

# Different prevalence and clinical outcome of Epstein-Barr virus positive diffuse large B-cell lymphoma between North American and non-Western populations

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Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma among adults, presenting heterogeneous biological and clinical features. The 2008 World Health Organization (WHO) classification of Epstein-Barr virus positive (EBV<sup>+</sup>) DLBCL of the elderly is limited to patients >50 years old without known immunodeficiency. The WHO classification was revised in 2016 to include immunocompetent patients of all ages and “EBV<sup>+</sup> DLBCL of the elderly” has been replaced by “EBV<sup>+</sup> DLBCL, not otherwise specified (EBV<sup>+</sup> DLBCL, NOS)” (1). There are two key words differentiating EBV<sup>+</sup> DLBCL, NOS from another lymphoma, “EBV<sup>+</sup>” and “immunocompetent”.

The study by Tracy *et al.* (2) was the first analysis under the EBV<sup>+</sup> DLBCL, NOS classification investigating the impacts of EBV infection and immunocompetent status on prognosis in a prospectively assembled large cohort of North American patients with *de novo* or transformed DLBCL. Their findings suggest that EBV positivity and immunosuppression do not affect the baseline clinical characteristics or clinical outcome of North American patients with DLBCL. This was consistent with findings in earlier studies by Ok *et al.* (3) involving 732 patients of all ages from western countries with *de novo* DLBCL in the International DLBCL Rituximab-CHOP Consortium Program, and Hoeller *et al.* (4) involving 258 European

patients with EBV<sup>+</sup> DLBCL of the elderly.

In the study by Tracy *et al.*, the initial study cohort included 1,081 newly diagnosed patients with DLBCL who enrolled in the molecular epidemiology resource (MER) of the University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE) from 2002 to 2012. Cases excluded from this study were those without enough tissue for microarray analysis, and patients with a primary central nervous system lymphoma, primary cutaneous lymphoma, primary mediastinal large B-cell lymphoma, history of organ transplant, or known infection with human immunodeficiency virus. As a result, a total of 362 cases formed the study cohort. With these inclusion criteria, a large number of available biopsies, systematically collected clinical information, and prognostic analysis of immunocompetent patients, this study was one of the largest evaluations of EBV<sup>+</sup> DLBCL in the upper Midwestern US population in the modern immunotherapy era.

This study found that EBV<sup>+</sup> DLBCL was rare (4.4%, 16 of 362), and occurred in patients of all age groups. This prevalence was similar to that in the previous study by Ok *et al.* (3), in which the EBV<sup>+</sup> prevalence in *de novo* DLBCL was 4% (28 of 732 patients of all age groups from developed Western countries). The prevalence of EBV<sup>+</sup> DLBCL of the elderly from the Tracy *et al.* study was 1.9%, which was

also in concordance with multiple reports from Western countries (4-6). In contrast, studies in Asian or Latin populations reported higher prevalence of EBV<sup>+</sup> DLBCL (7-15%) (6,7).

This study described the clinical characteristics of EBV<sup>+</sup> DLBCL compared with EBV negative (EBV<sup>-</sup>) DLBCL. No significant difference was found in performance status, Ann Arbor stages, number of extranodal sites, lactate dehydrogenase levels, and the International Prognostic Index score. Evidence was not found for association between EBV positivity and inferior prognosis. Again, these results were in contrast with the poor clinical feature and outcome of Asian patients with EBV<sup>+</sup> DLBCL of the elderly (7,8). For EBV<sup>+</sup> DLBCL in young patients, observation was inconsistent in both western studies (3,9) and Asian studies (7,8,10). Of note, in the study by Tracy *et al.* (2), whether age affected survival of patients with EBV<sup>+</sup> DLBCL and whether patients with EBV<sup>+</sup> DLBCL of the elderly had poorer prognosis than the overall EBV<sup>-</sup> DLBCL patients were not analyzed. Separate survival analysis for age-matched patients with versus without EBV<sup>+</sup> DLBCL were also not performed, likely due to the small number of EBV<sup>+</sup> DLBCL patients. However, in this study the EBV<sup>+</sup> group had a slightly higher proportion of patients with  $\leq 50$  years (42% in EBV<sup>+</sup> DLBCL, NOS *vs.* 19% in EBV<sup>-</sup> immunocompetent DLBCL;  $P=0.053$ ; if include immunosuppressed patients, 31% *vs.* 18%;  $P=0.19$ ), which could have confounded the survival analysis.

Nonetheless, this study found that EBV<sup>+</sup> DLBCL was associated with higher frequency of bone marrow involvement (43.8% *vs.* 18.5%;  $P=0.03$ ) (2). Whether the bone marrow involvement is concordant or discordant, which is associated with inferior and favorable prognosis, respectively (11), was not specified. In addition, EBV<sup>+</sup> DLBCL was associated with higher frequencies of CD30 positivity (CD30<sup>+</sup>) with a  $\geq 20\%$  cutoff pathologically (frequency, 25%), and non-germinal center B-cell subtype (frequency, 62.5%). These distinct pathologic and molecular features have been consistently observed in earlier Western and Asian studies (3,6,7,9,12). Interestingly, in the study by Ok *et al.*, although there was no significant difference in survival of patients with versus without EBV<sup>+</sup> DLBCL, DLBCL patients with both EBV<sup>+</sup> and CD30<sup>+</sup> expression had significantly poorer outcome (3,13), which was also observed by Slack *et al.* in a study of immunocompetent patients from British Columbia (12). Whether CD30<sup>+</sup> expression represented an inferior prognostic factor for EBV<sup>+</sup> DLBCL patients, and whether patients with CD30<sup>+</sup>

EBV<sup>+</sup> DLBCL had poorer survival than EBV<sup>-</sup> DLBCL patients, were not analyzed by Tracy *et al.* likely due to the small number of CD30<sup>+</sup> EBV<sup>+</sup> DLBCL patients ( $n=4$ ).

Immune suppression caused by aggressive chemotherapies and some novel targeted therapies is involved in the development of EBV<sup>+</sup> DLBCL (14). The therapy-related immune suppression, EBV reactivation, and the increased risk of EBV-driven Richter transformation were recapitulated in mouse models by a recent study (15). Importantly, this subset of EBV<sup>+</sup> DLBCL had poorer survival, but was sensitive *in vivo* to the combined ganciclovir and ibrutinib therapy which targets EBV replication and B-cell receptor signaling, respectively, providing rationale for combination therapy (15).

It is postulated that defective immune surveillance for EBV and immune senescence as a result of aging were relevant for the poor clinical outcome associated with EBV<sup>+</sup> DLBCL of the elderly (9,16-19). PD-L1 expression was commonly expressed in EBV<sup>+</sup> DLBCL regardless of age, which might implicate immune evasion (9,20). EBV DNA present in the plasma (viremia), an indication of EBV reactivation and possible failure of viral control by CD8<sup>+</sup> T cells, was found to be associated with aging (16). Notably, a Chinese study group found that detectable EBV DNA in whole blood, which was speculated as an indicator of presence of virions in the peripheral blood, showed stronger prognostic effect than EBER positivity in diagnostic samples; moreover, in monitoring patients after chemotherapy, EBV DNA in whole blood specimens showed value for predicting clinical outcome (8).

In the Tracy *et al.* study cohort, EBV<sup>+</sup> DLBCL patients did have a higher frequency of immunosuppressed patients (25% *vs.* 10%;  $P=0.06$ ), and all the four immunosuppressed patients with EBV<sup>+</sup> DLBCL were  $>50$  years old; in contrast, the ages of immunosuppressed patients with EBV<sup>-</sup> DLBCL were either  $>50$  ( $n=31$ ) or  $\leq 50$  ( $n=4$ ). Therefore, patients with known immunosuppression from organ transplants or human immunodeficiency virus infection were excluded and EBV<sup>+</sup> and EBV<sup>-</sup> immunocompetent patients were compared, and again no evidence that EBV positivity was associated with different clinical outcomes was found. The study also investigated the impact of immunosuppression on DLBCL's clinical outcome. There were 39 (10.8%) immunosuppressed cases which had a history of congenital immunodeficiency or recorded applications of medicines with immunosuppressive effects, including anti-arthritis drugs (methotrexate, cyclophosphamide, azathioprine, hydroxychloroquine), antiepileptic medicines, anti-tumor

necrosis factor monoclonal antibodies, and prednisone, and 323 immunocompetent cases in the study cohort. No differences in clinical characteristics and outcomes have been found between these two groups suggesting that immunosuppressive status is unlikely an independent marker for poor prognosis in DLBCL. However, prognosis and outcomes were not compared between immunocompetent and immunosuppressed patients with EBV<sup>+</sup> DLBCL (NOS, or of different age groups) in their study.

In summary, Tracy and colleagues provided predominantly prospective evaluation of EBV<sup>+</sup> DLBCL, NOS in one of the largest patient cohorts in the North American population. They found that the incidence of EBV<sup>+</sup> DLBCL is low in DLBCL, and EBV positivity or immunosuppression does not correlate with clinical outcome. Collectively, these data suggest lower prevalence rates and weaker associations of EBV with aggressive clinical features or inferior outcomes in Western versus non-Western populations. This study is largely consistent with earlier findings and brings new considerations to hematologists during their practice. However, these results should be verified in a larger DLBCL cohort with homogenous treatment, and the method for EBV detection, the cut-off for EBV positivity, and the definition of EBV<sup>+</sup> DLBCL subtypes need to be standardized. In addition, questions remain regarding to whether subsets of EBV<sup>+</sup> DLBCL have different biology, respond differentially to standard immunotherapy, and need tailored therapy. Predictive or prognostic factors for patients with EBV<sup>+</sup> DLBCL, the role of immune suppression in the pathogenesis and prognosis of EBV<sup>+</sup> DLBCL, and the efficacy of anti-PD-L1 immunotherapy in EBV<sup>+</sup> DLBCL may be revealed by future studies.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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