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Prognostic Factors and Effect Modifiers in Patients With Relapse or Refractory Diffuse Large B-Cell Lymphoma After Two Lines of Therapy: A Systematic Literature and Expert Clinical Review

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ABSTRACT

Objectives: The objective of this systematic literature review (SLR) combined with expert clinical review was to identify and rank prognostic factors and effect measure modifiers (EMMs) systematically and comprehensively in patients with relapsed or refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who initiate treatment after ≥2 prior lines of therapy (LoTs; 3L+ R/R DLBCL).

Methods: We performed an SLR of studies published between 2016 and 2021 and extracted study characteristics, prognostic factors, and EMMs. This was followed by clinical review and ranking of findings by subject matter experts using questionnaires, follow-up interviews, and quantitative ranking.

Results: Across 46 included studies, the SLR identified 36 prognostic factors significantly associated with ≥1 clinical outcome. Based on subject matter expert ranking of the SLR-derived list, the five most important prognostic variables in descending order are: early chemo-immunotherapy failure, Eastern Cooperative Oncology Group performance status, refractory to last LoT, number of prior LoTs, and double- or triple-hit lymphoma.

Conclusions: This SLR and expert clinical review is the first to provide a comprehensive assessment of prognostic factors for 3L+ R/R DLBCL. No statistically significant EMMs were identified. This robust multi-method approach can assist in selecting prognostic variables for comparative analyses between real-world studies and clinical trials.

1 | Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma [1, 2]. Despite the effectiveness of chemo-immunotherapy in the first-line treatment setting, 40% of patients with DLBCL are either refractory to the treatment or will relapse after achieving complete response (CR) [3–5]. Considering the relatively limited treatment options and generally poor outcomes, there is an unmet medical need to identify effective treatments for patients with relapsed or refractory (R/R) DLBCL, particularly for those requiring third-line treatment and above (3L+).

Since 2018, chimeric antigen receptor (CAR) T-cell therapy has significantly altered the treatment landscape for DLBCL, initially for patients with multiple relapses and more recently for those in earlier lines of therapy (LoTs) with proven efficacy and an acceptable safety profile. However, a substantial number of patients still experience relapse following therapy [6]. The use of CAR T-cell therapy remains impeded by several factors, including patient eligibility, rapidly progressing diseases, lengthy manufacturing time, need for bridging therapies, treatment-related toxicities (i.e., cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome), and financial challenges due to the high cost that may not be affordable in certain healthcare settings [5]. Other novel treatments, such as bispecific antibodies like epcoritamab and glofitamab, have also emerged as additional treatment options for patients with R/R DLBCL [1].

The use of external controls has been employed to contextualize single-arm trials of newer therapies in DLBCL (axicabtagene ciloleucel: SCHOLAR-1, tafasitamab: RE-MIND, and lisocabtagene maraleucel: NDS-NHL-001) [7–9]. These external controls can serve as a point of reference for comparing the results with clinical trials. Valid comparisons require balanced prognostic factors between trial participants and external controls, and an understanding of effect measure modifiers (EMMs) to inform the design of subgroup analyses. Such variables should be identified through a systematic review and pre-specified in a study protocol [10]. Given that sample-size considerations may preclude adjustment for all prognostic variables, ranking them by their importance can help researchers focus on the most critical prognostic variables. This approach is aligned with guidance provided by the Institute for Quality and Efficiency in Health Care [10], which requires that relevant confounders be pre-specified in the study protocol [10].

The objective of this systematic literature review (SLR) combined with expert clinical review was to identify and rank prognostic factors and EMMs systematically and comprehensively in patients with R/R DLBCL after two LoTs.

2 | Methods

This study was conducted in two stages. The first stage consisted of SLR-based identification of prognostic factors, followed by a second stage encompassing a clinical review and ranking of SLR findings by subject matter experts. The SLR followed the industry-accepted guidelines described by the Cochrane Handbook for Systematic Reviews of Interventions [11] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [12]. Guidelines from the European Medicines Agency [13], U.S. Food and Drug Administration [14], Institute for Quality and Efficiency in Health Care (IQWiG) [10], and UK National Institute for Health and Care Excellence [15, 16] were also reviewed for SLR methodology, as applicable.

A detailed protocol was developed prior to conducting the review, and the review was registered a priori in PROSPERO (registration ID: CRD42022307557).

2.1 | Search Strategy

Comprehensive literature searches were conducted using MEDical Literature Analysis and Retrieval System Online, Excerpta Medica Database, and Cochrane Central Register of Controlled Trials between January 1, 2016, and December 13, 2021 (complete search strategies are presented in Supporting Information S1: Appendix A). Searches were supplemented by conference abstract reviews for the American Society of Clinical Oncology, the European Society for Medical Oncology (ESMO), the American Society of Hematology, and the European Hematology Association conferences in 2021. Forward citation searches were undertaken using Google Scholar, based on 10 included references. The bibliographies of four recently published reviews on the related topic area, as well as ESMO and National Comprehensive Cancer Network guidelines, were also reviewed to identify additional relevant studies [17–22].

2.2 | Eligibility Criteria

The scope of the research and patient, intervention, comparison, outcome, time, and setting (PICOTS) criteria [11] for including and excluding studies are outlined in Supporting Information S1: Appendix B.

2.3 | Study Selection, Data Collection, and Risk of Bias Assessment

Unique records identified by the search were screened for eligibility by title and abstract, which was followed by full-text screening by two reviewers working independently. When there was uncertainty about inclusion/exclusion criteria, or there was a discrepancy between the two reviewers, a third reviewer adjudicated a decision to include or exclude. Data were collected from the eligible studies and entered into an Excel workbook for synthesis. For each study, key study methodological characteristics, patient characteristics, and results were extracted and tabulated. Data extraction of numeric values was conducted independently by two investigators, and the source document was checked by a third reviewer for any discrepancies. Risk of bias assessment of individual studies was performed using the quality in prognostic studies (QUIPS) tool (Supporting Information S1: Appendix C) [23].

2.4 | Data Synthesis

All eligible studies were included to describe the prognostic factors and/or EMMs reported for individual clinical outcomes. Results were synthesized narratively by the type of prognostic factors and EMMs, with findings tabulated.

2.5 | Clinical Review

Following the conduct of the SLR, the identified potential prognostic variables were evaluated by the study team to remove treatment-specific factors (e.g., those related to stem cell transplantation [SCT]) and post-baseline variables, determine their availability in the single-arm trial and in real-world data (RWD), and develop a questionnaire.

In the questionnaire (Supporting Information S1: Appendix D), prognostic variables were grouped by type of variable—patient demographics and clinical characteristics, disease characteristics, prior treatment characteristics, and imaging and laboratory values. Each prognostic variable was reviewed by an international panel comprising three clinical experts in the field of lymphoma who categorized the prognostic impact on treatment response and survival on a 5-point scale ranging from (*very high importance*) to (*not important*). A comprehensive approach was taken for the ranking of variables, that is, clinical experts were asked to categorize variables in terms of their prognostic impact on treatment response and survival. The clinicians were asked to consider possible correlations among the variables, consider possible effect modifiers, provide variable definitions (e.g., early chemo-immunotherapy failure), and assess whether there were any other prognostically important variables not captured in the questionnaire. For each variable, the clinical experts categorized the availability within RWD on a 3-point scale ranging from (*readily available*) to (*limited availability*).

The results of the three expert-completed questionnaires were reviewed, and the top 10 most important variables were determined by summing the clinicians' categorization of prognostic impact across the questionnaires and considering variable availability in the event of a tie. Individual interviews with each clinical expert were held to clarify variables and definitions, discuss discrepant categorization and the rationale for their decisions, and rank the prognostic variables from 1 to 10. Following the three interviews, the ranking of each variable was summed across the three experts to determine the final ranking. In the event of a tie, the variables were assigned the same rank.

3 | Results

3.1 | Studies Identified

The database searches identified a total of 2269 records. Following deduplication, 2247 records underwent title and abstract screening, of which 299 records were retained for full-text review. Following full-text review, 46 records meeting the eligibility criteria were included. Seven additional records were identified by other methods. Overall, 53 publications [24–76] (24 journal articles and 29 conference abstracts) reporting data on 46 studies were included in the review. The process of searching and screening was summarized in a PRISMA flow diagram (Figure 1).

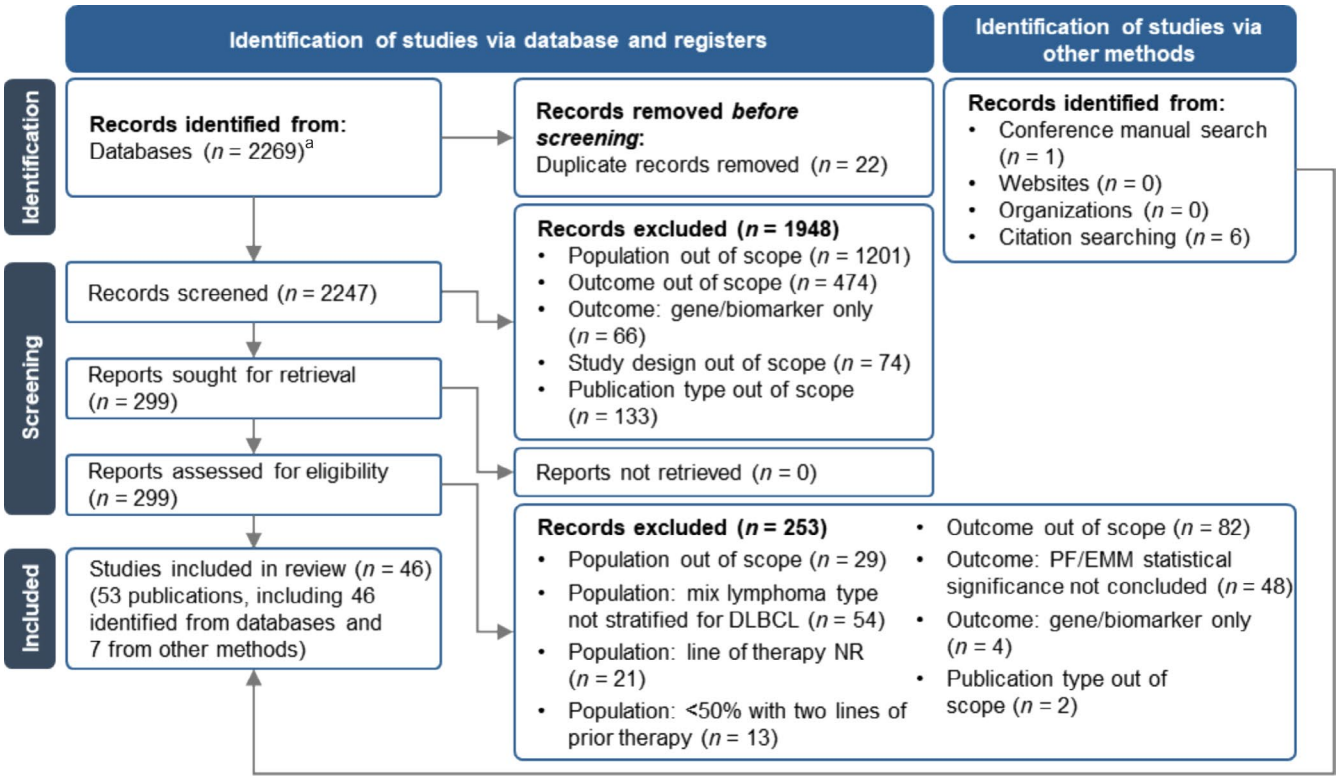

FIGURE 1 | PRISMA flow diagram. DLBCL = diffuse large B-cell lymphoma; EMM = effect measure modifier; NR = not reported; PF = prognostic factor. [a]Search was conducted on December 13, 2021.

3.2 | Study and Patient Characteristics

Characteristics of the included studies are summarized in Table S1 (Supporting Information S1: Appendix E). Among the 46 included studies, 32 unique population sources were involved. Five studies [24, 27–30] were conducted using data from two randomized controlled trials, four studies [31, 32, 34, 35] were conducted using data from three non-randomized controlled trials, and 37 observational studies [36–62, 64–71, 75, 76] were based on data from clinical centers or registries. In this review, clinical trials and observational studies were considered equal grade in the evidence synthesis. Some studies included patients from the same trial or overlapping data sources, but all studies were all included to capture important subpopulations and to ensure comprehensiveness. The sample size across the included studies varied from 17 [35] to 6947 [75], and the median follow-up time ranged from 4 [60] to 127 [62] months. The intervention type was SCT in 12 studies [42, 45, 50, 52, 61, 62, 64, 69–71, 75, 76], CAR T-cell therapy in eight studies [34, 36, 38, 41, 46, 55, 58, 59], polatuzumab vedotin-based therapy in six observational studies [37, 43, 44, 47, 49, 60], selinexor in four studies [24, 27, 29, 30], ibrutinib-based therapy in three studies [31, 32, 35], and combination chemotherapy in eight studies [28, 53, 54, 65–68]. The type of treatment was not reported in five studies [39, 40, 51, 56, 57]. Among the 46 studies, all patients had at least two prior LoTs in 21 studies, eight studies included populations in which at least 50% of the study population received at least two prior LoTs, and 17 studies included populations that had a median/mean of at least two prior LoTs. A total of 45 studies included only patients with DLBCL, whereas one study included two lymphoma types but had results stratified for the DLBCL population. Across the included study treatment arms, the median age ranged from 40 [74] to 72 [43] years, and the proportion of males varied from 33% [65] to 75% [28] across the studies. Among the 46 studies, only 10 studies [34, 37, 40, 45, 49, 52, 54, 62, 69, 73, 76] reported race/ethnicity information; four studies [34, 37, 49, 73, 76] were conducted in an Asian population, and six studies [40, 45, 52, 54, 62, 69] were conducted in a mixed population that was predominantly White (> 80%).

3.3 | Quality Assessment of Included Studies

Risk of bias was assessed using the QUIPS tool [23]. Most of the included studies had a high or moderate risk of bias due to lack of reporting, specifically in the "Study Attrition" and "Statistical Analysis and Reporting" domains. A graphical summary of the risk of bias assessment can be found in Supporting Information S1: Appendix F.

3.4 | Prognostic Factors and EMMs

3.4.1 | SLR

All 46 studies reported statistically significant associations ($p < 0.05$) between variables and clinical outcomes of interest. None of the studies identified statistically significant EMMs. Thirty-six prognostic factors were identified to have statistically significant associations with seven clinical outcomes, including overall survival (OS; 38 studies), progression-free survival (PFS;

TABLE 1 | Patient demographics and clinical characteristics—Summary of study count, directionality, example characteristics, and affected outcomes for statistically significant prognostic factors.

Prognostic factor	Study count	Directionality—characteristics associated with worse outcomes	Example characteristics (vs. reference)—category with favorable outcomes in bold	Clinical outcomes with study counts
ECOG performance status	$N = 9$[a]	Higher ECOG performance status	• ≥ 2 (vs. **< 2**) • 3–4 (vs. **0–2**)	OS: 9,[a] PFS: 1
Age[b]	$N = 7$[a]	Older age in five studies; younger age in two studies	• ≥ 65 years (vs. **< 65 years**) • ≥ 55 years (vs. **15–39 years**) • **> 50 years** (vs. younger)	OS: 5,[a] PFS: 1, NRM: 1, overall mortality: 1, CR: 1
KPS	$N = 3$	Lower KPS	• < 80% (vs. **80%–100%**) • **Admittance KPS status as continuous variable**	OS: 3, PFS: 1, relapse/progression: 1
Presence of comorbidities[c]	$N = 1$	Presence of significant comorbidities	• Significant comorbidities (vs. **without significant comorbidities**)	OS: 1, PFS: 1

Abbreviations: CIRS = Cumulative Illness Rating Scale; CR = complete response; ECOG = Eastern Cooperative Oncology Group; KPS = Karnofsky performance status; NRM = non-relapse mortality; OS = overall survival; PFS = progression-free survival.

[a]Two studies used the same data source and may have overlapping populations.

[b]Prognostic factor with conflicting directionality across studies.

[c]Presence of comorbidities: assessed by CIRS; significant comorbidities were defined as CIRS total score of ≥ 7 or CIRS score of 3 or 4 in ≥ 1 organ system [59].

TABLE 2 | Disease characteristics—Summary of study count, directionality, example characteristics, and affected outcomes for statistically significant prognostic factors.

Prognostic factor	Study count	Directionality—characteristics associated with worse outcomes	Example characteristics (vs. reference)—category with favorable outcomes in bold	Clinical outcomes with study counts
Refractory disease	$N = 10$[a]	Refractory disease	• Refractory disease (vs. **non-refractory disease**) • Primary refractory disease[b] (vs. **relapsed disease**)	OS: 5, PFS: 7,[a] CR: 2, ORR: 2
R-IPI or t-IPI	$N = 5$	Higher IPI score	• 3–5 (vs. **0–2**) • 4–5 (vs. **0–1**)	OS: 5, ORR: 1
Double-expressor or double-hit lymphoma[c]	$N = 4$	Double-expressor or double-hit lymphoma	• Double/triple expressor (vs. **no**) • DEL (vs. **non-DEL**) • DEL (vs. **neither DEL nor DHL**) • DHL (vs. **neither DEL nor DHL**) • Both DEL and DHL (vs. **non-DEL/non-DHL**; **DEL**)	OS: 3, PFS: 1, NRM: 1, ORR: 2[a]
MYC overexpression or mutation[d]	$N = 3$	Overexpression or mutation of MYC	• MYC mutation (vs. **others**) • MYC rearrangement (positive on FISH vs. **negative**) • cMYC $\geq 40\%$ tumor-positive cells (vs. **cMYC $< 40\%$ tumor-positive cells**)	OS: 2, ORR: 1
Transformed disease[e]	$N = 3$	Transformed disease in two studies; de novo disease in one study	• Transformed from follicular lymphoma (vs. **de novo**) • **Transformed (history unspecified)** (vs. de novo)	OS: 1, PFS: 1, DOR: 1
Cell of origin[e]	$N = 2$	Non-GCB and GCB in one study each	• Non-GCB (vs. **GCB**) • **Non-GCB** (vs. GCB)	OS: 1, ORR: 1
Ann Arbor stage	$N = 2$	Higher Ann Arbor stage	• III–IV (vs. **I–II**)	OS: 2
Disease bulk	$N = 2$	Bulky disease	• > 7.5 cm (vs. **≤ 7.5 cm**) • Yes (vs. **no**)	PFS: 1, ORR: 1
Time from diagnosis	$N = 2$	Shorter time from diagnosis	• Shorter (vs. **longer**) • **Days from diagnosis to ASCT (as continuous variable)**	ORR: 1, CR (after relapse/progression): 1
Tumor burden[f]	$N = 1$	High tumor burden	• High (vs. **low**)	PFS: 1, ORR: 1
BCL2 expression	$N = 1$	Overexpression of BCL2	• Positive (vs. **negative**)	OS: 1, PFS: 1

(Continues)

TABLE 2 | (Continued)

Prognostic factor	Study count	Directionality—characteristics associated with worse outcomes	Example characteristics (vs. reference)—category with favorable outcomes in bold	Clinical outcomes with study counts
Year of diagnosis of DLBCL	$N = 1$	Diagnosis of DLBCL before 2002	• Before 2002 (vs. **after 2002**)	OS: 1, PFS: 1, NRM: 1
B symptoms	$N = 1$	Presence of B symptoms	• Yes (vs. **no**)	OS: 1

Abbreviations: ASCT = autologous stem cell transplantation; BCL2 = B-cell lymphoma 2; CR = complete response; DEL = double-expressor lymphoma; DHL = double-hit lymphoma; DLBCL = diffuse large B-cell lymphoma; DOR = duration of response; FISH = fluorescence in situ hybridization; GCB = germinal center B-cell like; IPI = International Prognostic Index; NRM = non-relapse mortality; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R-IPI = revised International Prognostic Index; t-IPI = tertiary International Prognostic Index.

[a]Two studies used the same data source and may have overlapping populations.

[b]Primary refractory disease: defined as a duration of first remission of < 12 months in one study [68], but no additional definition was provided in other studies.

[c]DEL or DHL: DEL was defined as the dual expression of MYC and BCL2 proteins; DHL was defined as concurrent rearrangements of MYC and BCL2 and/or BCL6.

[d]MYC overexpression or mutation: MYC overexpression was defined as ≥ 40% positive cells in one study [74]; MYC positivity was determined by FISH in one study [59], which indicates MYC rearrangement in the context of DLBCL. MYC mutation was reported in one study [56] without further specification of whether it pertained to rearrangement specifically.

[e]Prognostic factor with conflicting directionality across studies.

[f]High tumor burden: defined as the maximum dimension of largest tumor of ≥ 4 cm or metabolic tumor volume of ≥ 100 cm^3 [31].

22 studies), objective response rate (eight studies), non-relapse mortality (four studies), CR (three studies), relapse/progression (two studies), and duration of response (one study). The prognostic variables were categorized into four groups: patient demographics and clinical characteristics, disease characteristics, treatment characteristics, and imaging and laboratory values. The associated clinical outcomes, directionality of the association, and study counts for each prognostic factor are summarized in Tables 1–4. The prognostic factors and their characteristics were captured as reported by the studies, with additional information for effect estimates and supporting evidence presented in Table S2 (Supporting Information S1: Appendix E). Among the identified prognostic factors, higher Eastern Cooperative Oncology Group (ECOG) performance status, older age, having (primary) refractory disease, not achieving response to current or prior therapy, higher International Prognostic Index (IPI) composite score, and elevated lactate dehydrogenase (LDH) levels were associated with worse outcomes in five or more studies (OS, 29; PFS, 13; others, eight). Four variables (age, transformed disease, non-germinal center B-cell DLBCL, and LDH level) had evidence of conflicting associational directions.

3.4.2 | Clinical Review

During the questionnaire and following individual interviews, no prognostic factors were considered missing by the clinical experts, and discussions were held with the experts to address discrepancies in grading from the questionnaire. The final ranked list of the 10 most important prognostic variables in descending order of importance was as follows: early chemo-immunotherapy failure, ECOG performance status, refractory to last LoT, number of prior LoTs, double- or triple-hit lymphoma, age at start of LoT, IPI risk classification, Ann Arbor disease stage, serum LDH, and Deauville score (Table 5).

4 | Discussion

The use of single-arm trials has allowed transformative therapies to be made more expeditiously available to patients with diseases that have high unmet needs. However, contextualizing the findings of these trials using external controls requires the identification of prognostic factors and pre-specification of variables for confounder adjustment. Despite the availability of multiple studies on prognostic factors across various diseases, they are often of variable quality and have inconsistent findings. The German IQWiG guidelines [77] suggest using SLR combined with an expert review of its results as a recommended method for identifying and pre-specifying prognostic variables and EMMs to support the use of RWD-derived external control arms. To the best of our knowledge, this is the first study combining SLR-based identification of prognostic factors with a clinical review by subject matter experts to systematically and comprehensively identify and rank prognostic factors and EMMs in patients with R/R DLBCL after two LoTs. A total of 36 disease and treatment characteristics were found to be important prognostic factors of clinical outcomes for patients with R/R DLBCL, as reported in the literature (see Table S2 in Supporting Information S1: Appendix E). However, no statistically significant EMMs were identified based on the SLR.

TABLE 3 | Treatment characteristics—Summary of study count, directionality, example characteristics, and affected outcomes for statistically significant prognostic factors.

Prognostic factor	Study count	Directionality—characteristics associated with worse outcomes	Example characteristics (vs. reference)—category with favorable outcomes in bold	Clinical outcomes with study counts
Response to current therapy	$N=8$[a]	Not achieving CR/PR to current therapy	• No response (SD/PD) (vs. **CR/PR**) • PD (vs. **CR/PR**)	OS: 7,[a] PFS: 1
Response to prior therapy	$N=5$[b]	Not achieving CR to therapy prior to SCT	*Response to therapy prior to SCT (remission status at transplantation)* • Non-CR (vs. **CR**) • PR (vs. **CR**)	OS: 5,[b] PFS: 3, NRM: 1, CR: 1, relapse/progression: 2
	$N=1$	Not achieving response to prior 3L treatment	*Response to prior 3L treatment* • SD/PD (vs. **CR/CRu**) • SD/PD (vs. **PR**)	OS: 1
Prior LoTs	$N=4$	Greater number of prior LoTs	• Per extra LoT/treatment (as continuous variable) • ≥2 (vs. **<2**)	OS: 1, PFS: 3
Conditioning regimen	$N=2$[b]	TBI or myeloablative conditioning	• TBI conditioning (vs. **no TBI conditioning**) • Myeloablative (vs. **reduced intensity conditioning/non-myeloablative conditioning**)	OS: 1, PFS: 1, NRM: 2,[b] overall mortality: 1
Prior ASCT	$N=2$	Not receiving prior ASCT	• No (vs. **yes**)	OS: 1, PFS: 1, ORR: 1
Time from ASCT to relapse/progression	$N=2$	Shorter time from ASCT to relapse/progression	• ≤1 year (vs. **>1 year**) • **Days from ASCT to relapse/progression (as continuous variable)**	OS: 2, PFS: 1, CR: 1
Early chemo-immunotherapy failure[c]	$N=1$	Early chemo-immunotherapy failure	• Yes (vs. **no**)	OS: 1
Primary intent of radiation therapy	$N=1$	Radiation delivered for palliative symptoms or bridging to another therapy	• Palliative symptoms (vs. **salvage**) • Bridge (vs. **salvage**)	OS: 1
CAR T-cell therapy eligibility	$N=1$	Not being eligible for CAR T-cell therapy	• Not eligible (vs. **eligible**)	OS: 1
Post-ASCT disease-free interval	$N=1$	Shorter post-ASCT disease-free interval	• <6 months (vs. **≥12 months**)	OS: 1
Graft type	$N=1$	Bone marrow grafts	• Bone marrow (vs. **peripheral blood**)	OS: 1
Time from autologous to allogeneic HCT	$N=1$	Shorter interval	• <12 months (vs. **≥12 months**)	PFS: 1, relapse/progression: 1
Type of donor	$N=1$	Unrelated donor transplantation	• URD/HLA-identical sibling (vs. **well-matched/partially matched**)	NRM: 1

Abbreviations: 3L = third line; ASCT = autologous stem cell transplantation; CAR = chimeric antigen receptor; CR = complete response; CRu = complete response unconfirmed; HCT = hematopoietic cell transplantation; HLA = human leukocyte antigen; LoT = line of therapy; NRM = non-relapse mortality; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SCT = stem cell transplantation; SD = stable disease; TBI = total body irradiation; URD = unrelated donor.

[a]Several studies used the same data sources and may have overlapping populations.

[b]Two studies used the same data source and may have overlapping populations.

[c]Early chemo-immunotherapy failure: defined as patients with primary refractory disease or relapse within 12 months of diagnosis [45].

TABLE 4 | Imaging and lab measures—Summary of study count, directionality, example characteristics, and affected outcomes for statistically significant prognostic factors.

Prognostic factor	Study count	Directionality—characteristics associated with worse outcomes	Example characteristics (vs. reference)—category with favorable outcomes in bold	Clinical outcomes with study counts
LDH[a]	*N* = 7	Elevated LDH in six studies; lower LDH in one study	• Elevated (vs. **normal**) • > 450 U/L (vs. **≤ 450 U/L**) • **LDH (as continuous variable)**[a]	OS: 6, PFS: 1
Deauville score[b]	*N* = 4	Higher Deauville score	• > 3 (vs. **≤ 3**) • Grade 5 (**vs. Grade 1–4**)	OS: 3, PFS: 3
SUV_{max} on pre-transplant PET/CT	*N* = 2	Higher SUV_{max}	• > 17.1 (vs. **< 17.1**) • SUV_{max} (as continuous variable)	OS: 1, response (not defined): 1
ALC/AMC	*N* = 2	Lower ALC, lower ALC/AMC ratio, or high-risk ALC/AMC prognostic score	• ALC < 1000/μL (vs. **ALC ≥ 1000/μL**) • ALC/AMC ratio ≤ 1.5 (vs. **> 1.5**) • ALC/AMC prognostic score as high-risk (vs. **low-risk; intermediate-risk**)	OS: 2, ORR: 1
TLG value on pre-transplant PET/CT	*N* = 1	Higher TLG value	• TLG value (as continuous variable) • High (vs. **low**)	OS: 1, PFS: 1
Minimal residual disease detected by circulating tumor DNA	*N* = 1	Positive minimal residual disease	• Positive (vs. **negative**)	OS: 1, PFS: 1

Abbreviations: ALC = absolute lymphocyte count; AMC = absolute monocyte count; CT = computed tomography; LDH = lactate dehydrogenase; ORR = objective response rate; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; SUV_{max} = maximum standardized uptake value; TLG = total lesion glycolysis.
[a]Prognostic factor with conflicting directionality across studies.
[b]The Deauville 5-point scale is based on a visual comparison between the uptake of lymphoma tissue and that of the liver and mediastinum in PET/CT.

TABLE 5 | Final ranked prognostic variables based on expert clinical review.

Variable	Rankings			Sum of rankings	Final ranking
	Clinical Expert 1	Clinical Expert 2	Clinical Expert 3		
Early chemo-immunotherapy failure[a]	2	1	3	6	1
ECOG performance status	5	2	1	8	2
Refractory to last LoT[b]	1	5	2	8	2
Number of prior LoTs	3	6	7	16	4
Double- or triple-hit lymphoma	4	7	6	17	5
Age at start of LoT	9	3	5	17	5
IPI risk classification	6	10	4	20	7
Ann Arbor disease stage	7	8	8	23	8
Serum LDH	10	4	9	23	8
Deauville score	8	9	10	27	10

Note: Variables were assessed before each LoT if not otherwise specified.
Abbreviations: ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; LDH = lactate dehydrogenase; LoT = line of therapy.
[a]Defined in the questionnaire as no complete response after the first LoT or relapse or progression within 12 months of initial diagnosis. Following clinical expert discussions, defined as primary refractory or relapse within 12 months of the first LoT with the following options: primary refractory (no response or early relapse [i.e., within < 6 months]), relapse within 6–12 months, or response and no relapse within the first 12 months.
[b]Following clinical expert discussions, defined as no response (stable disease or progressive disease) or relapse within 6 months of completion of the most recent LoT.

This review captured the most recent evidence published since 2016, and it is the first SLR focusing on the 3L+ R/R DLBCL patient population. In comparison with prior reviews and published indices on the prognostic factors for DLBCL [78–82], this review confirmed that several disease and treatment characteristics, as well as lab measures, are important prognostic factors of clinical outcomes in patients with 3L+ R/R DLBCL. This review identified several additional prognostic factors, such as Karnofsky performance status, refractory disease, response to prior therapy, number of prior LoTs, prior autologous stem cell transplantation (ASCT), use of myeloablative conditioning regimen, and time from ASCT to relapse/progression of disease.

To ensure clinical context and a holistic approach, an international panel of expert clinicians reviewed the list of the 10 most significant prognostic variables identified through SLR. The decision to have a single, consolidated list of prognostic variables for all outcomes was based on the fact that it is not possible to pre-specify whether a variable is a confounder or not, as this depends on the specific study, and is consistent with previous publications [9, 83]. The use of a clinical expert review involving a questionnaire followed by individual interviews provides several advantages, particularly in its mixed methods research design that combines both quantitative and qualitative approaches. By doing so, the responses can be consolidated, while still offering an in-depth understanding of the clinical experts' perspectives. Moreover, the inclusion of clinical experts from different countries ensures a diverse range of clinical experiences. While invaluable, it should be noted that conducting a clinical review by experts following an SLR can lengthen timelines considerably, which underscores the need to plan in advance and conduct the review in close proximity to the SLR.

This study has certain limitations that should be noted when interpreting the results. First, the demographics, clinical and treatment characteristics, as well as treatment received by patients during the study period varied across the included studies. Although considered a strength of real-world studies, the presence of heterogeneity may complicate interpretations of prognostic association estimates. Additionally, since most of the studies predominantly involved White or Asian populations when reported, the study findings may not be generalizable across all racial and ethnic subgroups. Furthermore, only variables and clinical outcomes with statistically significant associations ($p < 0.05$) were extracted. Given that statistical significance is highly influenced by sample and effect size, this study may not include an exhaustive list of every prognostic factor or EMM relevant to the patient population. In addition, there are several instances in which only one study reported a significant prognostic factor-clinical outcome association, limiting the reliability of conclusions drawn regarding such associations. Most of the included studies had a high or moderate risk of bias due to lack of reporting, specifically in the "Study Attrition" and "Statistical Analysis and Reporting" domains. This may be due to insufficient reporting, particularly in conference abstracts, and the fact that many prognostic factor analyses were exploratory in nature and not typically the primary objective of the included studies. Finally, although we recognize the importance of the pivotal trials of CAR T-cell therapies [84–86] and polatuzumab vedotin [87] in shaping the current standard of care for R/R DLBCL, these trials were excluded from our review based on pre-specified methodological criteria, as no statistically significant prognostic factor or EMM was reported in these studies. The exclusion of these pivotal studies may affect the generalizability of our findings and highlight a gap in our understanding of the prognostic factors and EMMs among patients treated with these established therapies based on clinical trial evidence. However, multiple studies reporting prognostic factors in patients treated with CAR T-cell therapies or polatuzumab vedotin in real-world practice have been identified and included in this SLR, reflecting the current standard of care. With the growing role of CAR T-cell therapy in the treatment landscape, and the increasing availability of data on patients for whom it fails, previous use of CAR T-cell therapy may become an important factor to consider for the prognosis of patients with R/R DLBCL, especially for those receiving later LoTs.

5 | Conclusions

SLR-based a priori identification of prognostic factors combined with expert clinical review provides a robust multi-method approach to evaluating and ranking the level of evidence to assist in selecting prognostic factors for pre-specified comparative analyses, such as those between single-arm trials and real-world cohorts.

Author Contributions

B.v.T., P.A., I.Z., Á.S.P., Y.K., J.U., M.S., L.W., E.T., K.C., E.R., C.H., J.J.J., A.N.A., Y.X., Sh.A., Sr.A., H.M., Q.M., and A.J.U. made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work. M.S. wrote the manuscript. All authors reviewed the work critically for important intellectual content. All authors provided final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Ethics Statement

This systematic literature review did not require ethics approval or consent to participate. The information used in this review was reported in published articles and reported in the aggregate.

Conflicts of Interest

B.v.T. is an advisor or consultant for Allogene, Amgen, BMS/Celgene, Cerus, Gilead Kite, Incyte, IQVIA, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Miltenyi, Novartis, Noscendo, Pentixapharm, Pfizer, Pierre Fabre, Qualworld, Regeneron, Roche, Serb, Sobi, and Takeda; has received honoraria from AbbVie, AstraZeneca, BMS/Celgene, Gilead Kite, Incyte, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Novartis, Roche, Serb, and Takeda; reports research funding from Esteve (Inst), Merck Sharp & Dohme (Inst), Novartis (Inst), and Takeda (Inst); reports travel support from AbbVie, AstraZeneca, Gilead Kite, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, and Takeda; and is a member of steering committees for Regeneron (Inst) and Takeda. P.A. has received honoraria from AbbVie, AstraZeneca, BeiGene, BMS,

Genmab, Incyte, Janssen, Regeneron, and Roche. I.Z. and Á.S.P report no conflicts of interest. Y.K., J.U., L.W., E.T., K.C., and E.R. are employees of IQVIA Inc. M.S. was an employee of IQVIA Inc. when the study was conducted, was supported by the National Institutes of General Medical Sciences grant T32GM-075766 from 2019 to 2022, while at the University of Pennsylvania Perelman School of Medicine, and received an International Society for Pharmacoepidemiology Grant Scholarship in 2022. The funding bodies had no role in the design and conduct of this study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the abstract; or the decision to submit for publication. C.H., J.J.J., A.N.A., Y.X., H.M., and Q.M. are employees of Regeneron Pharmaceuticals Inc. Sr. A. was an employee of Regeneron Pharmaceuticals Inc. when the study was conducted as is a current employee of Beam Therapeutics. Sh.A. was an employee of Regeneron Pharmaceuticals Inc. when the study was conducted and is a current employee of Landmark Science Inc. A.J.U. has received honoraria from AbbVie, Eli Lilly, Gilead Kite, Incyte, Janssen, Regeneron, Roche, and Sandoz.

Data Availability Statement

For full transparency, we have made available in the manuscript and Supporting Information S1: Appendix: the search strategy, PRISMA flow diagram with reasons for exclusion, study level risk of bias, full list of references of included studies, table of study characteristics, and table of outcome data.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.