parametric tests (Chi square test or Fisher's exact test). The coefficient of correlation (r) between the 2 groups was calculated using the Spearman rank-sum test. OS for the two groups were compared by the Kaplan-Meier analysis and the log-rank test. Prognosis factors were included to perform univariate and multivariate analyses by using Cox proportional hazard model. All statistical analyses were performed using IBM SPSS Statistics 21 software, and the optimal cut-off value for AGR was determined using X-tile 3.6.1 software 20 (Yale University) [20]. All tests were two-sided, and P-value $< .05$ was considered to indicate significant differences.

3. Results

3.1. Identification of the optimal cut-off value for AGR

To examine whether the pretreatment AGR could be used as a diagnostic marker of DLBCL patients, X-tile program was used to calculate the optimal cut-off value for AGR (Fig. 2). This critical value of AGR was 1.3 consistent with previous studies in natural killer/T-cell lymphoma (NKTCL)[21] and patients were then divided into two groups for further analysis (AGR < 1.3 and ≥ 1.3). Kaplan–Meier survival analysis indicated that AGR < 1.3 was significantly associated with decreased OS ($p = .001$).

3.2. Patient characteristics

The clinical characteristics and comparison between patients with a low or high AGR are shown in Table 1. We examined 335 DLBCL patients with available pretreatment AGR from January 2010 to

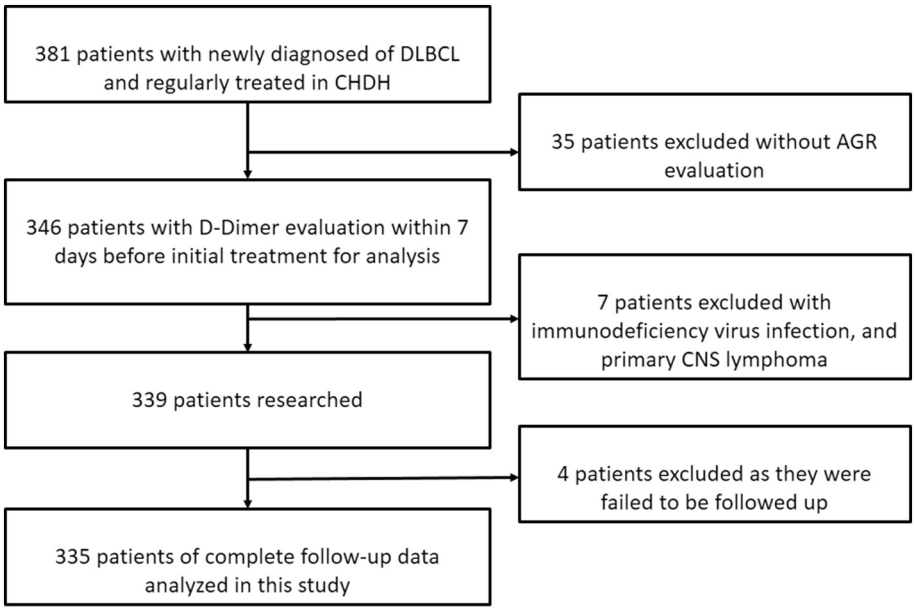

Fig. 1. The flow chart of DLBCL cases screening in this study.