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Prognostic Factors and Effect Modifiers in Patients with Relapsed or Refractory Diffuse Large B-cell Lymphoma Who Failed At Least 2 Prior Lines of Therapy: A Systematic Literature Review

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Background

- Approximately 40% of patients with diffuse large B cell lymphoma (DLBCL) are refractory to or develop relapsed disease after first-line chemoimmunotherapy[1]
- DLBCL is an aggressive lymphoma type. There is substantial unmet need to identify durable, effective, and safe treatments, especially among those requiring third line and above (3L+) treatment
- Despite the rapidly evolving treatment landscape for relapsed or refractory (r/r) DLBCL, prognostic factors and effect measure modifiers in later line settings in DLBCL have not been assessed systematically
- Considering that r/r DLBCL in later lines affects a relatively small population, and there is no established standard of care to support an ethical randomized controlled trial (RCT), population adjusted indirect comparisons using literature summary data and trial patient-level data is inevitable. Increasingly, patient-level real world data for external control arm studies have been used as supportive evidence of clinical effectiveness. In such comparative studies, pre-specification of prognostic factors for adjustment is required
- The identification of prognostic factors and effect measure modifiers through a systematic literature review (SLR) while leveraging the expertise of subject matter experts is a rigorous approach to pre-specify confounder adjustment in comparative analyses

Objective

- To systematically identify and catalog prognostic factors and effect measure modifiers in adult patients with r/r DLBCL who failed at least 2 lines of prior therapy as reported in the literature

Methods

- An SLR was conducted using Medical Literature Analysis and Retrieval System Online (MEDLINE), Excerpta Medica Database (Embase), and Cochrane Central Register of Controlled Trials (CENTRAL) between January 1, 2016 and December 13, 2021. Searches were supplemented by conference abstract review (ASCO, ESMO, ASH, EHA in 2021), forward-citation searches, and bibliography review of key publications
- The approach and methods followed the guidelines set forth by the Cochrane Handbook for Systematic Reviews of Interventions[2] and PRISMA.[3] Guidelines from EMA,[4] FDA,[5] IQWiG,[6] and NICE[7,8] have also been consulted
- The scope of the research and criteria for including and excluding studies are outlined in Table 1
- Study selection and data extraction were performed by 2 independent reviewers. Risk of bias assessment of individual studies was performed using the quality in prognostic studies (QUIPS) tool[9]
- The protocol for the SLR was registered on the International Prospective Register of Systematic Reviews (PROSPERO) as CRD42022307557

Table 1. PICOTS criteria

Criteria	Description
Populations	• Adult patients with r/r DLBCL who failed at least 2 lines of therapy (3L+) **Other applicable eligibility criteria:** • **Lymphoma type:** Include only studies with 100% DLBCL patients or if results were stratified for DLBCL; exclude studies with mixed lymphoma types where results were not stratified; CNS lymphoma or PMBCL were not considered subtypes of DLBCL, and excluded based on clinician input • **Line of therapy**: Include studies where at least 50% of patients received 3L+ therapy (i.e., median or mean of at least 2 prior lines of therapy); exclude studies that didn't report the number of prior lines of therapy
Interventions	• Any or none
Comparators	• Not applicable
Outcomes***	• Potential prognostic factors* or effect measure modifiers** that were associated with objective response rate (ORR), overall survival (OS), progression free survival (PFS), time to next treatment (TTNT), complete response rate (CR), duration of response (DOR), or disease control rate (DCR)
Time	• Publication date limit: January 1, 2016 to December 13, 2021
Study design	• Include: RCT, non-randomized trial, observational study • Exclude: Case reports, evidence synthesis studies or reviews (flag for bibliography), health economic modeling/economic/resource use studies
Other	• Exclude: Non-human, pediatric/pregnancy; publication type as editorials, letters, notes, commentaries • Geography: Global • Language: English (journal article or conference abstract)

**Defined as variables, including confounders, that are associated with subsequent health outcomes among people with a particular health condition.*

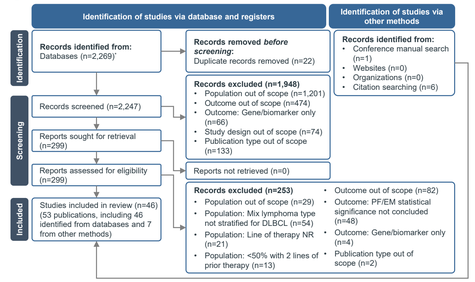
***Defined as factors that modify the effect of the putative causal factor(s) under study; effect measure modification occurs when the magnitude of the effect differs depending on the level of a third variable.*

****Notes for outcomes: 1) The search and screening were kept broad in order to capture studies reporting on prognostic factors, predictive factors, correlation, association, confounders, effect measure modifiers, subgroups, and other related concepts. 2) Information was extracted for the statistically significant variables only. If multiple models are reported within a study, results were extracted from the most adjusted model. Studies were excluded if statistical significance was not concluded for any model variables.*

Results

- Overall, 53 publications (24 journal articles and 29 conference abstracts) reporting data on 46 studies were included in the SLR (see Figure 1)

Figure 1. PRISMA flow diagram

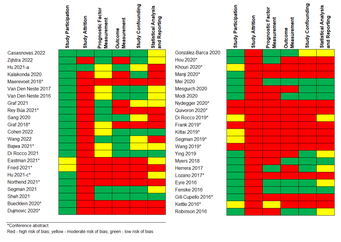


**Search was conducted on December 13, 2021*

Study and patient characteristics

- Data sources used among the 46 studies varied, and included RCT, non-randomized trials, and observational studies (clinical centers or registries)
  - 5 studies were conducted using data from 2 RCTs
  - 4 studies were conducted using data from 3 non-randomized trials
  - 37 studies were observational and based on data from clinical centers or registries
  - Some studies included patients from the same trial or overlapping data sources, but were all included to capture important sub-populations and to ensure comprehensiveness
- Risk of bias for the included studies (assessed using the QUIPS tool) are presented in Figure 2
  - Most of the included studies were rated high or moderate risk of bias due to lack of reporting, specifically in the "Study Attrition" and "Statistical Analysis and Reporting" domains
- Sample size across the included studies varied from 17 to 6947, and the median follow-up time ranged between 4 and 127 months
- Reported treatments included stem cell transplant (SCT, 12 studies), chimeric antigen receptor T-cell therapy (CAR-T; 8 studies), polatuzumab vedotin-based therapy (6 studies), selinexor (4 studies), ibrutinib-based therapy (3 studies), and combination chemotherapy (8 studies). Type of treatment was not reported in 5 studies
- Among the 46 studies, all patients had at least 2 lines of prior therapy (21 studies), or at least 50% of the study population received at least 2 lines of prior therapy (8 studies) or had a median/mean of at least 2 lines of prior therapy (17 studies). A total of 45 studies included 100% DLBCL patients, while 1 study included two lymphoma types and had results stratified for the DLBCL population
- Median age of patients ranged from 40 to 72 years, and the proportion of male patients varied from 33% to 75% across the studies

Figure 2. Risk of bias for included studies



**Conference abstract*

Red - high risk of bias; yellow - moderate risk of bias; green - low risk of bias

Prognostic factors and effect measure modifiers

- A total of 36 prognostic factors had statistically significant associations (p <0.05) with 7 outcomes
  - OS (in 38 studies)
  - PFS (in 22 studies)
  - ORR (in 8 studies)
  - Non-relapse mortality (NRM; in 4 studies)
  - CR (in 3 studies)
  - Relapse/progression (in 2 studies)
  - DOR (in 1 study)
- Among the identified prognostic factors, higher Eastern Cooperative Oncology Group (ECOG) score, 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 ≥ 5 studies (OS: 29; PFS: 13; others: 8)
- Most prognostic factors showed consistent directionality across studies and outcomes. However, conflicting evidence was observed for 4 prognostic factors
  - **Age:** Older age was associated with worse OS, NRM, and overall mortality in 5 studies, however, better OS, PFS, and CR was associated with older age in another 2 studies
  - **Transformed disease:** Transformed disease was associated with worse OS and duration of response in 2 studies; however, better PFS was associated with transformed disease in 1 study
  - **Cell of origin:** Non-germinal center B-cell (GCB) DLBCL was associated with worse OS in 1 study, however, higher ORR was associated with Non-GCB DLBCL in another study
  - **LDH:** Elevated LDH was associated with worse OS and PFS in 6 studies, however, it was associated with better OS in 1 study
- See Table 2 for demographics and clinical characteristics, Table 3 for disease characteristics, Table 4 for treatment characteristics, and Table 5 for imaging and lab measures identified as prognostic factors
- None of the studies identified statistically significant (p <0.05) effect measure modifiers

Table 2. Patient demographics and clinical characteristics – summary of study count, directionality, example characteristics, 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 labeled in green	Clinical outcomes with study counts
ECOG performance score	N=9[§]	Higher ECOG performance score	• ≥2 (vs. <2) • 3-4 (vs. 0-2)	OS: 9[§], PFS: 1
Age‡	N=7[§]	Older age in 5 studies; younger age in 2 studies	• ≥65 years (vs. <65 years) • ≥55 years (vs. 15-39 years) • >50 years (vs. younger)‡	OS:5[§], PFS: 1, NRM: 1, Overall mortality: 1, CR: 1
Karnofsky performance score	N=3	Lower KPS	• <80 (vs. 80-100) • Admittance KPS status as continuous variable	OS: 3, PFS: 1, Relapse/ progression: 1
Presence of comorbidities*	N=1	Presence of significant comorbidities	• Significant comorbidities (vs. without significant comorbidities)	OS: 1, PFS: 1

*[‡]Prognostic factors with conflicting directionality across studies. [§]Two studies used the same data source and may have overlapping population. *Assessed by Cumulative Illness Rating Scale.*

Table 3. Disease characteristics – summary of study count, directionality, example characteristics, directionality, 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 labeled in green	Clinical outcomes with study counts
Refractory disease	N=10[§]	Refractory disease	• Refractory disease (vs. non-refractory disease) • Primary refractory disease (vs. relapsed disease)	OS: 5, PFS: 7[§], 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/ triple expressor or double-hit lymphoma subtype	N=4	Double/triple expressor or double-hit lymphoma	• Double or triple expressor (vs. No) • DHL (vs. Neither DEL nor DHL)	OS: 3, PFS: 1, NRM: 1, ORR: 2
MYC status	N=3	Overexpression or mutation of MYC	• MYCm (vs. others) • cMYC ≥40% tumor positive cells (vs. cMYC <40% tumor positive cells)	OS: 2, ORR: 1
Transformed disease‡	N=3	Transformed disease in 2 studies; de novo disease in 1 study	• Transformed from follicular lymphoma (vs. de novo) • Transformed (history unspecified) (vs. de novo)‡	OS: 1, PFS: 1, DOR: 1
Cell of origin‡	N=2	Non-GCB and GCB in 1 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

Table 3. Disease characteristics – summary of study count, directionality, example characteristics, directionality, affected outcomes for statistically significant prognostic factors (cont'd)

Prognostic factor	Study count	Directionality – characteristics associated with worse outcomes	Example characteristics (vs. reference) – category with favorable outcomes labeled in green	Clinical outcomes with study counts
Tumor burden	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
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

[‡]Prognostic factors with conflicting directionality across studies. [§]Two studies used the same data source and may have overlapping population.

Table 4. Treatment characteristics – summary of study count, directionality, example characteristics, directionality, 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 labeled in green	Clinical outcomes with study counts
Response to current therapy	N=8[§§]	Not achieving CR/PR to current therapy	• No response (SD/PD) (vs. CR/PR) • PD (vs. CR/PR)	OS: 7[§§], PFS: 1
Response to prior therapy	N=5[§]	Not achieving CR to therapy prior to stem cell transplantation	*Response to therapy prior to stem cell transplantation (remission status at transplantation)* • Non-CR (vs. CR) • PR (vs. CR)	OS: 5[§], PFS: 3, NRM: 1, CR: 1, Relapse/ progression: 2
	N=1	Not achieving response to prior third-line regimen	*Response to prior third-line regimen* • SD/PD (vs. CR/CRu) • SD/PD (vs. PR)	OS: 1
Prior lines of therapy	N=4	Greater number of prior lines of therapy	• Per extra line of therapy/ treatment (as continuous variable) • ≥2 (vs. <2)	OS: 1, PFS: 3
Conditioning regimen	N=2[§]	Total body irradiation or myeloablative conditioning	• TBI conditioning (vs. No TBI conditioning) • Myeloablative (vs. Reduced intensity conditioning/non-myeloablative conditioning)	OS: 1, PFS: 1, NRM: 2[§], 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 or progression	• ≤1 year (vs. >1 year) • Days from ASCT to REL/POD (as continuous variable)	OS: 2, PFS: 1, CR: 1
Early chemoimmunotherapy failure	N=1	Early chemoimmuno-therapy 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 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 auto to alloHCT	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

[‡]Prognostic factors with conflicting directionality across studies. [§]Two studies used the same data source and may have overlapping population. [§§]Several studies used the same data sources and may have overlapping population.

Table 5. Imaging and lab measures – summary of study count, directionality, example characteristics, directionality, 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 labeled in green	Clinical outcomes with study counts
LDH‡	N=7	Elevated LDH in 6 studies; lower LDH in 1 study	• Elevated (vs. Normal) • >450 U/l (vs. ≤450 U/l) • LDH (as continuous variable)‡	OS: 6, PFS: 1
Deauville score*	N=4	Higher Deauville score	• >3 (vs. ≤3) • Grade 5 (vs. Grade 1-4)	OS: 3, PFS: 3
SUVmax on pre-transplant PET/CT	N=2	Higher SUVmax	• >17.1 (vs. <17.1) • SUVmax (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 value of TLG	• 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

*[‡]Prognostic factors with conflicting directionality across studies. *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.*

Limitations

- Patient clinical and treatment characteristics, as well as treatment received during the study period varied across the included studies. While considered a strength of real-world studies, presence of heterogeneity may complicate interpretations of prognostic association estimates, particularly since not all patients were necessarily 3L+
- Across studies, there were some overlap in data sources, which may cause some factors to be represented more than once and appear more important
- 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 effect measure modifier relevant to the patient population. This SLR also did not report variables that were non-significant
- A majority of the included studies were rated 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 especially 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

Conclusion

- To the best of our knowledge, this SLR is the first to provide a systematic, comprehensive assessment of prognostic factors and potential confounders in patients treated for 3L+ r/r DLBCL, on the basis of scientific literature
- Thirty-six distinct clinical characteristics and disease and treatment characteristics were found to be important prognostic factors of clinical outcomes for patients with r/r DLBCL. However, no statistically significant effect measure modifiers were identified based on the SLR
- Higher ECOG score, older age, having (primary) refractory disease, not achieving response to current or prior therapy, higher IPI composite score, and elevated LDH levels were associated with worse survival or response outcomes in ≥ 5 studies
- The prognostic factors identified through this SLR in r/r DLBCL can inform the selection of variables in pre-specified comparative analyses especially between clinical trial populations and real-world data derived cohorts

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Disclosures

This study was sponsored by Regeneron Pharmaceuticals, Inc. Christian Hampp, Qiufei Ma, Alexi N Archambault, Jessica J Jalbert, Yingxin Xu, Srikanth Ambati and Hesham Mohamed are employees of Regeneron Pharmaceuticals, Inc. Yuting Kuang, Krystal Cantos, Emaan Rashidi, and Jennifer Uyei are employees of IQVIA Inc. IQVIA Inc. received funding from Regeneron Pharmaceuticals, Inc. to conduct this study

Abbreviations *– ALC/AMC: Absolute lymphocyte/absolute monocyte count; allo: allogenic; auto: autologous; CAR-T: Chimeric antigen receptor T cell; CR: Complete response; DEL/DHL: Double expressor/double-hit lymphoma; DLBCL: Diffuse large B-cell lymphoma; DOR: Duration of response; ECOG: Eastern Cooperative Oncology Group; GCB: Germinal center B-cell; HSCT: Hematopoietic stem cell transplantation; KPS: Karnofsky performance score; LDH: Lactate dehydrogenase; NRM: Non-relapse mortality; OS: Overall survival; ORR: Overall response rate; PET/CT: Positron emission tomography/computed tomography; PFS: Progression free survival; PD: Progressive disease; PR: Partial response; R-IPI: Revised international prognostic index; SD: Stable disease; SUV: Standardize uptake value; TBI: Total body irradiation; t-IPI: Tertiary international prognostic index; TLG: Total lesion glycolysis; URD/HLA: Unrelated donor/human leukocyte antigen*