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# Confounder Validation in Diffuse Large B-Cell Lymphoma: Findings from an Expert Panel of German and Austrian Hematologists

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# Confounder Validation in Diffuse Large B-Cell Lymphoma: Findings from an Expert Panel of German and Austrian Hematologists

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**Abstract:**

Background: Robust confounder identification is essential for valid indirect treatment comparisons (ITCs), particularly in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL), where treatment pathways are heterogeneous and comparative evidence between chimeric antigen receptor T-cell (CAR-T) therapies remains limited. This study aimed to validate clinically relevant prognostic factors and treatment-effect modifiers for comparative effectiveness analyses in DLBCL using a structured expert consensus approach.

Methods: Candidate variables were identified through a prior systematic literature review and refined by clinical review. A panel of six experienced hematologists and oncologists from Germany and Austria participated in a two-round expert elicitation process. Experts assessed the importance of each variable as a prognostic factor and/or treatment-effect modifier using a three-point Likert scale. Variables were categorized into relevance tiers according to predefined consensus thresholds and subsequently allocated to specific clinical endpoints, including progression-free survival (PFS), overall survival (OS), response outcomes, and CAR-T–related toxicities.

Results: Several variables achieved high consensus as prognostic factors. Tier A prognostic factors included ECOG performance status, age, disease histology, International Prognostic Index (IPI), disease stage, elevated lactate dehydrogenase (LDH), bulky disease, extranodal involvement, tumor burden, primary refractory disease, number of relapses, time to relapse, and prior lines of therapy. Unanimous agreement was observed for ECOG performance status, IPI, disease histology, disease stage, elevated LDH, and primary refractory disease as prognostic factors for survival outcomes. Compared with prognostic factors, substantially lower agreement was observed for treatment-effect modifiers, particularly for response-based outcomes. Tier A effect modifiers included primary refractory disease, time to first relapse, best response to prior therapy, bridging therapy, CAR-T product type, and CAR-T–related response characteristics. Bridging therapy was the only modifier achieving unanimous agreement for complete and overall response rates. Tumor burden–related variables were considered

important for both efficacy and toxicity outcomes, including cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome.

Conclusions: Clinicians demonstrated strong consensus regarding established prognostic factors related to disease aggressiveness, treatment resistance, patient fitness, and tumor burden in R/R DLBCL. Agreement on treatment-effect modifiers was more limited, reflecting greater uncertainty regarding factors influencing relative treatment effects. These findings provide a transparent, clinically validated framework that can support covariate selection in indirect treatment comparisons, matching-adjusted indirect comparisons, and other comparative effectiveness analyses of CAR-T therapies in DLBCL.

Key summary points

- A structured two-round expert consensus process was used to validate prognostic factors and treatment-effect modifiers for comparative effectiveness analyses in relapsed/refractory diffuse large B-cell lymphoma.
- Experts demonstrated strong consensus for established prognostic factors related to disease aggressiveness, tumor burden, treatment resistance, and patient fitness, particularly for survival outcomes.
- Agreement on treatment-effect modifiers was more limited, with bridging therapy emerging as the only variable achieving unanimous consensus for response outcomes.
- The validated framework provides a transparent and clinically informed approach to selecting adjustment variables for indirect treatment comparisons and population-adjusted analyses of CAR-T therapies.
- These findings support more robust and reproducible comparative effectiveness research by reducing the risk of residual confounding in future studies.

## Introduction

In indirect treatment comparisons, it is essential to identify and appropriately adjust for variables that may confound the results. VanderWeele (2019) emphasizes that confounder selection should be guided by causal reasoning rather than purely statistical associations, ideally informed by knowledge of the underlying causal structure [1]. The identification of clinically relevant prognostic variables and treatment-effect modifiers is particularly important for population-adjusted indirect comparison methods such as matching-adjusted indirect comparisons (MAICs) and simulated treatment comparisons (STCs), where unbiased estimation depends on adjustment for all important cross-trial differences. Inappropriate adjustment, such as for colliders or instrumental variables, can introduce bias, whereas true confounders causally influence both exposure and outcome. In this context, it is important to distinguish between variables that are prognostic for outcomes and variables that modify relative treatment effects. Necessary adjustments must be specific to the type of analysis. In the absence of a common comparator, unanchored indirect treatment comparisons (ITCs) require adjustment for both prognostic factors and treatment-effect modifiers. In contrast, anchored ITCs, which include a common comparator arm, generally require adjustment only for treatment effect modifiers [2], because the benefits of randomization are preserved within each study. However, even anchored ITCs have been found to perform poorly unless all effect modifiers were known and included [3]. Because causal relationships cannot be reliably inferred from observational data alone, expert clinical judgment remains essential for identifying variables that are both clinically meaningful and causally relevant to comparative analyses.

Health technology assessment agencies, including the Institute for Quality and Efficiency in Health Care (IQWIG) in Germany, recommend structured frameworks for the identification and validation of adjustment variables [4]. These recommendations build on methodological work by Pufulete et al. [5], who proposed a systematic approach to confounder identification that combines a systematic literature review, qualitative clinician interviews, and a quantitative expert survey. While the initial step, namely confounder identification through a systematic literature review, has already been completed and reported elsewhere [6], the present study focuses on validating these findings through consultation with clinical experts.

Building on earlier applications, Pufulete et al. developed and applied their framework in the context of dual antiplatelet therapy for Acute Coronary Syndrome [5], while the Institute for Quality and Efficiency in Health Care subsequently adopted and further evaluated this approach in Relapsing-Remitting Multiple Sclerosis [4]. These studies demonstrated both the feasibility and the methodological value of a structured, multi-step process for confounder identification. However, despite the increasing reliance on real-world evidence in hemato-oncology, this framework has not yet been applied to aggressive lymphoid malignancies. In the present work, we extend this methodology to the indication of Diffuse Large B-Cell Lymphoma (DLBCL), thereby addressing an important gap and supporting robust confounder control in comparative effectiveness analyses in this indication.

DLBCL is the most common subtype of non-Hodgkin lymphoma (NHL), accounting for approximately 32.5% of newly diagnosed NHL cases annually. The incidence of DLBCL is estimated at 5.6 per 100,000 population in Germany[7], 7.2 in the US [8] and 11.1 in Japan [9]. It is associated with a substantial economic burden on healthcare systems and shows increasing incidence across Europe and the United States [10,11]. DLBCL represents a particularly relevant and challenging setting for confounder validation. Treatment pathways are highly heterogeneous, encompassing multiple lines of therapy, varying eligibility criteria for intensive treatments, and rapidly evolving therapeutic options. Clinical decision-making is influenced by numerous patient-, disease-, and treatment-related characteristics, many of which are also associated with outcomes. At the same time, advanced therapies for relapsed or refractory DLBCL are associated with substantial healthcare costs [12] and are increasingly scrutinized within health technology assessments [13]. Together, these factors create a setting in which even small imbalances in key prognostic variables or treatment-effect modifiers may meaningfully bias comparative effectiveness estimates, making DLBCL a particularly informative case study for the application and validation of structured confounder identification frameworks.

The current standard of care for newly diagnosed patients consists of chemoimmunotherapy, combining chemotherapy with the monoclonal anti-CD20 antibody rituximab [14]. For most of the approximately 40% of patients who relapse early (≤1 year) or do not respond adequately to first-line treatment, chimeric antigen receptor (CAR) Tcell therapy has become the standard of care [15,16]. This approach involves collecting a

patient's immune cells via leukapheresis, genetically modifying them ex vivo, and reinfusing them into the patient [17].

Despite its widespread clinical use, head-to-head randomized controlled trials comparing different CAR-T products remain lacking, underscoring the need for well-designed ITCs in this setting. This, in turn, highlights the importance of rigorous confounder selection and validation. Therefore, this study aimed to validate clinically relevant adjustment variables for ITCs in DLBCL through an expert panel of German and Austrian hematologists.

## Methods

### *Expert Panel Selection and Data Management*

Six board-certified hematologists and oncologists from academic institutions and large community centers in Germany and Austria were invited to participate in a structured expert elicitation process. Expert participants were identified by the lead author according to predefined eligibility criteria based on clinical expertise and experience in the management of relapsed or refractory diffuse large B-cell lymphoma. Recruitment was coordinated by LinkCare GmbH through email invitations that included study information and data protection documentation. Participation was voluntary and required written informed consent. Participant answers were anonymized, and no communication occurred between the participants during the study. Data were collected using the online survey platform QuestionPro and exported to Microsoft Excel for data management and analysis. Data quality and participant confidentiality were ensured through pseudonymization of all survey responses, with identifying information stored separately in secure allocation files. The study was conducted in accordance with the General Data Protection Regulation (GDPR), and all participants provided GDPR-compliant informed consent before participation.

### *Identification of Candidate Variables*

A prior systematic literature review (SLR) identified a comprehensive set of prognostic factors [4] and potential treatment effect modifiers relevant to outcomes in patients undergoing CAR-T cell therapy. Based on the SLR findings, two independent clinicians reviewed and consolidated the identified variables into a refined list of candidate

prognostic factors and effect modifiers (Table 1). This step aimed to remove redundancies, harmonize terminology, and ensure clinical relevance.

Table 1: Prognostic Factors and Effect Modifiers

| | |
|---|---|
| **Patient characteristics** | Age |
| | Sex |
| | Ethnicity |
| | ECOG PS |
| | HCT-CI |
| | Comprehensive geriatric assessment score |
| | Comorbidities (Sarcopenia by skeletal muscle index, hepatic disease, heart valve disease, elevated liver enzymes, renal insufficiency (moderate/severe), pulmonary disease) |
| **Blood Biomarkers** | Baseline ferritin |
| | Baseline IL-6 |
| | Peak serum IL-10 and IL-15 |
| | IFN |
| | Hemoglobin levels |
| | Hematocrit levels |
| | Platelet count |
| | Serum albumin |
| | CRP |
| | ALC at leukapheresis |
| | PD-L1 expression on tumor cells |
| **Diagnosis / Tumor biology** | Disease histology |
| | Cell of origin |
| | Molecular subtype |
| | Double/triple hit lymphoma |
| | Disease stage |
| | IPI |
| | Bulky disease |
| | LDH > ULN |
| | MTV |
| | Extranodal sites |
| | Tumor burden |
| **Disease status** | Primary refractory disease |
| | Number of relapses |
| | Time to first relapse from diagnosis |
| | Time to first relapse post ASCT |
| | Best response to last therapy |

| | |
|---|---|
| | B symptoms |
| **Prior treatments** | Number of prior lines of therapy |
| | Prior SCT/ASCT/HSCT |
| | Bridging therapy |
| | Corticosteroid use |
| **CAR-T therapy** | CAR-T cell product |
| | Response (CAR-T cell treatment vs. non-CAR-T cell treatment, number of CAR-T cells after infusion, response rate, immune cell markers, expansion patterns) |

***Abbreviations**: ALC: absolute lymphocyte count, CRP: C-reactive protein, DLBCL: diffuse large B-cell lymphoma, ECOG PS: Eastern Cooperative Oncology Group Performance status, HCT-CI: Hematopoietic Cell Transplant Comorbidity Index, HSCT: hematopoietic stem-cell transplantation, IFN: Interferon, IPI: International Prognostic Index, LDH: lactate dehydrogenase, MTV: Metabolic tumor volume, NHL: Non-Hodgkin Lymphoma, R/R: relapsed/refractory, ULN: Upper limit of normal*

In addition to general prognostic factors, CAR-T–specific characteristics with potential effect-modifying properties were included. The SLR categorized variables according to their relevance across the following clinical endpoints: Progression-free survival (PFS), Overall survival (OS), Complete response rate (CRR), Overall response rate (ORR), Duration of response (DoR), Best overall response rate (BORR), Safety outcomes, including immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS). While overall survival (OS) is generally regarded as the most clinically meaningful endpoint by clinicians [18], many clinical trials rely on surrogate endpoints, including various response-based criteria which can be evaluated more rapidly.

*Expert Elicitation Procedure*

A two-round questionnaire-based process was conducted to validate and prioritize the identified variables. In the first round, experts were asked to independently assess each variable with respect to its importance as:

1. A prognostic factor (PF),
2. A treatment effect modifier (EM), or
3. Both.

Experts rated the influence of each variable using a simplified three-point Likert scale to minimize participant burden and assess overall directional agreement:

- 1 (Not at all influential): Not a relevant prognostic factor or effect modifier
- 2 (Somewhat influential): Relevant and desirable to adjust for if feasible
- 3 (Very influential): Critical and should be adjusted for in all analyses

Experts were explicitly informed that prognostic factors and effect modifiers are not mutually exclusive. Prognostic factors were defined as variables associated with outcomes irrespective of treatment exposure, affecting absolute risk. In contrast, effect modifiers were defined as variables that alter the magnitude or direction of the treatment effect across patient subgroups. An illustrative figure (Figure 1) was provided to ensure consistent understanding of these concepts. At this stage, experts also had the opportunity to add PF and EM that were not listed in table 1.

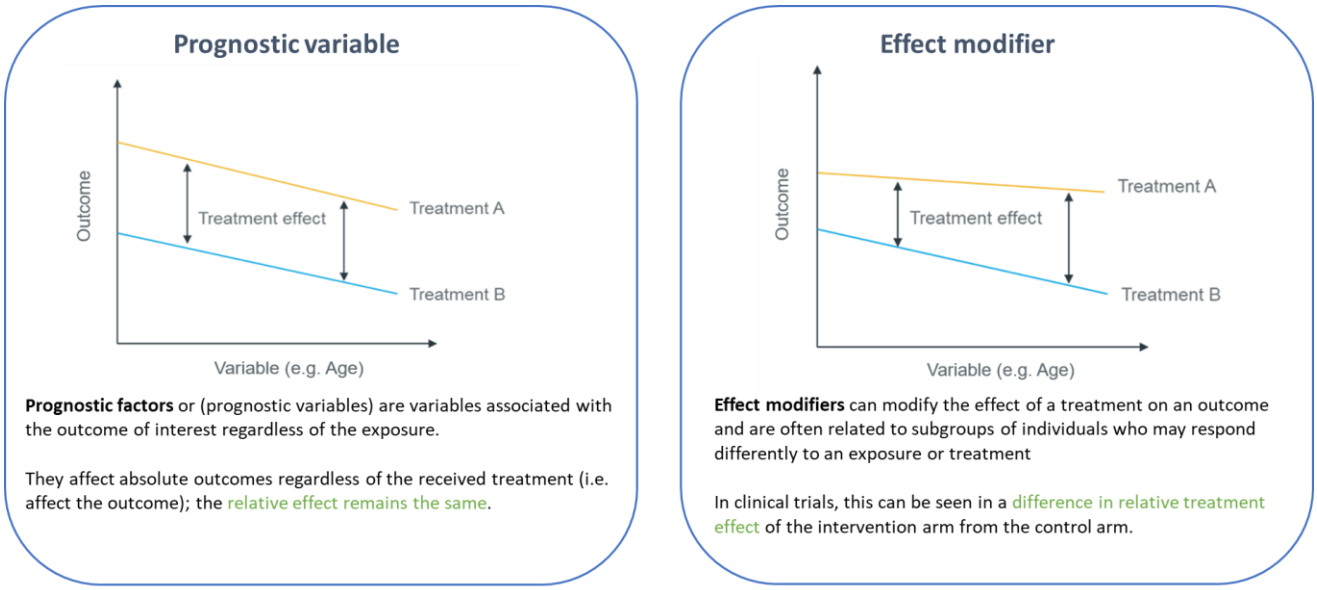



Figure 1: Illustration of Prognostic Variable and Effect Modifier

*Variable Categorization and Tiering*

Following the first round, variables were ranked and categorized into tiers based on predefined quantitative thresholds:

- Tier A (strong relevance): ≥70% of experts rated the variable as “very influential” (score = 3) or mean score ≥2.5
- Tier B (moderate relevance): ≥70% of experts rated the variable as “somewhat influential” or “very influential” (score ≥2) or mean score ≥2.0
- Tier C (low relevance): Variables not meeting the above criteria

This tiering approach (Figure 2) was used to prioritize variables for further evaluation and potential inclusion in adjustment sets for comparative analyses.

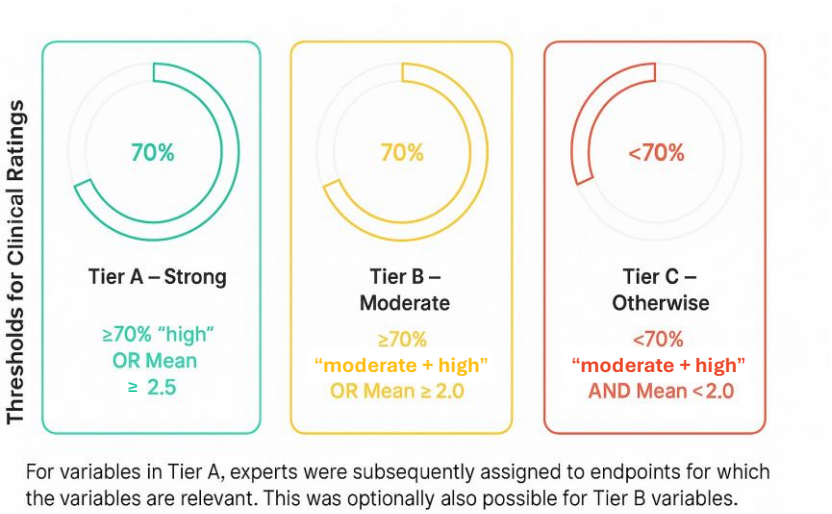



Figure 2: Construction of Tier A, B, and C variables to categorize outputs from first round

In the second round, experts were presented with the subset of variables classified as Tier A and Tier B. For each variable, experts were asked to specify:

- Whether the variable acts as a prognostic factor, an effect modifier, or both
- The specific clinical endpoints for which the classification applies (PFS, OS, CRR, ORR, DoR, BORR, ICANS, CRS)

## Results

The expert panel consisted of six clinicians, including one female and five male experts. Panel members had a mean of 15.7 years of clinical experience in the treatment of diffuse

large B-cell lymphoma (DLBCL), ranging from 8 to 35 years, and treated a mean of 63 DLBCL patients annually (range: 40–100 patients per year).

For prognostic factors, Tier A variables included several patient-, disease-, treatment-, and CAR-T-related characteristics (Table 2). Among patient characteristics, age and ECOG performance status (ECOG PS) were considered highly important. Disease- and tumor biology-related Tier A factors included disease histology, International Prognostic Index (IPI), bulky disease, elevated lactate dehydrogenase (LDH > ULN), disease stage, extranodal sites, and tumor burden. Disease status variables classified as Tier A included primary refractory disease, number of relapses, time to first relapse from diagnosis, and time to first relapse following autologous stem cell transplantation (ASCT). The number of prior lines of therapy was identified as an important prior-treatment-related prognostic factor. In addition, CAR-T-related treatment response variables, including CAR-T versus non-CAR-T treatment status, CAR-T cell expansion, response rates, immune cell markers, and expansion patterns, were also considered Tier A prognostic factors. Of note, ECOG-PS and IPI are interrelated as ECOG PS is a subcategory of the IPI. The IPI incorporates five independent risk factors, including age, Ann Arbor stage III/IV disease, elevated lactate dehydrogenase (LDH), ECOG-PS $\geqslant$2, and involvement of more than one extranodal site [19].

Tier B prognostic factors included HCT-CI, comprehensive geriatric assessment score, comorbidities, molecular subtype, double/triple-hit lymphoma, metabolic tumor volume (MTV), best response to last therapy, prior SCT/ASCT/HSCT, bridging therapy (BT), and CAR-T cell type. Tier C prognostic factors primarily comprised demographic variables and exploratory biomarkers, including sex, ethnicity, cell of origin, inflammatory and hematologic biomarkers, and corticosteroid use. The classification of double-hit and triple-hit lymphoma as Tier B likely reflects uncertainty regarding its independent contribution after adjustment for other high-risk disease characteristics, despite substantial evidence associating these genomic abnormalities with adverse outcomes.

Table 2: Perceived Importance of Prognostic Factors

| **Tier** | **Prognostic Factor** | | **Mean Score** |
|---|---|---|---|
| **Tier A** | | Age | 2.5 |

| | | | |
|---|---|---|---|
| | **Patient characteristics** | ECOG PS | 2.8 |
| | **Diagnosis / Tumor biology** | Disease histology | 2.5 |
| | | IPI | 2.7 |
| | | Bulky disease | 2.7 |
| | | LDH > ULN | 2.7 |
| | | Disease stage | 2.5 |
| | | Extranodal sites | 2.5 |
| | | Tumor burden | 2.5 |
| | **Disease status** | Primary refractory disease | 2.8 |
| | | Number of relapses | 2.7 |
| | | Time to first relapse from diagnosis | 2.7 |
| | | Time to first relapse post ASCT | 2.7 |
| | **Prior treatments** | Number of prior lines of therapy | 2.8 |
| | **CAR-T therapy** | Response (CAR-T cell treatment vs. non-CAR-T cell treatment, number of CAR-T cells after infusion, response rate, immune cell markers, expansion patterns) | 2.5 |
| **Tier B** | **Patient characteristics** | HCT-CI | 2.3 |
| | | Comprehensive geriatric assesment score | 2.0 |
| | | Comorbidities (Sarcopenia by skeletal muscle index, hepatic disease, heart valve disease, elevated liver enzymes, renal insufficiency (moderate/severe), pulmonary disease) | 2.3 |
| | | Molecular subtype | 2.0 |
| | | Double/triple hit lymphoma | 2.3 |
| | | MTV | 2.3 |
| | **Disease status** | Best response to last therapy | 2.3 |
| | **Prior treatments** | Prior SCT/ASCT/HSCT | 2.3 |
| | | Bridging therapy | 2.3 |
| | **CAR-T therapy** | CAR-T cell type (axi-cel vs. tisa-cel) | 2.0 |
| **Tier C** | | Sex | 1.2 |

| | | | |
|---|---|---|---|
| | **Patient characteristics** | Ethnicity | 1.2 |
| | **Diagnosis / Tumor biology** | Cell of origin | 1.8 |
| | **Blood biomarkers** | Baseline ferritin | 1.7 |
| | | Baseline IL-6 | 1.5 |
| | | Peak serum IL-10 and IL-15 | 1.5 |
| | | IFN | 1.7 |
| | | Hemoglobin levels | 1.5 |
| | | Hematocrit levels | 1.2 |
| | | Platelet count | 1.7 |
| | | Serum albumin | 1.5 |
| | | CRP | 1.5 |
| | | ALC at leukapheresis | 1.5 |
| | | PD-L1 expression on tumor cells | 1.0 |
| | **Disease status** | B symptoms | 1.5 |
| | **Prior treatments** | Corticosteroid use | 1.5 |

***Abbreviations**: ALC: absolute lymphocyte count, CRP: C-reactive protein, DLBCL: diffuse large B-cell lymphoma, ECOG PS: Eastern Cooperative Oncology Group Performance status, HCT-CI: Hematopoietic Cell Transplant Comorbidity Index, HSCT: hematopoietic stem-cell transplantation, IFN: Interferon, IPI: International Prognostic Index, LDH: lactate dehydrogenase, MTV: Metabolic tumor volume, NHL: Non-Hodgkin Lymphoma, R/R: relapsed/refractory, ULN: Upper limit of normal*

Regarding treatment effect modifiers, Tier A variables included primary refractory disease, time to first relapse from diagnosis, best response to last therapy, BT, CAR-T cell type, and CAR-T-related response characteristics (table 3). Tier B effect modifiers included age, ECOG PS, comorbidities, platelet count, disease histology, disease stage, LDH > ULN, MTV, extranodal sites, tumor burden, molecular subtype, number of relapses, time to relapse post-ASCT, number of prior therapy lines, and prior SCT/ASCT/HSCT. Variables assigned to Tier C largely overlapped with those categorized as low-priority prognostic factors.

Table 3. Perceived Importance of Effect Modifiers

| Tier | Effect Modifier | | Mean Score |
|---|---|---|---|
| Tier A | **Disease status** | Primary refractory disease | 2.8 |
| | | Time to first relapse from diagnosis | 2.5 |
| | | Best response to last therapy | 2.8 |
| | **Prior treatments** | Bridging therapy | 2.8 |
| | **CAR-T therapy** | CAR-T cell type (axi-cel vs. tisa-cel) | 2.5 |
| | | Response (CAR-T cell treatment vs. non-CAR-T cell treatment, number of CAR-T cells after infusion, response rate, immune cell markers, expansion patterns) | 2.5 |
| Tier B | **Patient characteristics** | Age | 2.0 |
| | | ECOG PS | 2.3 |
| | | Comorbidities (Sarcopenia by skeletal muscle index, hepatic disease, heart valve disease, elevated liver enzymes, renal insufficiency (moderate/severe), pulmonary disease) | 2.0 |
| | **Blood biomarkers** | Platelet count | 2.0 |
| | **Diagnosis / Tumor biology** | Disease histology | 2.2 |
| | | Disease stage | 2.0 |
| | | LDH > ULN | 2.2 |
| | | MTV | 2.0 |
| | | Extranodal sites | 2.0 |
| | | Tumor burden | 2.3 |
| | | Molecular subtype | 2.0 |
| | **Disease status** | Number of relapses | 2.3 |
| | | Time to first relapse post ASCT | 2.3 |
| | **Prior treatments** | Number of prior lines of therapy | 2.0 |
| | | Prior SCT/ASCT/HSCT | 2.3 |
| Tier C | **Patient characteristics** | Sex | 1.2 |
| | | Ethnicity | 1.2 |
| | | HCT-CI | 1.7 |
| | | Comprehensive geriatric assessment score | 1.5 |

| | | | |
|---|---|---|---|
| | **Blood biomarkers** | Baseline ferritin | 1.7 |
| | | Baseline IL-6 | 1.5 |
| | | Peak serum IL-10 and IL-15 | 1.3 |
| | | IFN | 1.5 |
| | | Hemoglobin levels | 1.8 |
| | | Hematocrit levels | 1.5 |
| | | Serum albumin | 1.5 |
| | | CRP | 1.8 |
| | | ALC at leukapheresis | 1.7 |
| | | PD-L1 expression on tumor cells | 1.3 |
| | **Diagnosis / Tumor biology** | Cell of origin | 1.7 |
| | | Double/triple hit lymphoma | 1.8 |
| | | IPI | 1.7 |
| | | Bulky disease | 1.8 |
| | | B symptoms | 1.5 |
| | **Prior treatments** | Corticosteroid use | 1.5 |

***Abbreviations**: ALC: absolute lymphocyte count, CRP: C-reactive protein, DLBCL: diffuse large B-cell lymphoma, ECOG PS: Eastern Cooperative Oncology Group Performance status, HCT-CI: Hematopoietic Cell Transplant Comorbidity Index, HSCT: hematopoietic stem-cell transplantation, IFN: Interferon, IPI: International Prognostic Index, LDH: lactate dehydrogenase, MTV: Metabolic tumor volume, NHL: Non-Hodgkin Lymphoma, R/R: relapsed/refractory, ULN: Upper limit of normal*

Table 4: Prognostic factors (PF) allocated to endpoints (TIER A)

| Prognostic Factor | | PFS | OS | CRR | ORR | DoR | BORR | ICANS | CRS |
|---|---|---|---|---|---|---|---|---|---|
| **Patient characteristics** | Age | 5 | 5 | 3 | 3 | 3 | 3 | 5 | 5 |
| | ECOG PS | 6 | 6 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Diagnosis / Tumor biology** | Disease histology | 6 | 6 | 6 | 5 | 4 | 4 | 1 | 1 |
| | IPI | 6 | 6 | 6 | 5 | 5 | 4 | 1 | 1 |
| | Bulky disease | 3 | 3 | 5 | 5 | 4 | 5 | 5 | 5 |
| | LDH > ULN | 6 | 6 | 4 | 4 | 4 | 4 | 4 | 4 |
| | Disease stage | 6 | 6 | 6 | 5 | 4 | 4 | 4 | 4 |
| | Extranodal sites | 4 | 4 | 5 | 4 | 4 | 4 | 2 | 1 |
| | Tumor burden | 4 | 4 | 5 | 4 | 4 | 4 | 6 | 6 |
| **Disease status** | Primary refractory disease | 6 | 6 | 5 | 4 | 4 | 3 | 0 | 0 |
| | Number of relapses | 5 | 5 | 4 | 4 | 4 | 3 | 0 | 0 |
| | Time to first relapse from diagnosis | 5 | 5 | 5 | 5 | 5 | 3 | 0 | 0 |
| | Time to first relapse post ASCT | 6 | 6 | 6 | 6 | 6 | 4 | 0 | 0 |
| **Prior treatments** | Number of prior lines of therapy | 5 | 5 | 5 | 5 | 5 | 4 | 0 | 0 |
| **CAR-T therapy** | Response (CAR-T cell treatment vs. non-CAR-T cell treatment, number of CAR-T cells after infusion, response rate, immune cell markers, expansion patterns) | 5 | 5 | 4 | 4 | 4 | 4 | 1 | 1 |

***Abbreviations**: ECOG PS: Eastern Cooperative Oncology Group Performance status, HCT-CI: Hematopoietic Cell Transplant Comorbidity Index, HSCT: hematopoietic stem-cell transplantation, IFN: Interferon, IPI: International Prognostic Index, LDH: lactate dehydrogenase, MTV: Metabolic tumor volume, NHL: Non-Hodgkin Lymphoma, R/R: relapsed/refractory, ULN: Upper limit of normal, PFS: Progression-free survival, OS: Overall survival, CRR: Complete response rate, ORR: Overall response rate, DoR: Duration of response, BORR: Best overall response rate, ICANS: immune effector cell-associated neurotoxicity syndrome (ICANS), CRS: cytokine release syndrome (CRS).*

*Color scale indicates the number of clinicians who identified each factor as prognostic for the selected endpoint(s)*


6
5
4
3
2
1
0

Table 5: EM allocated to endpoints (TIER A)

| **Effect Modifier** | | **PFS** | **OS** | **CRR** | **ORR** | **DoR** | **BORR** | **ICANS** | **CRS** |
|---|---|---|---|---|---|---|---|---|---|
| **Disease status** | Primary refractory disease | 5 | 5 | 3 | 1 | 1 | 1 | 0 | 0 |
| | Time to first relapse from diagnosis | 3 | 3 | 1 | 0 | 0 | 0 | 0 | 0 |
| | Best response to last therapy | 5 | 5 | 4 | 5 | 4 | 4 | 1 | 1 |
| **Prior treatments** | Bridging therapy | 5 | 5 | 6 | 6 | 3 | 3 | 4 | 3 |
| **CAR-T therapy** | CAR-T cell type (axi-cel vs. tisa-cel) | 4 | 4 | 3 | 4 | 3 | 3 | 4 | 4 |
| | Response (CAR-T cell treatment vs. non-CAR-T cell treatment, number of CAR-T cells after infusion, response rate, immune cell markers, expansion patterns) | 5 | 5 | 4 | 4 | 5 | 4 | 0 | 0 |

***Abbreviations**: ECOG PS: Eastern Cooperative Oncology Group Performance status, HCT-CI: Hematopoietic Cell Transplant Comorbidity Index, HSCT: hematopoietic stem-cell transplantation, IFN: Interferon, IPI: International Prognostic Index, LDH: lactate dehydrogenase, MTV: Metabolic tumor volume, NHL: Non-Hodgkin Lymphoma, R/R: relapsed/refractory, ULN: Upper limit of normal, PFS: Progression-free survival, OS: Overall survival, CRR: Complete response rate, ORR: Overall response rate, DoR: Duration of response, BORR: Best overall response rate, ICANS: immune effector cell-associated neurotoxicity syndrome (ICANS), CRS: cytokine release syndrome (CRS).*

*Color scale indicates the number of clinicians who identified each factor as prognostic for the selected endpoint(s)*

| 6 | 5 | 4 | 3 | 2 | 1 | 0 |
|---|---|---|---|---|---|---|

Table 6: PF allocated to endpoints (TIER B)

| Prognostic Factor | | PFS | OS | CRR | ORR | DoR | BORR | ICANS | CRS |
|---|---|---|---|---|---|---|---|---|---|
| **Patient characteristics** | HCT-CI | 2 | 3 | 0 | 0 | 0 | 0 | 2 | 2 |
| | Comprehensive geriatric assessment score | 1 | 2 | 0 | 0 | 0 | 0 | 2 | 2 |
| | Comorbidities (Sarcopenia by skeletal muscle index, hepatic disease, heart valve disease, elevated liver enzymes, renal insufficiency (moderate/severe), pulmonary disease) | 5 | 5 | 3 | 3 | 3 | 3 | 4 | 3 |
| **Disease status** | Best response to last therapy | 3 | 3 | 4 | 3 | 2 | 2 | 1 | 1 |
| **Diagnosis / Tumor biology** | Molecular subtype | 4 | 3 | 2 | 2 | 2 | 2 | 0 | 0 |
| | Double/triple hit lymphoma | 5 | 5 | 5 | 4 | 4 | 4 | 0 | 0 |
| | MTV | 4 | 4 | 5 | 4 | 4 | 4 | 5 | 5 |
| **Prior treatments** | Prior SCT/ASCT/HSCT | 4 | 5 | 2 | 1 | 1 | 1 | 0 | 0 |
| | Bridging therapy | 4 | 3 | 4 | 3 | 3 | 3 | 5 | 5 |

***Abbreviations**: ECOG PS: Eastern Cooperative Oncology Group Performance status, HCT-CI: Hematopoietic Cell Transplant Comorbidity Index, HSCT: hematopoietic stem-cell transplantation, IFN: Interferon, IPI: International Prognostic Index, LDH: lactate dehydrogenase, MTV: Metabolic tumor volume, NHL: Non-Hodgkin Lymphoma, R/R: relapsed/refractory, ULN: Upper limit of normal, PFS: Progression-free survival, OS: Overall survival, CRR: Complete response rate, ORR: Overall response rate, DoR: Duration of response, BORR: Best overall response rate, ICANS: immune effector cell-associated neurotoxicity syndrome (ICANS), CRS: cytokine release syndrome (CRS).*

*Color Scales based on number of clinicians chooses the factor as Prognostic Factor for selected endpoints*

| 6 | 5 | 4 | 3 | 2 | 1 | 0 |
|---|---|---|---|---|---|---|

Table 7: EM allocated to endpoints (TIER B)

| Effect Modifier | | PFS | OS | CRR | ORR | DoR | BORR | ICANS | CRS |
|---|---|---|---|---|---|---|---|---|---|
| **Patient characteristics** | Age | 4 | 4 | 1 | 1 | 1 | 1 | 3 | 3 |
| | ECOG PS | 3 | 4 | 0 | 0 | 0 | 0 | 3 | 3 |
| | Comorbidities (Sarcopenia by skeletal muscle index, hepatic disease, heart valve disease, elevated liver enzymes, renal insufficiency (moderate/severe), pulmonary disease) | 3 | 4 | 0 | 0 | 0 | 0 | 4 | 3 |
| **Blood biomarkers** | Platelet count | 2 | 2 | 0 | 1 | 0 | 0 | 0 | 0 |
| **Diagnosis / Tumor biology** | Disease histology | 3 | 3 | 2 | 1 | 0 | 0 | 0 | 0 |
| | Disease stage | 2 | 2 | 2 | 1 | 0 | 0 | 2 | 2 |
| | LDH > ULN | 2 | 3 | 3 | 2 | 1 | 1 | 3 | 3 |
| | MTV | 3 | 3 | 4 | 3 | 3 | 2 | 3 | 3 |
| | Extranodal sites | 3 | 3 | 3 | 2 | 1 | 1 | 0 | 0 |
| | Tumor burden | 3 | 3 | 4 | 3 | 3 | 3 | 4 | 4 |
| | Molecular subtype | 3 | 3 | 1 | 0 | 0 | 0 | 0 | 0 |
| **Disease status** | Number of relapses | 4 | 4 | 3 | 2 | 2 | 2 | 0 | 0 |
| | Time to first relapse post ASCT | 4 | 4 | 2 | 1 | 1 | 1 | 0 | 0 |
| **Prior treatments** | Number of prior lines of therapy | 4 | 4 | 3 | 2 | 2 | 2 | 0 | 0 |
| | Prior SCT/ASCT/HSCT | 5 | 5 | 2 | 1 | 1 | 1 | 0 | 0 |

***Abbreviations**: ECOG PS: Eastern Cooperative Oncology Group Performance status, HCT-CI: Hematopoietic Cell Transplant Comorbidity Index, HSCT: hematopoietic stem-cell transplantation, IFN: Interferon, IPI: International Prognostic Index, LDH: lactate dehydrogenase, MTV: Metabolic tumor volume, NHL: Non-Hodgkin Lymphoma, R/R: relapsed/refractory, ULN: Upper limit of normal, PFS: Progression-free survival, OS: Overall survival, CRR: Complete response rate, ORR: Overall response rate, DoR: Duration of response, BORR: Best overall response rate, ICANS: immune effector cell-associated neurotoxicity syndrome (ICANS), CRS: cytokine release syndrome (CRS).*

*Color scale indicates the number of clinicians who identified each factor as effect modifier for the selected endpoint(s)*

| 6 | 5 | 4 | 3 | 2 | 1 | 0 |
|---|---|---|---|---|---|---|

When Tier A prognostic factors were allocated to clinical endpoints, several factors achieved full consensus among all six experts (Table 4). ECOG PS was identified by all experts as relevant for both progression-free survival (PFS) and overall survival (OS). Disease histology reached complete consensus for PFS, OS, and complete response rate (CRR), while IPI likewise achieved full agreement for these three endpoints. Elevated LDH (> ULN) and disease stage were considered important prognostic factors for both PFS and OS by all experts, with disease stage also reaching complete agreement for CRR. Primary refractory disease was consistently identified as relevant for PFS and OS. Time to first relapse following ASCT demonstrated the strongest consensus overall, with all six experts selecting it as relevant for PFS, OS, CRR, ORR, and duration of response (DoR). In addition, all experts associated tumor burden with the toxicity endpoints immune effector cell-associated neurotoxicity syndrome (ICANS) and cytokine release syndrome (CRS).

Among Tier A effect modifiers, full consensus was achieved only for BT as an effect modifier of CRR and ORR. No other Tier A effect modifier reached complete agreement across endpoints (Table 5).

For Tier B prognostic factors, no efficacy endpoint achieved full consensus; however, several factors demonstrated moderate-to-high levels of agreement (Table 6). Comorbidities were considered relevant across both efficacy and safety outcomes, particularly for PFS, OS, and immune-related toxicities such as ICANS. Double-/triple-hit lymphoma was frequently selected as relevant for efficacy endpoints including PFS, OS, CRR, ORR, and DoR. Metabolic tumor volume (MTV) was also consistently associated with efficacy outcomes and toxicity endpoints, including ICANS and CRS. BT and prior SCT/ASCT/HSCT demonstrated moderate importance across several efficacy endpoints.

For Tier B effect modifiers, no variable achieved complete agreement among all experts for any endpoint (Table 7). Nevertheless, prior SCT/ASCT/HSCT showed the highest level of agreement for PFS and OS, while tumor burden and MTV were frequently considered important effect modifiers for both efficacy and toxicity endpoints. Age, ECOG PS, and comorbidities were more commonly associated with survival outcomes and toxicity endpoints than with response-based outcomes. Overall, agreement on Tier B effect

modifiers was less pronounced than for Tier A prognostic factors, reflecting greater uncertainty regarding their modifying effects on CAR-T treatment outcomes.

## Discussion

In this expert consensus study, clinicians identified several key prognostic factors and treatment effect modifiers relevant to comparative analyses in R/R DLBCL. Among prognostic factors, the expert panel identified the IPI as highly important for OS, PFS, and complete response rate (CRR). The panel findings are consistent with contemporary evidence demonstrating that higher IPI scores are associated with inferior outcomes following CAR-T therapy in R/R DLBCL [20, 21]. Interestingly, several individual components of the IPI such as ECOG-PS and elevated LDH were also separately prioritized by the experts which aligns with the literature [22]. Elevated LDH (> ULN) for instance is significantly linked to inferior survival outcomes in patients [23,24,25]. In one analysis LDH > ULN is associated with substantially worse OS, with hazard ratios ranging between 2 and 3 [26] .

Although not reaching unanimous agreement, age was still considered an important prognostic factor for survival by five of six experts. This perception may reflect its association with frailty, comorbidities, and treatment tolerance rather than chronological age being an independent predictor of CAR-T outcomes [27,28]. The lower level of consensus compared with ECOG-PS is consistent with the growing recognition that functional status and frailty are more informative than age alone in determining treatment outcomes in modern hematologic oncology.

Another important finding of this study relates to BT. BT was the only treatment effect modifier for which unanimous agreement was reached, specifically regarding CRR and ORR. BT is commonly administered during the interval between leukapheresis and CAR-T cell infusion to stabilize disease progression while CAR-T cells are manufactured [17]. In real-world clinical practice, the majority patients undergoing CAR-T therapy receive some form of BT [29]. This is largely because patients with rapidly progressive disease or high tumor burden cannot safely wait for cell production without interim treatment. Moreover, response to BT appears to be particularly informative. Recent evidence suggests that patients achieving complete or partial responses to BT have significantly

improved PFS and OS after CAR-T therapy compared with non-responders [30], irrespective of the BT modality used. Response to BT may reflect underlying disease sensitivity and prognosis. In patients achieving a major response to BT before CAR-T infusion, it may be difficult to separate the contribution of BT from the subsequent CAR-T effect.

Overall, the consensus findings from this study suggest that clinicians primarily rely on established markers of disease aggressiveness, treatment resistance, patient fitness, and tumor burden when evaluating prognosis in CAR-T-treated R/R DLBCL. This echoes findings from a recent expert clinical assessment, which identified early chemoimmunotherapy failure, ECOG performance status, refractoriness to the most recent line of therapy, number of prior treatment lines, and double- or triple-hit lymphoma as key prognostic factors in patients with third-line or later relapsed/refractory DLBCL.[31].

In contrast, fewer treatment effect modifiers achieved high levels of agreement. This alignment may suggest that clinicians are generally more familiar with determinants of patient prognosis, whereas factors that influence relative treatment effects are less well understood and often more difficult to identify in clinical practice. Accordingly, identifying treatment-effect modifiers is generally more challenging than identifying prognostic factors. Apparent differences in treatment effects across patient subgroups may arise by chance or through exploratory analyses without a plausible biological rationale. Therefore, potential effect modifiers should be selected based on prior clinical and scientific evidence and assessed using formal interaction analyses rather than informal subgroup comparisons. The relevance of effect modification has increased in oncology with the advent of targeted therapies. Whereas the relative effects of conventional cytotoxic treatments are often assumed to be similar across patient groups, the effectiveness of targeted agents may depend on specific tumor or patient characteristics. Consequently, careful identification and adjustment for treatment-effect modifiers is essential in oncology-focused indirect treatment comparisons [32].

Our findings may inform future evidence syntheses and comparative effectiveness studies, facilitating more reliable indirect comparisons between CAR-T therapies. Although most published indirect treatment comparisons of CAR-T therapies apply statistical adjustments for confounding, the selection of adjustment variables is often poorly justified and lacks

transparency [33,34]. The first Health Technology Assessment on European level also concluded that: “As the methods used to identify the final list of potential prognostic and effect-modifying variables was not transparently reported, it is not possible to establish whether the identification process was comprehensive or whether this list is likely to be complete” [35].Consequently, it is often unclear whether covariates were chosen based on clinical relevance, prognostic value, treatment-effect modification, data availability, or statistical criteria alone. This point raises concerns about whether the key assumptions underlying unanchored ITCs have been sufficiently evaluated. Given the strong and largely untestable assumptions required for unanchored analyses, careful assessment of residual uncertainty remains essential.

*Strengths and Limitations*

The key strength of this study is the use of a structured expert consensus methodology to identify clinically relevant prognostic factors and treatment effect modifiers for comparative analyses in R/R DLBCL, with a particular focus on the CAR-T setting. The panel comprised experienced clinicians with expertise in the management of aggressive lymphoma and CAR-T therapies, ensuring that the identified variables reflect current clinical practice and decision-making. Furthermore, the systematic and transparent approach used to elicit and prioritize variables provides a clear rationale for covariate selection and may help address the lack of consistency and transparency that has characterized some previous ITCs in this field. From a clinical perspective, the identified Tier A factors largely reflect four overarching domains that influence outcomes in R/R DLBCL: disease aggressiveness, tumor burden, treatment resistance, and patient fitness. The consistency with which experts prioritized these domains suggests that future comparative analyses omitting such variables may be vulnerable to residual confounding

The study also has several limitations. The number of participating experts was relatively small, reflecting the highly specialized nature of CAR-T therapy; consequently, the findings may not fully capture variation in clinical perspectives across different institutions, healthcare systems, or geographic regions. Furthermore, consensus was achieved within the context of currently available evidence and treatment pathways, which continue to evolve rapidly in R/R DLBCL. As CAR-T therapies move into earlier lines of treatment and novel cellular and bispecific therapies become more widely adopted, the relative

importance of individual prognostic factors and treatment effect modifiers may change over time. An additional limitation is that some variables identified as important by clinicians may not be consistently reported across clinical trials or real-world datasets, potentially limiting their feasibility for adjustment in practice. Conversely, variables that are routinely available in datasets may not always be considered the most clinically relevant. This highlights the ongoing challenge of balancing clinical relevance with data availability when conducting comparative effectiveness research and indirect treatment comparisons.

## *Declarations.*

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***Conflicts of interest:*** BvT is an advisor or consultant for AbbVie, 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); and reports travel support from AbbVie, AstraZeneca, Gilead Kite, Janssen-Cilag, Lilly, Merck Sharp & Dohme, Pierre Fabre, Roche, Takeda, and Novartis; is member of steering committees for Regeneron (Inst) and Takeda.

JMH reports research funding from Incyte, MorphoSys, and Novartis; has received honoraria or is an advisor or consultant for Incyte, Roche, Novartis, Miltenyi Biotec, SOBI, and SERB Pharmaceuticals; received travel support from SOBI, and SERB Pharmaceuticals.

RZ, SR, and JM are employees of Miltenyi Biomedicine.

***Ethics:*** Participants were fully informed about the study's objectives and the intent to publish the results. Consent was given voluntarily through signed contracts. Data protection adhered to GDPR regulations, with analyses conducted pseudonymously to ensure privacy. Ethical committee consultation was unnecessary as the study only involved physician responses, with no patient information and no interference with personal integrity.

***Data Availability:*** Raw data is available from the corresponding author upon reasonable request.

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