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DA-EPOCH-R improves the prognosis of patients with double-expressor lymphoma

A single-center retrospective study and meta-analysis

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Abstract

Purpose: Double-expressor lymphoma (DEL) is associated with a poor prognosis. The standard treatment for patients with DEL remains controversial. A comparison of the safety and feasibility of R-CHOP and DA-EPOCH-R as the first-line therapy for patients with DEL is urgently needed.

Methods: The clinical and treatment outcomes of 75 DEL patients were retrospectively analyzed. The role of DA-EPOCH-R was determined and compared to that of R-CHOP in DEL patients. PubMed, Embase, the Cochrane Central Library, and ClinicalTrials.gov were systematically searched up to November 1, 2021 and were evaluated by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. Articles comparing DA-EPOCH-R versus R-CHOP in patients with DEL were included.

Results: Overall, 49 and 26 DEL patients received R-CHOP and DA-EPOCH-R, respectively. Although the difference in response for patients who received R-CHOP and DA-EPOCH-R was not significant ($P = .347$), DA-EPOCH-R may improve the prognosis compared to R-CHOP ($P = .056$ for progression-free survival [PFS], $P = .009$ for overall survival [OS]). A systematic review and meta-analysis including 412 DEL patients in six articles were conducted. The event rate for 3-year PFS was significantly lower in patients receiving DA-EPOCH-R treatment than in those undergoing R-CHOP treatment (OR = 0.63, 95% CI = 0.42–0.94, $P = .02$), whereas no statistically significant difference was found in the HRs for both PFS and OS or the event rate for 3-year OS.

Conclusion: The results of this study indicated that DA-EPOCH-R might improve the prognosis of DEL patients compared with R-CHOP.

Abbreviations: CIs = confidence intervals, CNS = central nervous system, COO = cell-of-origin, CR = complete response, CT = computed tomography, CTCAE = Common Terminology Criteria for Adverse Events, DEL = Double-expressor lymphoma, DHL = double-hit lymphoma, DLBCL = diffuse large B-cell lymphoma, EPOCH-R = etoposide, prednisone, vincristine (Oncovin), cyclophosphamide, hydroxydaunorubicin, and rituximab, GCB = germinal center B cell-like, G-CSF = granulocyte colony-stimulating factor, HBcAb = hepatitis B core antibody, HBV = hepatitis B virus, HIV = human immunodeficiency virus, HR = hazard ratio, IPI = International Prognostic Index, LDH = lactate dehydrogenase, NOS = Newcastle–Ottawa Scale, ORs = odds ratios, OS = overall survival, PET = positron emission tomography, PFS = progression-free survival, PR = partial response, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis, R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), and prednisone, SCT = stem cell transplantation.

Keywords: DA-EPOCH-R, double-expressor lymphoma, prognosis, R-CHOP, therapy

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

This retrospective study was approved by the Ethical Committee of Peking Union Medical College Hospital and all patients signed informed consent forms before sample collection.

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1. Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent subtype of non-Hodgkin lymphoma, accounting for over 30% of all cases.[1] Immunochemotherapy consisting of rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), and prednisone (R-CHOP) contributes to high average cure rates (approximately 70%) and an excellent prognosis in DLBCL patients.[2,3] Therefore, the R-CHOP regimen has been regarded as a standard treatment for DLBCL in recent years.

However, in terms of the molecular and morphologic heterogeneities of different pathologic subtypes, increasingly more attention has been given to several subgroups of B-cell lymphoma with poor outcomes after R-CHOP treatment, especially double-hit lymphoma (DHL) and double-expressor lymphoma (DEL). DHL is defined as B-cell lymphoma with a genetic rearrangement of the MYC as well as BCL2 and/or BCL6 genes, which has been newly categorized into an individual subtype named "high-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 translocations".[4] The median overall survival (OS) duration of patients with DHL is only approximately 13 to 16.8 months for patients treated with R-CHOP.[4–7] DEL is defined as DLBCL with concurrent overexpression of the MYC and BCL2 proteins and represents 18% to 34% of all patients with DLBCL.[8,9] Several studies have demonstrated an abysmal prognosis for patients with DEL treated with R-CHOP alone, with 5-year progression-free survival (PFS) and OS rates of less than 40%.[7–9] There is an urgent need to identify the clinical characteristics of patients with DHL and DEL and to determine other therapeutic strategies for these patients which are more beneficial than R-CHOP.

The immunochemotherapy regimen consisting of etoposide, prednisone, vincristine (Oncovin), cyclophosphamide, hydroxydaunorubicin, and rituximab (EPOCH-R) was first designed by Wilson in 1993.[10] Considering the individual differences in drug clearance, the regimen was improved through individual dose adjustment.[11] Although DA-EPOCH-R treatment suggested significant prognostic improvements for patients with DHL in prior retrospective studies,[12–14] prognostic data on patients with DEL treated with DA-EPOCH-R are limited and controversial.[15,16]

Due to the largely unmet medical needs of this population, we conducted this retrospective clinical study, aiming to analyze and compare the clinical characteristics and survival outcomes of Chinese DEL and non-DEL patients as well as to determine and compare the safety and feasibility of first-line DA-EPOCH-R and R-CHOP regimens in DEL patients using subset analyses. The results of this study will provide more clinical evidence to improve risk-stratified treatment decisions.

2. Methods

2.1. Patients

This was a retrospective clinical study that included 286 consecutive patients with de novo DLBCL diagnosed at Peking Union Medical College Hospital between January 2015 and December 2018. All patients were diagnosed based on clinical symptoms and biopsy results according to the World Health Organization classification criteria.[4] Fifty-two patients without available pathological specimens, 11 patients who had not received any induction treatment in our institution, and 148 patients without DEL were excluded. The median follow-up time after diagnosis was 44.5 months.

2.2. Clinical data collection

Data on clinical laboratory characteristics, including sex, age, stage based on the Ann Arbor staging system,[17] lymphoma International Prognostic Index (IPI) score, serum lactate dehydrogenase (LDH), initial induction regimen, and adverse events, were collected retrospectively from computer databases or telephone interviews. All patients received contrast-enhanced computed tomography (CT) scans or[18] F-fluorodeoxyglucose positron emission tomography (PET) and bone marrow biopsy to evaluate the number of extranodal disease sites and disease stages. Lumbar puncture was performed to determine central nervous system (CNS) involvement. LDH ≥ 250 IU/L and an IPI ≥ 3 were considered high.

2.3. Histopathological examination

Two experienced morphological and pathological specialists restained all 223 formalin-fixed, paraffin-embedded samples and independently reanalyzed them for accurate immunohistochemistry results. Any discrepancy was resolved by discussion. As previously described,[4,18] the positive cutoff values for the MYC, BCL2, and BCL6 proteins were 40%, 50%, and 30%, respectively. DLBCL with concurrent overexpression of the MYC and BCL2 proteins was considered a DEL. Additionally, the germinal center B cell-like (GCB) and non-GCB subtypes were determined with cell-of-origin (COO) classification, according to the Hans algorithm based on the histologic results of the CD10, BCL6, and MUM1 proteins.[19]

2.4. Induction treatment details

The initial induction treatment was categorized into two subgroups: the R-CHOP regimen (21 days): rituximab (375 mg/m^2, day 1), cyclophosphamide (750 mg/m^2, day 1), doxorubicin (50 mg/m^2, day 1), vincristine (1.4 mg/m^2, day 1), and prednisone (100 mg/m^2, day 1–5); the DA-EPOCH-R regimen (21 days): rituximab (375 mg/m^2, day 1), etoposide (50 mg/m^2/d, 96 hours, days 1–4), prednisone (60 mg/m^2/bid, days 1–5), vincristine (0.8 mg/m^2/d, 96 hours, days 1–4), cyclophosphamide (750 mg/m^2/d, day 5), and doxorubicin (15 mg/m^2/d, 96 hours, days 1–4) (dose adjustment was conducted as described in previous articles[11,20]; in our clinical practice, based on twice weekly complete blood counts, if the minimum neutrophil count in one cycle is over 0.5×10^9/L, the dose is increased by 20% for the next cycle; if one or two measurements are below 0.5×10^9/L, the dose is maintained; and if three consecutive measurements are below 0.5×10^9/L, the dose is reduced by 20%). Additionally, the rationale for the use of the DA-EPOCH-R regimen for each patient is shown in Table S1, Supplemental Digital Content 1, http://links.lww.com/MD/H337. Our center has only been routinely testing for DEL in DLBCL patients since 2019, that is, this was not tested for routinely during the period covered by this study. Therefore, only some of the patients in this study were found to have DEL during treatment. Patients who were initially treated with R-CHOP for less than four courses and later converted into the DA-EPOCH-R because of DHL or DEL rather than disease progression were categorized into the DA-EPOCH-R regimen group. CNS prophylaxis was used in patients with tumors at specific localizations, including the paranasal sinus, epidural tissue, bone marrow, testis, breast, adrenal gland, female genital organs, skin, and with more than two extranodal disease sites. CNS prophylaxis was defined as intrathecal injections of cytosine arabinoside and dexamethasone or a combination of methotrexate with induction treatment.

2.5. Supportive treatment details

During treatment, long-lasting granulocyte colony-stimulating factor (G-CSF) and prophylactic broad-spectrum antibiotics were applied when the peripheral blood leukocyte counts were $<2.0 \times 10^9$/L. For all patients who received DA-EPOCH-R, G-CSF (5 μg/kg/d) was used from day six until the leukocyte count was $>5.0 \times 10^9$/L. Patients who were infected with human

immunodeficiency virus (HIV) received trimethoprim-sulfamethoxazole as *Pneumocystis carinii* prophylaxis. Hepatitis B core antibody (HBcAb)-positive patients received entecavir or tenofovir as hepatitis B virus (HBV) reactivation prophylaxis. An infusion of concentrated red blood cells was conducted when the hemoglobin concentration was <60 g/L or when the patient had a complication of severe cardiopulmonary decompensation. Thrombopoietin, which was approved in China for chemotherapy-induced thrombocytopenia, was employed when the platelet count was $<50 \times 10^9$/L. Concentrated platelet therapy was used when the platelet count was $<20 \times 10^9$/L.

2.6. Treatment evaluation

Treatment outcomes and disease progression were evaluated with lumbar puncture, an 18F-fluorodeoxyglucose PET scan, or a contrast-enhanced CT scan in compliance with the revised International Workshop Group response criteria for malignant lymphoma.[21] Imaging evaluations were performed after the fourth cycle and at the end of the regular treatment course. An additional evaluation was performed when physicians suspected disease progression. The PFS duration was defined as the duration between the date of diagnosis and the date of disease progression, recurrence, or death from any cause. The OS duration was defined as the interval between the date of diagnosis and the date of death or the last follow-up.

2.7. Meta-analysis of DEL patients

We conducted this systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[22] All published studies concerning DEL patients were searched in the following databases: PubMed, Embase, the Cochrane Central Library, and ClinicalTrials.gov up to November 1, 2021. The following free text words were used: "double-expressor," "MYC BCL2," "DLBCL," "EPOCH," and "CHOP." We checked the reference lists of all relevant studies obtained from our search with the formulas described in Table S2, Supplemental Digital Content 2, http://links.lww.com/MD/H338. This meta-analysis adhered to the Newcastle–Ottawa Scale (NOS) Checklist.[23] Eligibility assessment was conducted by two independent reviewers (Z.J. and Y.S.J.). Disagreements between reviewers were eliminated by sufficient discussion.

Studies were included based on the following criteria: study design: compared R-CHOP versus DA-EPOCH-R in DEL patients; outcome reported: the hazard ratio (HR), 3-year OS rates, 3-year PFS rates; and language: English only. The exclusion criteria were as follows: type of article: reviews, conference abstracts, case reports, systematic reviews; and participants < 15 per arm; and (3) NOS score < 4 points.

2.8. Statistical analysis

The database for the collection of all clinical outcomes was established using Excel software (version 2016). One investigator examined data from a random sample of more than one dozen patients to ensure the accuracy and quality of the data entered. Data on clinical characteristics were analyzed using SPSS software (version 25.0). Dichotomous statistical analyses were performed with the chi-square test or Fisher exact test. The Kaplan–Meier method and log-rank test were used to evaluate the survival time. The HRs and 95% confidence intervals (CIs) of PFS and OS were estimated and calculated with Cox proportional hazards models. Characteristics with a P value <.15 in the univariate analyses were considered potential correlative factors in the multivariate analyses using the Cox regression test.

The comparisons from meta-analysis and publication bias were analyzed by Review Manager 5.3 and Stata. 16.0 Meta-analysis was conducted to calculate pooled odds ratios (ORs) with 95% confidence intervals (CIs). If the HR and survival rates were not available, an additional calculation was conducted with the methods described by Tierney et al.[24] Survival rates from Kaplan–Meier curves were read using Engauge Digitizer 10.8, and the resulting data were then entered into the calculation spreadsheet attached to Tierney paper. The level of significance in all tests was defined as a P value <.05.

3. Results

3.1. Patient characteristics and treatment choice

The clinical characteristics and treatment choices are summarized in Table 1. The median age for all DEL patients was 56 years (range 13–83), and DA-EPOCH-R was applied in patients with a maximum age of 77. The median ages of patients in the R-CHOP and DA-EPOCH-R groups were 60 and 49 years, respectively. A total of 58 (77.3%) patients were diagnosed at an advanced stage (III–IV), and 40 (53.3%) patients had a high IPI. The majority of patients had elevated levels of serum LDH (44, 58.7%) and less than 1 different extranodal disease site at diagnosis (39, 52%). The non-GCB subtype (49, 65.3%) was relatively more common than the GCB subtype. Only 48 patients had explicit FISH results, and 3 patients (6.2%) were positive for genetic rearrangements involving MYC and BCL2, which is mostly consistent with the results reported in previous studies. Generally, there was no significant difference in the baseline clinical characteristics between the DEL and non-DEL groups.

For treatment, a total of 7 (9.3%) patients received frontline stem cell transplantation (SCT) regardless of the autologous or allogeneic status. Consolidative radiation therapy and CNS prophylaxis were applied in 5 (6.7%) and 36 (48.0%) patients, respectively. In summary, treatment choices were comparable, with no significant differences between the DEL and non-DEL groups.

3.2. Response and toxicity

As illustrated in Table 2, in the R-CHOP subgroup, 25 (51.0%) and 12 (24.5%) patients achieved a complete response (CR) and partial response (PR), respectively. Similar results were observed in the DA-EPOCH-R subgroup: 17 (65.4%) patients achieved CR, and 5 (19.2%) achieved PR. The difference in response for DEL patients who received R-CHOP or DA-EPOCH-R was not significant (P = .347).

Furthermore, according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0, toxicity was noted in 131 patients treated with R-CHOP and 51 patients treated with DA-EPOCH-R. Patients treated with R-CHOP were less likely to have grade 3/4 neutropenia (17, 34.6% vs 18, 69.2%, P = .004 < 0.05) and thrombocytopenia (7, 14.3% vs 9, 34.6%, P = .04 < 0.05) than patients treated with DA-EPOCH-R. However, the incidence of anemia (5, 10.2% vs 5, 19.2%, P = .302) and neutropenic fever (9, 18.4% vs 7, 26.9%, P = .389) seemed similar in the R-CHOP and DA-EPOCH-R subgroups. Treatment-related mortality, defined as death due to infection or massive hemorrhage rather than disease progression, was observed in 2 (4.1%) patients and 2 (7.7%) patients who received R-CHOP and DA-EPOCH-R treatment, respectively (P = .606).

3.3. Survival outcomes

Generally, there were significant differences in survival outcomes between the R-CHOP and DA-EPOCH-R subgroups (P = .056 for PFS; P = .009 for OS) (Fig. 1). The median PFS times for the R-CHOP and DA-EPOCH-R subgroups were 37.1 and 48.1 months, and the median OS times were 43.1 and 56.8,

Table 1

Clinical characteristics of 75 patients diagnosed with DEL.

Parameter	Total	R-CHOP (n = 49) n (%)	DA-EPOCH-R (n = 26) n l(%)	*P*
Sex				
Male	34	21 (42.9)	13 (50.0)	.554
Female	41	28 (57.1)	13 (50.0)	
Age groups				
<60	39	23 (46.9)	16 (61.5)	.228
≥60	36	26 (53.1)	10 (38.5)	
Staging				
I–II	17	12 (24.5)	5 (19.2)	.605
III–IV	58	37 (75.5)	21 (80.8)	
IPI score				
Low (0–2)	35	22 (44.9)	13 (50.0)	.673
High (3–5)	40	27 (55.1)	13 (50.0)	
Serum LDH				
Normal	31	21 (42.9)	10 (38.5)	.713
High	44	28 (57.1)	16 (61.5)	
Extranodal disease sites				
<2	39	24 (49.0)	15 (57.7)	.472
≥2	36	25 (51.0)	11 (42.3)	
COO				
GCB	26	14 (28.6)	12 (46.2)	.128
Non-GCB	49	35 (71.4)	14 (53.8)	
BCL6				
+	10	6 (12.2)	4 (15.4)	.731
–	65	43 (87.8)	22 (84.6)	
DHL				
No	45	25 (92.6)	20 (94.9)	1.000†
Yes	3	2 (7.4)	1 (5.1)	
Not determined	27	22	5	
CNS prophylaxis				
No	39	27 (55.1)	12 (46.2)	.460
Yes	36	22 (44.9)	14 (53.8)	
Radiotherapy				
No	70	46 (93.9)	24 (92.3)	1.000†
Yes	5	3 (6.1)	2 (7.7)	
SCT				
No	68	45 (91.8)	23 (88.5)	
Yes	7	4 (8.2)	3 (11.5)	.688†

CNS = central nerve system, COO = cell-of-origin, DEL = double-expressor lymphoma, DHL = double-hit lymphoma, DLBCL = diffuse large B cell lymphoma, EPOCH-R = etoposide, prednisone, vincristine (Oncovin), cyclophosphamide, hydroxydaunorubicin, and rituximab, GCB = germinal center B-cell-like, IPI = International Prognostic Index, LDH = lactate dehydrogenase, R-CHOP = rituximab, cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin), and prednisone, SCT = stem cell transplantation.

*Pearson chi-squared test.

†Yates correction for continuity.

Table 2

Response rates according to treatment.

Parameter	Response, n (%)		Disease, n (%)		*P*
	CR	PR	PD	SD	
R-CHOP	25 (51.0)	12 (24.5)	7 (14.3)	5 (10.2)	.347
DA-EPOCH-R	17 (65.4)	5 (19.2)	4 (15.4%)	0 (0)	

CR = complete response, DA-EPOCH-R = rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, PD = progressive disease, PR = partial response, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, SD = stable disease.

respectively. The 3-year PFS rates for the R-CHOP subgroup and DA-EPOCH-R subgroup were 49.2% and 76.4%, and the 3-year OS rates were 58.8% and 84.6%, respectively.

To evaluate the impacts of clinical characteristics and therapeutic factors on prognostic outcomes, we carried out univariate analyses on several factors, including age, stage, IPI, LDH, extranodal site involvement, COO, BCL6 expression, frontline regimens, CNS prophylaxis, radiotherapy, and SCT, in a total of 75 patients with DEL (Table 3). The univariate analysis suggested that a high IPI (HR 2.371, 95% CI 1.148–4.897, *P* = .020) and high LDH (HR 2.329, 95% CI 1.081–5.015, *P* = .031) were significantly associated with reduced PFS. BCL6 positive expression (HR 0.310, 95% CI 0.126–0.763, *P* = .011) was significantly related to improved PFS. Similar results were observed in univariate analysis for OS: high IPI (HR 2.596, 95% CI 1.118–6.031, *P* = .026) had a significantly inferior outcome, but BCL6 positive expression (HR 0.370, 95% CI 0.138–0.993, *P* = .048) and DA-EPOCH-R regimen (HR 0.262, 95% CI 0.089–0.768, *P* = .015) had a significantly superior outcome.

Furthermore, all factors with a *P* value <.15 in the univariate analysis were included in the multivariate analysis (Table 4). Only the DA-EPOCH-R regimen (HR 0.324, 95%

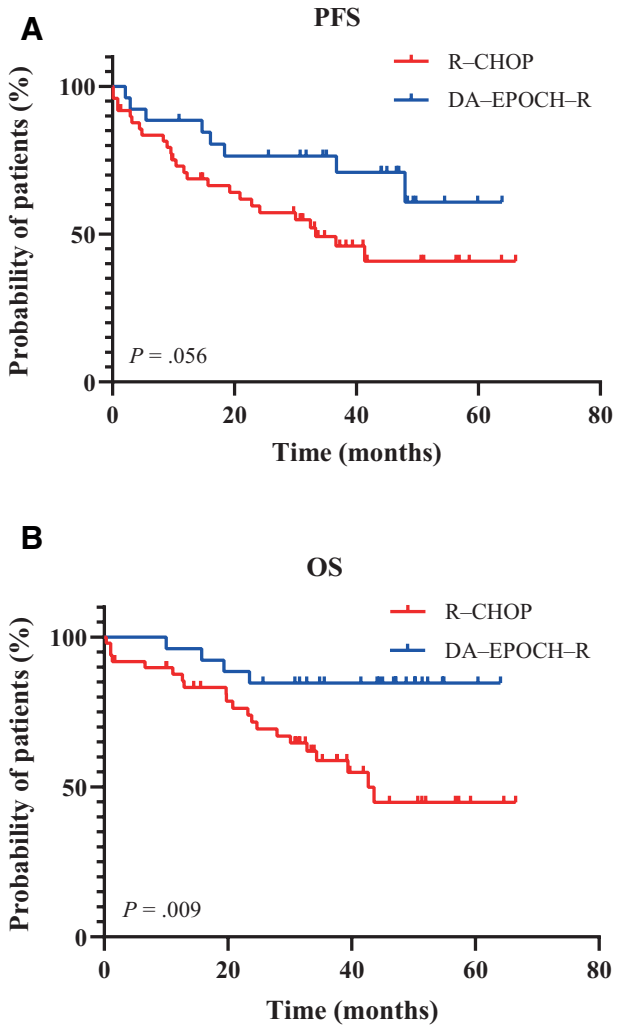

Figure 1. Survival curves and log-rank estimates of PFS (A) and OS (B) in DEL patients treated with R-CHOP and DA-EPOCH-R (R-CHOP, n = 49; DA-EPOCH-R, n = 26). CI = confidence interval, DA-EPOCH-R = rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, DEL = double-expressor lymphoma, HR = hazard ratio, OS = overall survival, PFS = progression-free survival, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

CI 0.135–0.775, *P* = .011) and BCL6 positive expression (HR 0.254, 95% CI 0.094–0.684, *P* = .007) were considered independent prognostic factors for superior PFS outcomes. LDH levels were included excluded with a *P* value of .05. For OS outcomes, the DA-EPOCH-R regimen (HR 0.137, 95% CI 0.040–0.469, *P* = .002), BCL6 positive expression (HR 0.195, 95% CI 0.063–0.600, *P* = .004) and high LDH (HR 2.743, 95% CI 1.119–6.720, *P* = .027) were all observed as independent prognostic factors with statistical significance.

The results suggested that the prognostic results were superior in DEL patients treated with DA-EPOCH-R than in those treated with R-CHOP, indicating that DA-EPOCH-R immunochemotherapy may be able to overcome the poor prognosis associated with DEL. Considering the sample size, the impact of treatment regimens in different age subgroups was not further explored in this study.

3.4. Meta-analysis of DEL patients

With the search strategy described above, 1531 publications were identified, and 5 controlled studies comparing induction regimens (R-CHOP vs DA-EPOCH-R in DEL patients) fulfilled the inclusion criteria (Fig. 2).[15,16,25–27] The characteristics of the 5 studies are presented in Table 5. Our meta-analysis included 412 patients in this research and 5 studies who were diagnosed with DLBCL in 4 different countries. A total of 235 DEL patients received the R-CHOP regimen, and 177 patients received DA-EPOCH-R as first-line treatment. The results of the quality assessment of the included articles are detailed in Table S3, Supplemental Digital Content 3, http://links.lww.com/MD/H339.

The HR of PFS, OS, 3-year PFS rate, and 3-year OS rate were calculated with the method mentioned above. As illustrated in Figure 3A and 3B, the HRs for both PFS and OS were not statistically significant, with values of 0.70 (95% CI = 0.44–1.10, *P* = .12) and 0.70 (95% CI = 0.40–1.24, *P* = .22), respectively. The event rate for 3-year PFS was 37.3% (66/177) in the DA-EPOCH-R group and 48.1% (113/235) in the R-CHOP group ([OR] = 0.63, 95% CI = 0.42–0.94, *P* = .02 < 0.05) (Fig. 3C). The event rate for 3-year OS was 29.9% (53/177) in the DA-EPOCH-R group and 35.7% (84/235) in the R-CHOP group ([OR] = 0.75, 95% CI = 0.49–1.15, *P* = .18) (Fig. 3D). Funnel plots for the event rate are presented in Figure S1, Supplemental Digital Content 4, http://links.lww.com/MD/H340. There was no obvious asymmetry in all funnel plots, and all evaluated outcomes lay inside the limits of the 95% CI. Given that the accuracy of funnel plots may be limited by the small

Table 3

Correlation with outcomes of 75 patients with DEL by univariate analyses.

		PFS			OS		
Parameter	**n**	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Male vs female	41/34	1.137	0.570–2.269	.715	0.741	0.338–1.625	.454
Age ≥60 vs <60	36/39	1.649	0.825–3.294	.157	1.867	0.837–4.163	.127
Staging (III–IV vs I–I)	58/17	2.675	0.940–7.614	.065	2.802	0.838–9.375	.094
High IPI vs low IPI	40/35	2.371	1.148–4.897	.020	2.596	1.118–6.031	.026
High LDH vs normal	44/31	2.329	1.081–5.015	.031	2.257	0.942–5.411	.068
Extranodal sites ≥2 vs <2	36/39	0.979	0.493–1.945	.952	0.771	0.346–1.716	.523
Non-GCB vs GCB	49/26	1.833	0.851–3.949	.122	1.607	0.511–5.050	.417
BCL6+ vs BCL6–	65/10	0.310	0.126–0.763	.011	0.370	0.138–0.993	.048
DA-EPOCH-R vs R-CHOP	26/49	0.466	0.210–1.038	.062	0.262	0.089–0.768	.015
CNS prophylaxis (yes vs no)	36/39	1.010	0.510–2.001	.977	0.750	0.340–1.654	.477
Radiotherapy (yes vs no)	5/70	0.712	0.169–2.991	.642	0.044	0.000–32.31	.354
SCT (yes vs no)	7/68	0.039	0.000–3.226	.150	0.041	0.000–8.094	.236

CI = confidence interval, CNS = central nerve system, DA-EPOCH-R = rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, DEL = double-expressor lymphoma, GCB = germinal center B-cell-like, HR = hazard ratio, IPI = International Prognostic Index, LDH = lactate dehydrogenase, OS = overall survival, PFS = progression-free survival, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, SCT = stem cell transplantation.

Table 4

Correlation with outcomes of 65 patients with DEL by multivariate analyses.

	PFS				OS		
Parameter	**HR**	**95% CI**	***P***	**Parameter**	**HR**	**95% CI**	***P***
LDH	2.194	1.000–4.815	.050	LDH	2.743	1.119–6.720	.027
BCL6	0.254	0.094–0.684	.007	BCL6	0.195	0.063–0.600	.004
DA-EPOCH-R vs R-CHOP	0.324	0.135–0.775	.011	DA–EPOCH–R vs R–CHOP	0.137	0.040–0.469	.002

CI = confidence interval, DA-EPOCH-R = rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, DEL = double-expressor lymphoma, HR = hazard ratio, LDH = lactate dehydrogenase, OS = overall survival, PFS = progression-free survival, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone.

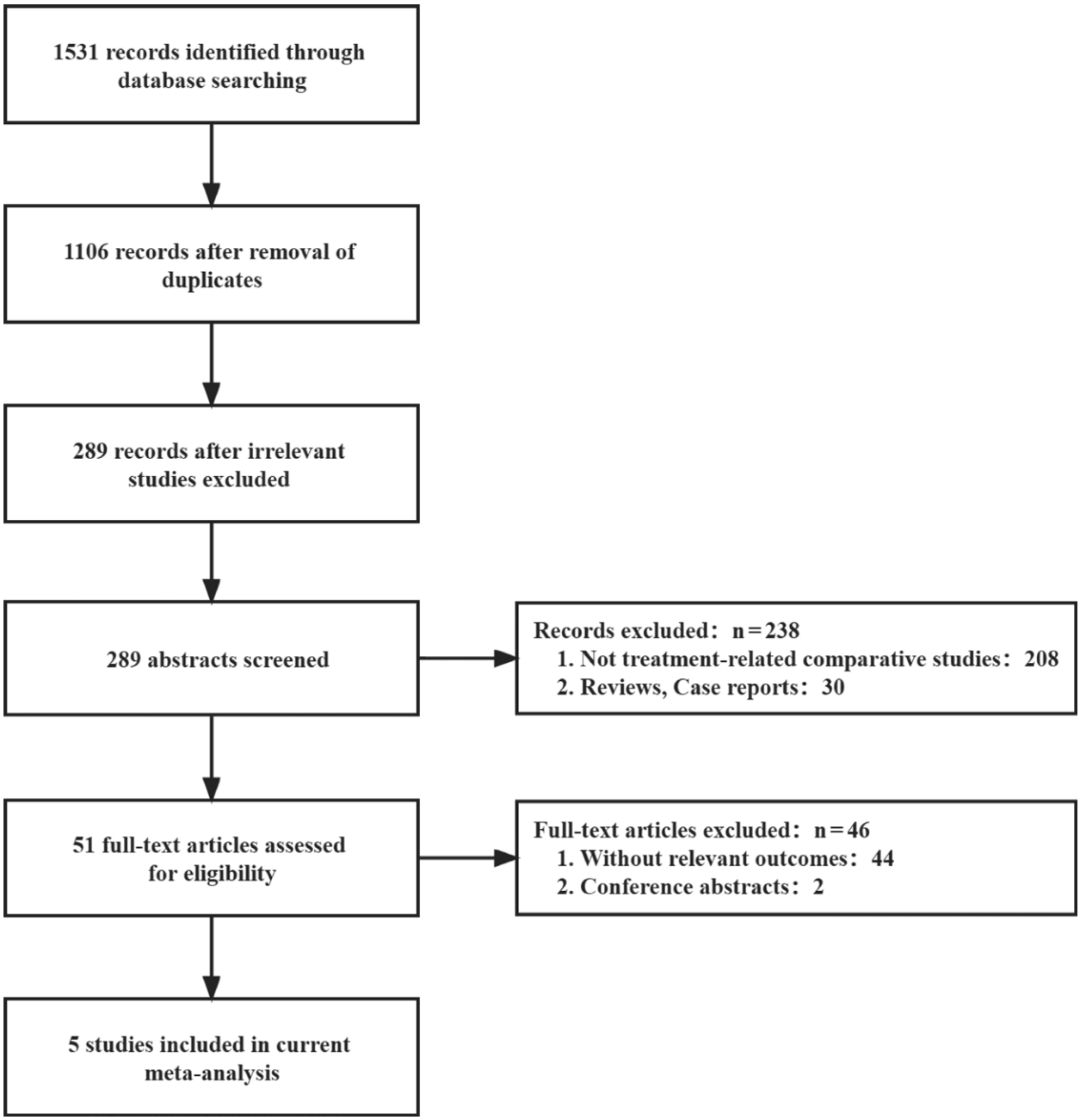

Figure 2. Flow chart of the study selection.

number of studies, Egger test was conducted as a supplement to statistically check for publication bias.[28] Egger test suggested no significant publication bias for the HR of PFS (P = .220), HR of OS (P = .444), 3-year PFS rate (P = .072) or 3-year OS rate (P = .225).

4. Discussion

DEL is a relatively common subgroup of DLBCL and is associated with a poorer prognosis when treated with the R-CHOP regimen. The poor prognosis of DEL is likely associated with

Table 5

Study characteristics.

Year	First author	Design	E group patents number	Median age	Male percentage	C group patents number	Median age	Male percentage
2021	Christopher	Retro	39	66	57%	46	66	50%
2019	Zhang	Retro	24	NA	NA	29	NA	NA
2019	Dodero	Retro	51	58	63%	63	65	60%
2019	Bartlett	RCT subgroup	20	NA	NA	22	NA	NA
2017	Pedersen	Retro	17	NA	NA	26	NA	NA

C group = the group of patients receiving R-CHOP treatment, E group = the group of patients receiving DA-EPOCH-R treatment, NA = not available, RCT = randomized controlled trail, Retro = retrospective.

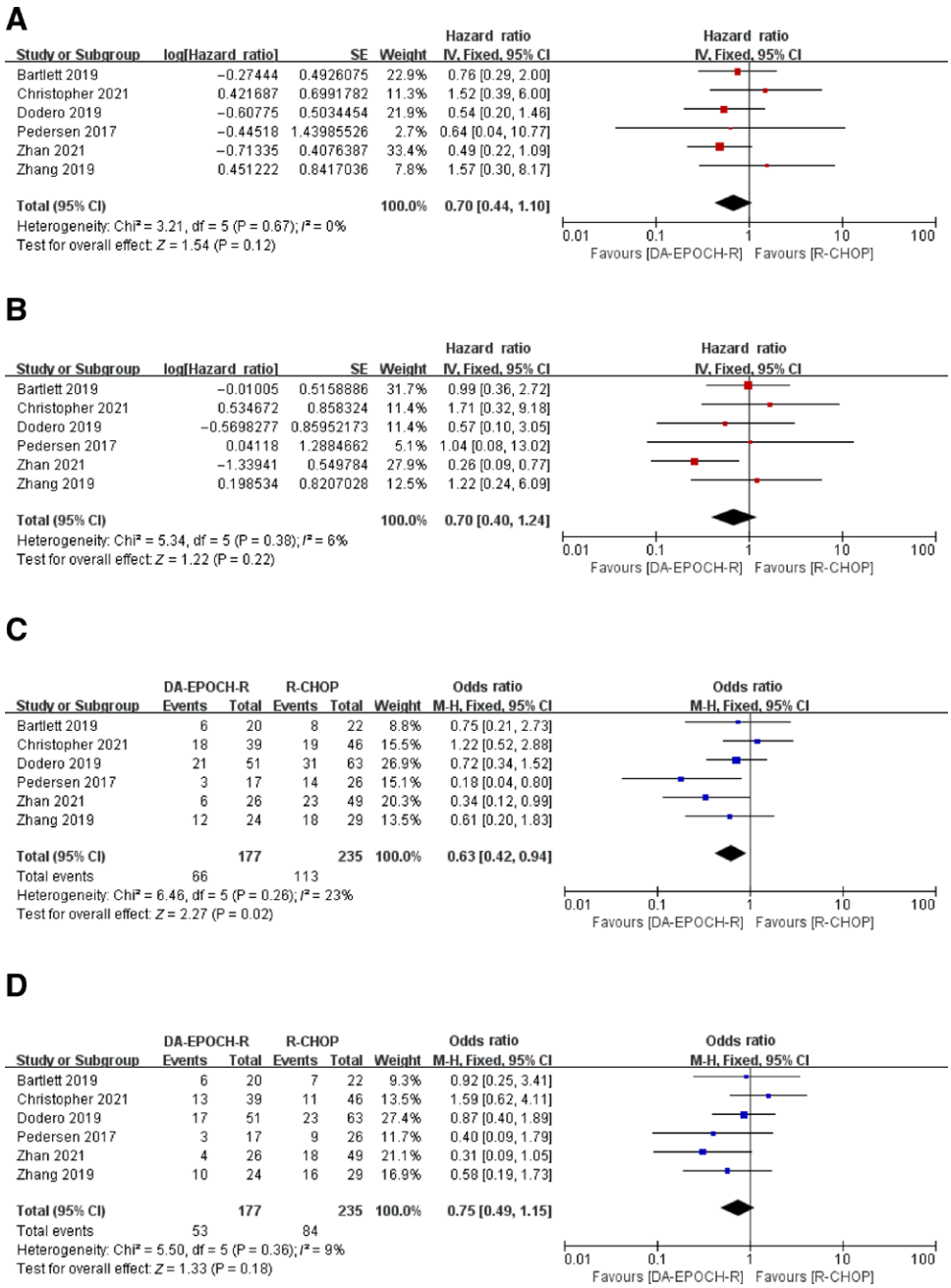

Figure 3. Forest plot for hazard ratio of PFS (A), OS (B), 3-year PFS (C), and 3-year OS (D) in DEL patients treated with R-CHOP vs DA-EPOCH-R alone. CI = confidence interval, DA-EPOCH-R = rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, DEL = double-expressor lymphoma, OS = overall survival, PFS = progression-free survival, R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone, SE = standard error.

aggressive tumor properties and inferior response rates.[29] Furthermore, double expressor status was reported to be associated with higher CNS relapse rates in the phase 3 GOYA study.[30] The DA-EPOCH-R regimen has demonstrated promising results in patients with DHL, relapsed or refractory DLBCL, and certain subgroups of DLBCL associated with high proliferation.[31,32] The optimal therapeutic strategies for DEL remain a significant challenge because published reports have revealed some controversial findings.

Therefore, the main aim of this retrospective study was to identify the feasibility of the DA-EPOCH-R regimen in DEL patients. From an efficacy perspective, after determining that the clinical characteristics of the two groups were comparable, the log-rank test was carried out between the DA-EPOCH-R group and R-CHOP group and confirmed the prognostic superiority of the DA-EPOCH-R regimen ($P = .056$ for PFS, $P = .009$ for OS). Moreover, the DA-EPOCH-R regimen resulted in a higher overall response rate (22/26) than the R-CHOP regimen (37/49) in patients with DEL. These findings are in accordance with many single-arm articles, which have confirmed the prognostic advantage of DA-EPOCH-R over R-CHOP, by demonstrating that the DA-EPOCH-R regimen was able to eliminate the inferior prognosis of DEL over non-DEL to some extent.[33,34] However, the significant prognostic superiority of DA-EPOCH-R was not observed in unplanned subgroup analyses from other trials, potentially due to their limited sample sizes and small proportions of patients with the GCB subtype, who exhibited superior survival rates to the non-GCB subtype among those with DLBCL.[35]

For medication safety, although R-chemo was generally well tolerated as a first-line treatment in patients with DLBCL,[36] DA-EPOCH-R significantly resulted in a higher incidence rate of adverse events such as grade 3/4 neutropenia and thrombocytopenia in our study. Therefore, overall considerations of age, comorbidities, tolerance of the initial chemotherapy, performance status, and bone marrow function are necessary to provide individualized induction therapy, especially in elderly DLBCL patients. Adequate supportive treatment is a prerequisite for the safety of the DA-EPOCH-R regimen. Hematological toxicities were common in the DA-EPOCH-R group, whereas they did not necessarily increase the incidence of neutropenic fever or treatment-related mortality in this research, which is possibly due to the active application of prophylactic antibiotics and long-lasting G-CSF.

Univariate and multivariate Cox analyses were also conducted, which indicated several independent factors that represented the superior prognosis of DEL patients, such as normal levels of serum LDH, the positive expression status of BCL6, and the DA-EPOCH-R regimen. BCL6 (B-cell lymphoma 6) is a key oncoprotein that can repress the transcription of checkpoint genes and DNA damage sensor genes.[37] It can also repress numerous oncogenes in germinal center B cells, including MYC and BCL2, which may be the mechanisms for the prognostic superiority of the positive expression status of BCL6 in DEL. Additionally, frontline SCT seemingly resulted in fewer prognostic benefits than DA-EPOCH-R in patients with DEL despite the lack of significant differences, which may support the notion that DLBCL is a "one-shot" disease. Kawashima et al[38] retrospectively demonstrated the prognostic differences between DEL and non-DEL patients, even after allogeneic hematopoietic cell transplantation. The definite benefits of SCT and DA-EPOCH-R for patients with DEL should be determined with larger randomized trials.

There are some limitations of our study, such as the retrospective nature and the small sample size. Since several studies proved that the prognostic benefit of DA-EPOCH-R was found mainly in DEL patients younger than 60 years, another important limitation of our study is that the impact of treatment regimens in different age subgroups was not explored due to the sample size. Additionally, because many patients are treated without definite DEL status, there may be a potential treatment selection bias. Although the chi-square analysis in Table 1 showed no significant differences in clinical characteristics between treatment choices, there may still be selection bias due to high-risk clinical characteristics. To further confirm our findings in the retrospective part, a meta-analysis was conducted comparing the survival outcomes between DA-EPOCH-R and R-CHOP, which has not been evaluated in the previous meta-analysis. After processing data from six articles that enrolled a total of 412 patients, our analyses indicated that the events rate for 3-year PFS was significantly lower in patients receiving DA-EPOCH-R treatment than in those undergoing R-CHOP treatment (OR = 0.63, 95% CI = 0.42–0.94, $P = .02$), whereas no statistically significant difference was found in the HRs for both PFS and OS and the events rate for 3-year OS. Of the other 5 published studies, only one was a subgroup analysis of an RCT, and four were retrospective studies, whereas there was no significant heterogeneity in this research (maximum $I^2 = 23\%$, $P = .26$). The present meta-analysis provided an assessment of current evidence regarding the efficacy of DA-EPOCH-R versus R-CHOP based on 6 high-quality articles on DEL. To our current knowledge, this meta-analysis is the first on this topic, contributing to a reliable result and a more extensive application of analysis results.

Innovative strategies are urgently needed to improve the outcomes of DEL patients. Several innovative targeted drugs, such as ABT-199[39,40] (a BCL2 inhibitor that was associated with a high CR rate in patients with DEL after combination with the CHOP-based regimen in a phase I trial), lenalidomide (a targeted drug for drivers of MYC expression that was demonstrated to exhibit the safety and feasibility of lenalidomide when combined with the DA-EPOCH-R regimen in patients with DHL and DEL in a phase I study),[41] ibrutinib (a BTK inhibitor that was confirmed to improve the PFS and OS in DEL patients)[42] and several advanced immunotherapies, such as checkpoint inhibitors and cellular immunotherapies,[43] have provided a framework for future therapeutic strategies. The combination of new targeted drugs with the R-CHOP or DA-EPOCH-R regimen may show additional superiority over the conventional DA-EPOCH-R regimen in terms of survival in the future and may provide more treatment opportunities for patients with DEL. Although additional medical evidence and further confirmation are needed, this therapeutic strategy represents a promising approach; thus, we recommend DA-EPOCH-R immunochemotherapy for patients with DEL, especially young patients.

5. Conclusions

In conclusion, the results of this retrospective study and meta-analysis indicated that DA-EPOCH-R immunochemotherapy might improve the prognosis of DEL patients. More definite results should be considered for future prospective randomized clinical trials on a large number of patients.

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Author contributions

Study design: W.Z. and J.Z. Data collection: J.Z., S.J.Y., W.Z., D.B.Z., Y.Z., W.W., and C.W. Literature search: J.Z. and S.J.Y. Study selection: J.Z. Study draft and revision: J.Z., S.J.Y., and W.Z. All authors read and approved the final manuscript.

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