

Obesity and lymphoma: from pathobiology to clinical outcomes

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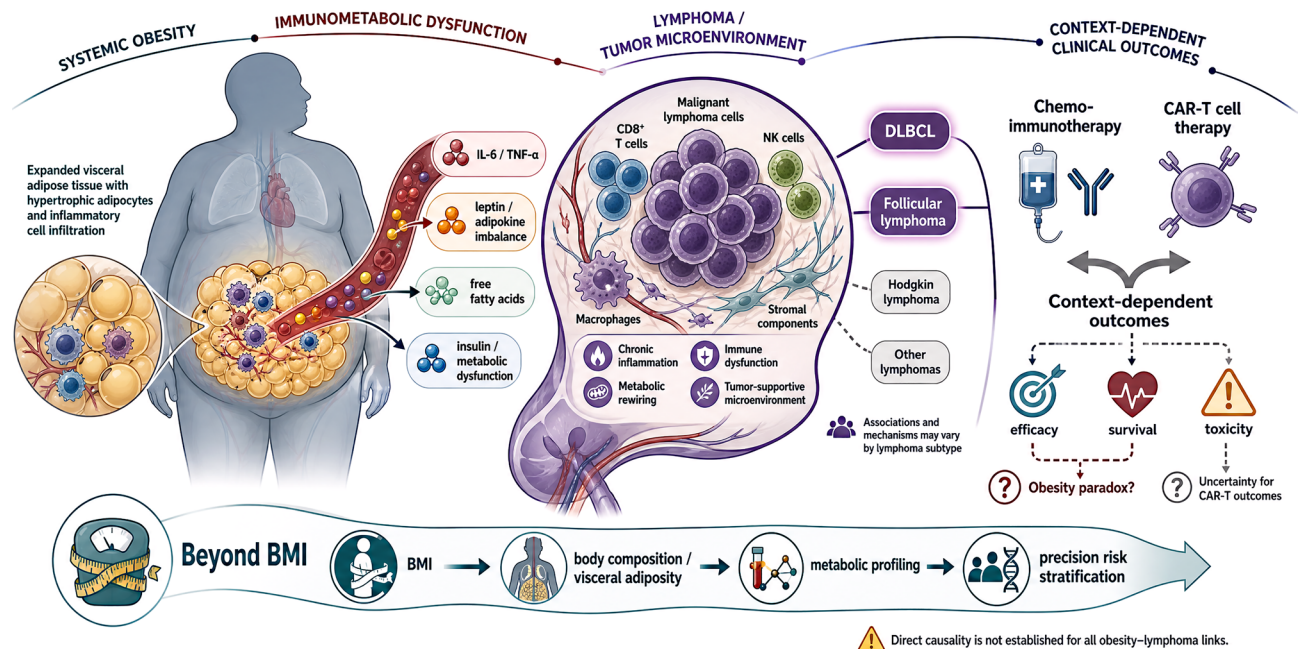
Abstract

Obesity is increasingly recognized as a systemic immunometabolic disorder that influences lymphoma risk, tumor biology, treatment response, and survivorship. Epidemiological evidence links obesity to an increased incidence of several lymphoid malignancies, particularly diffuse large B-cell lymphoma and follicular lymphoma, although these associations vary across lymphoma subtypes, sex, age, and metabolic phenotype. Mechanistically, obesity promotes chronic inflammation, adipokine imbalance, and metabolic stress, leading to activation of oncogenic pathways including IL-6/STAT3, NF- κ B, insulin/IGF-1, and PI3K/AKT/mTOR signaling, as well as lipid metabolic rewiring and stromal-myeloid remodeling within the lymphoma microenvironment. Importantly, recent advances in single-cell and spatial transcriptomics, multi-omics profiling, and integrative bioinformatic analyses have further refined our understanding of these immunometabolic interactions. Clinically, obesity exerts a complex and context-dependent influence. Several studies describe a controversial “obesity paradox” in selected DLBCL cohorts treated with rituximab-based chemoimmunotherapy, although these findings may reflect reverse causality, collider bias, and limitations of BMI-based analyses. In contrast, emerging, although heterogeneous, evidence suggests that obesity and obesity-associated metabolic alterations may influence CAR-T-cell kinetics and inflammatory toxicity, while their impact on therapeutic efficacy remains uncertain. Importantly, body mass index remains an imperfect surrogate for biologically relevant adiposity, as it does not adequately capture visceral fat accumulation, insulin resistance, inflammatory activation, muscle depletion, or sarcopenic obesity. Collectively, this review highlights the need to move beyond BMI-based classifications by integrating body composition assessment, metabolic profiling, and emerging multi-omics approaches to improve lymphoma risk stratification, biomarker discovery, and precision therapeutic strategies.

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Graphical Abstract



Keywords Obesity · Lymphoma · Adipokines · Immunometabolism · Leptin · Chemotherapy · mTOR · CAR-T · Obesity paradox

Introduction

Obesity represents a major and rapidly expanding global health burden. According to World Health Organization estimates, in 2022 approximately one in eight individuals worldwide was living with obesity, with over 890 million affected adults and more than 160 million children and adolescents meeting diagnostic criteria. The global prevalence of adult obesity has more than doubled since 1990, while pediatric and adolescent obesity has increased nearly fourfold, highlighting the early-life and lifelong nature of this condition [1]. It is widely recognized as a systemic condition that promotes chronic low-grade inflammation, insulin resistance, and metabolic dysregulation—all of which are key risk factors for cancer development [2, 3]. Among hematologic malignancies, lymphoma has shown a progressive increase in incidence that parallels the global rise in obesity [4–6]. Epidemiological studies consistently indicate that excess adiposity is associated with an elevated risk of both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), with stronger associations observed for diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma (FL) [3, 7, 8]. Although the magnitude of this risk varies by age, sex, and metabolic profile, obesity is now recognized as an independent risk factor for lymphomagenesis. However, these associations are not uniform across lymphoma subtypes and patient populations, suggesting a complex and context-dependent relationship. The biological mechanisms connecting obesity and lymphoma are multifactorial and involve a complex interplay of systemic inflammation, endocrine imbalance, and immune–metabolic reprogramming [9–13]. Adipose tissue, particularly the visceral compartment, functions as an active endocrine organ that releases cytokines and metabolites capable of influencing immune surveillance and lymphoid homeostasis [14, 15]. Recent advances in high-throughput technologies have considerably expanded our understanding of lymphoma biology. Single-cell RNA sequencing (scRNA-seq), spatial transcriptomics, and integrative multi-omics approaches now enable high-resolution characterization of the lymphoma microenvironment, revealing cellular heterogeneity, immune-cell interactions, and metabolic programs that

cannot be captured by conventional bulk analyses [16, 17]. In obesity, adipocyte hypertrophy and hypoxia trigger macrophage recruitment and the release of inflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), and interleukin-1 β (IL-1 β), alongside altered levels of adipokines including leptin, adiponectin and resistin [18–22]. These signals activate oncogenic pathways such as NF- κ B, JAK/STAT3, and PI3K/AKT/mTOR, which collectively sustain lymphocyte proliferation, inhibit apoptosis, and remodel the tumor microenvironment (TME) [18, 23–25].

At the immunological level, obesity leads to impaired adaptive and innate responses, characterized by reduced cytotoxic activity of NK and CD8⁺ T cells, altered T-helper polarization, and expansion of regulatory T cells [26]. These changes contribute to an immunosuppressive milieu that facilitates malignant transformation and tumor progression [18, 27]. Concurrently, metabolic alterations, such as insulin resistance, dyslipidemia, and mitochondrial stress, modulate energy metabolism within both tumor and immune cells, shaping the metabolic plasticity of the lymphoma microenvironment [28, 29].

Paradoxically, several clinical studies have reported that obese patients with DLBCL show improved outcomes and treatment responses compared to normal-weight individuals [30–36]. This so-called “obesity paradox” has been attributed to diverse mechanisms, including pharmacokinetic differences, preserved metabolic reserves, and potential immunomodulatory effects, although it remains controversial and may be influenced by methodological biases.

Overall, obesity exerts a dual and context-dependent influence on lymphoma, increasing disease susceptibility while potentially modulating therapeutic response and survival once malignancy is established. In this review, we integrate current epidemiological and mechanistic evidence linking obesity to lymphoma risk and outcome, and discuss the molecular and immunometabolic pathways underlying this association. We further examine the clinical implications of obesity, including its role as a prognostic and predictive factor, and critically address the concept of the obesity paradox. Finally, we highlight emerging evidence on therapeutic strategies, including chemoimmunotherapy, targeted approaches, and CAR-T cell therapy, outlining the overall structure and rationale of this review.

To enhance transparency and provide a structured synthesis of the literature, this narrative review was informed by a targeted search of PubMed, Web of Science, Scopus, and ClinicalTrials.gov. Searches were conducted using combinations of terms related to obesity and adiposity (“obesity”, “overweight”, “body mass index”, “BMI”, “adiposity”, “visceral adipose tissue”), lymphoma (“lymphoma”, “non-Hodgkin lymphoma”, “Hodgkin lymphoma”, “diffuse large B-cell lymphoma”, “follicular lymphoma”), and relevant biological and clinical domains (“inflammation”, “adipokines”, “leptin”, “adiponectin”, “insulin resistance”, “immunometabolism”, “JAK/STAT”, “PI3K/AKT/mTOR”, “tumor microenvironment”, “treatment response”, “survival”, and “CAR-T”). We prioritized peer-reviewed epidemiological, clinical, and translational studies published between 2020 and 2026, with prioritization of epidemiological, clinical, and translational evidence relevant to lymphoma.

Obesity: definition and assessment

Accurate characterization of obesity is essential to interpret its relationship with lymphoma, yet commonly used metrics may not fully capture its biological complexity. Obesity is conventionally defined using anthropometric criteria, most commonly body mass index (BMI), calculated as body weight divided by height squared (kg/m^2). According to World Health Organization (WHO) guidelines, overweight is defined as a BMI of 25.0–29.9 kg/m^2 , while obesity corresponds to BMI values $\geq 30 \text{ kg/m}^2$, further stratified into class I (30.0–34.9), class II (35.0–39.9), and class III (≥ 40). Although BMI is widely used in epidemiological studies, it represents a crude surrogate of adiposity and does not capture key biological dimensions such as visceral fat distribution, metabolic dysfunction, muscle mass, or sarcopenic obesity. These factors may have distinct and, in some cases, opposing effects on lymphoma risk and clinical outcomes, highlighting the need for more refined measures of body composition. In fact, additional anthropometric indices have been proposed to better capture central adiposity, which is more

closely linked to metabolic and inflammatory risk. Waist circumference (WC) thresholds exceeding 88 cm in women and 102 cm in men, as well as waist-to-hip ratio (WHR) values greater than 0.80 in women and 0.95 in men, are commonly used to define abdominal obesity [37, 38]. These parameters have been shown to more accurately reflect visceral fat accumulation [39, 40]. Moreover, new imaging-based approaches (CT, DEXA) and indices such as the visceral-to-subcutaneous fat ratio (VSR) or sarcopenic obesity index provide superior risk discrimination compared with BMI alone [41, 42]. Sarcopenic obesity cut-off values, defined as the coexistence of excess adiposity and reduced muscle mass, vary across studies and populations, limiting standardization. The main limitations and characteristics of BMI and alternative metrics are summarized in Table 1. Nonetheless emerging metrics for obesity characterization, BMI remains a practical and standardized measure for obesity classification. These limitations underscore the importance of integrating body composition and metabolic profiling into future studies to better define the role of obesity in lymphoma.

Obesity as a systemic immunometabolic disorder: foundational evidence

The biological link between obesity and lymphoma is driven by a complex interplay of inflammatory, metabolic, and immune-related pathways [43–48]. In fact, at the molecular level, obesity-associated immune dysregulation is driven by sustained activation of inflammatory signaling pathways within both adipocytes and infiltrating immune cells [49, 50]. Excess nutrient availability and adipocyte hypertrophy promote endoplasmic reticulum stress, mitochondrial dysfunction, and hypoxia, leading to activation of pattern-recognition receptors such as Toll-like receptor 4 (TLR4) in response to free fatty acids and damage-associated molecular patterns (DAMPs) [27, 51–54]. This, in turn, triggers downstream signaling cascades involving IKK β /NF- κ B and c-Jun N-terminal kinase (JNK), resulting in increased transcription of proinflammatory cytokines, including TNF- α , IL-6, and IL-1 β [55–60].

These cytokines directly interfere with insulin signaling by inducing serine phosphorylation of insulin receptor substrate-1 (IRS-1), thereby impairing downstream PI3K/AKT signaling and promoting systemic insulin resistance [61–63]. In parallel, chronic inflammatory signaling promotes proinflammatory immune-cell polarization and functional dysregulation, while adipokine imbalance further contributes to persistent immune activation [64–66]. Conversely, obesity is generally characterized by reduced circulating adiponectin, an adipokine with insulin-sensitizing and anti-inflammatory properties that can activate AMPK-dependent metabolic programs [67]. However, the relationship between adiponectin and lymphoma appears more complex than would be predicted from obesity biology alone. AdipoR1 and AdipoR2 expression has been demonstrated in NHL specimens, and higher circulating adiponectin levels were associated with childhood NHL and adverse clinical features in a nationwide case-control study [68]. Higher adiponectin concentrations and a positive correlation between adiponectin and IL-10 have also been reported in adult NHL patients [69], while serum proteomic profiling identified increased adiponectin abundance in patients with DLBCL compared with matched controls [70]. Nevertheless, available clinical findings are heterogeneous, and these observational data do not establish a functional

Table 1 Limitations of BMI and emerging metrics for obesity characterization in lymphoma

Metric	Measurement	Parameter assessed	Key limitations
BMI	Weight (kg) / height (m ²)	Overall body mass	Does not distinguish fat vs. muscle; no fat distribution info
Waist circumference/ WHR	Anthropometric measurement (abdomen $\pm$ hip circumference)	Central (visceral) adiposity	No information on muscle mass or ectopic fat
CT- or DEXA-based body composition	Cross-sectional imaging (CT) or dual-energy X-ray absorptiometry	Visceral fat, subcutaneous fat, lean body mass	Requires imaging; not routinely standardized
Sarcopenic obesity	Derived from CT (e.g. L3 skeletal muscle index) or DEXA	Fat mass + reduced muscle mass	Requires imaging; lacks standardized cut-offs

adiponectin–AMPK mechanism in lymphoma cells. Thus, although the adiponectin–AMPK axis represents a biologically plausible interface between metabolic status and tumor biology, direct experimental validation of adiponectin-dependent AMPK signaling in neoplastic B cells remains limited, and its specific contribution to obesity-associated lymphomagenesis remains to be established.

Emerging evidence from single-cell and spatial transcriptomic analyses indicates that immune cells within obese adipose tissue undergo profound metabolic reprogramming, characterized by enhanced glycolysis, altered lipid handling, and mitochondrial stress, which collectively shape their inflammatory phenotype and functional persistence [71–80]. In addition, adipocyte-derived extracellular vesicles and components of the senescence-associated secretory phenotype (SASP) contribute to immune cell activation and cytokine propagation, further stabilizing the inflammatory network within adipose tissue and beyond [81–87]. By promoting chronic inflammation, immune dysfunction, and sustained activation of oncogenic signaling pathways, obesity creates a permissive biological environment for development of several cancer [88–92], including lymphoma [93–98]. Moreover, beyond high-resolution molecular profiling, patient-derived three-dimensional models are emerging as complementary platforms for functional precision oncology. In lymphoma, patient-derived organoid and organotypic systems can partially preserve tumor–immune–stromal interactions and provide experimentally tractable platforms to investigate microenvironmental dependencies and patient-specific therapeutic responses. Integration of these functional models with single-cell, spatial, and multi-omics approaches may therefore help bridge molecular characterization with functional interrogation of lymphoma biology and treatment response [99–101]. Collectively, these systemic inflammatory and metabolic perturbations provide a biologically plausible background through which obesity may influence lymphoma susceptibility and the tumor microenvironment [102].

Epidemiological and clinical evidence linking obesity and lymphoma

Obesity is associated with an increased risk of lymphoma, although this relationship varies across disease subtypes and patient characteristics, and its clinical implications remain complex and context-dependent.

Overview of epidemiologic associations

The epidemiological link between obesity and lymphoma has been consistently observed in multiple large-scale cohort studies and meta-analyses over the past two decades. Overall, excess body weight is associated with an elevated risk of both Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), with subtype- and sex-specific differences [3, 7, 8, 103, 104]. Similarly, meta-analyses have demonstrated a dose-dependent relationship between body mass index (BMI) and NHL incidence, especially for DLBCL and follicular lymphoma (FL) [3].

Willett and Roman (2006) reported that obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$) was associated with a more than two-fold increased risk of HL compared with normal weight (OR 2.2, 95% CI 1.1–4.3), with a stronger association observed among men. A seminal pooled analysis including over 30 prospective cohorts demonstrated that both overweight and obesity are consistently associated with a higher incidence of lymphoma, independent of potential confounders such as smoking, alcohol consumption, and physical activity [104, 105]. Complementary evidence comes from a prospective twin-cohort study conducted in Sweden and Finland, which followed more than 70,000 participants for up to 20 years. In that analysis, overweight and obese individuals showed increased relative risks of hematologic malignancies, including NHL and multiple myeloma, even after controlling for shared genetic and environmental factors [106]. Moreover, in a Japanese case-control study, Kanda et al. (2010) found that higher BMI in early adulthood was associated with an increased risk of malignant lymphoma (OR 1.33, 95% CI 1.13–1.55 per 5-kg/m² increase in BMI), with subtype analyses showing a significant association with DLBCL [107]. In the landmark UK cohort of 5.8 million adults, Strongman et al. demonstrated a significant positive correlation between BMI and HL incidence, showing an approximate 10% increase in risk for every 5 kg/m² increase in BMI [7]. The association followed a *J-shaped curve*, suggesting that both underweight and obesity

might predispose to lymphomagenesis through distinct metabolic and immunological pathways. Similarly, Aune et al. analyzed 1.7 million Norwegian participants and confirmed that obesity particularly increases the risk of early-onset HL in women, with hazard ratios exceeding 1.5 for BMI > 30 kg/m² [8]. Moreover, meta-analyses and pooled cohort studies confirm that obesity increases the risk of NHL by approximately 7–15%, with the strongest associations for DLBCL and FL [3, 103, 108]. Larsson and Wolk [103] conducted one of the earliest quantitative meta-analyses assessing the link between BMI and NHL, pooling data from 15 prospective studies and reporting a 7% increase in overall NHL risk for each 5 kg/m² increment in BMI, with stronger effects observed among women and Western populations. The landmark InterLymph pooled analysis integrating > 10,000 cases showed that BMI ≥ 30 kg/m² was linked to a significant increase in DLBCL and FL incidence, whereas T-cell lymphomas showed no clear relationship [105]. Castillo et al. [108] subsequently confirmed a ~30% higher DLBCL risk in obese versus normal-weight subjects, supporting a dose–response gradient. More recent studies have refined these observations. Teras et al. (2022) examined NHL subtypes within a U.S. population-based cohort and found that sustained obesity from early adulthood conferred the highest DLBCL risk, whereas transient overweight had minimal effect [109]. Hidayat et al. extended this analysis to anthropometric markers beyond BMI—such as height and waist circumference—showing that central adiposity correlated most strongly with B-cell lymphomas, reinforcing the role of metabolically active visceral fat in lymphomagenesis [110]. Conversely, Atak et al. (15) found that BMI did not significantly affect treatment response or survival outcomes in patients with DLBCL, underscoring that the prognostic implications of adiposity might differ from its etiologic role. Moreover, BMI was not significantly associated with clinical outcomes among patients with DLBCL, HL or FL, in three prospective phase III clinical trials [33]. Recent mechanistic hypotheses suggest that adipokine dysregulation might mediate the observed epidemiologic associations. In addition, Lichtman (2010) provided a mechanistic explanation, suggesting that the metabolic, endocrine, and inflammatory alterations resulting from obesity may increase mutation rates, impair DNA repair, and induce epigenetic changes that favor malignant transformation [4]. Interestingly, while obesity appears to elevate the risk of developing lymphoma, its influence on prognosis remains complex. Importantly, recent genetic evidence supports a causal role of obesity in lymphomagenesis. Using a Mendelian randomization approach, Liu et al. (2026) demonstrated that genetically predicted higher body mass index is associated with an increased risk of lymphoma, particularly B-cell subtypes, independently of lifestyle and socioeconomic confounders. These findings strengthen the interpretation that obesity is not merely a correlated condition but a biologically relevant driver of lymphoma risk, providing a causal framework that complements observational epidemiology [111]. In summary (see Table 2), extensive epidemiologic data from cohort and pooled analyses confirm that excess body weight contributes to an increased incidence of lymphoma, with consistent patterns across populations and lymphoma subtypes. Taken together, these data indicate that excess adiposity contributes to lymphoma risk in a heterogeneous and context-dependent manner, highlighting the need to explore the underlying biological mechanisms.

Age, sex, and histologic variability and lymphoma risk

The relationship between obesity and lymphoma risk is further modulated by demographic and biological variables, including age, sex, and histologic subtype. In the Norwegian cohort by Aune et al., obesity was linked to a 60% increase in HL risk in individuals under 50 years, whereas no clear association was detected in older participants [8]. This age-dependent pattern is consistent with evidence that higher BMI early in life is associated with increased risk of adult hematologic malignancies, supporting a long latency between metabolic exposure and lymphomagenesis [121]. Sex-related differences have also emerged in several population studies. In Norwegian [8] cohorts, the risk elevation associated with obesity was more pronounced in women, a trend that might be explained by differences in body fat distribution, sex hormone metabolism, and adipose-derived cytokine profiles. Recently, Kelly et al. also found a women-specific trend [113], whereas others found the same trend for both sex [3, 108]. Sex-stratified meta-analyses also report stronger associations between BMI and lymphoma risk in women than in men, particularly in Western populations [122]. Histologic subtype also modifies the impact of

Table 2 Key epidemiologic and clinical studies evaluating the association between obesity and lymphoma risk or outcome

Study (Year)	Design Setting/ N	Lymphoma subtype	Exposure/ Metric	Main finding	Axis
Strongman et al. (2019) [7]	Population cohort (U.K. CPRD; $n \approx 5.8$ M)	HL (incidence)	BMI continuous (+5 kg/m ²)	+10% HL risk per +5 kg/m ² ; J-shaped curve	Risk
Söderberg et al. (2009) [112]	Twin cohorts (Sweden/Finland; $n \approx 70$ k)	Hematologic (HL/NHL/MM/Leukemia)	Overweight (25–29.9), Obese (≥ 30)	No clear lymphoma-specific association; obesity $\rightarrow$ $\uparrow$ myeloma risk (RR 2.1)	Risk
Renehan et al. (2008) [3]	Systematic review/meta-analysis (221 datasets; 141 articles)	NHL	BMI continuous (+5 kg/m ²)	$\uparrow$ BMI $\rightarrow$ modest $\uparrow$ NHL risk (RR < 1.20) in both sexes	Risk
Larsson & Wolk (2007) [103]	Meta-analysis (16 studies; 21,720 cases)	NHL subtypes	Overweight (BMI 25–<30); obesity (BMI ≥ 30 kg/m ²)	Obesity $\rightarrow$ $\uparrow$ NHL risk (RR 1.20), particularly DLBCL (RR 1.40)	Risk
Kanda et al. (2010) [107]	Case–control (Japan; 782 cases, 3,910 controls)	NHL/DLBCL	BMI > 27 vs. ≤ 23	Increased ML risk in early-adulthood with high BMI (OR 1.33 per +5 kg/m ²); significant for DLBCL	Risk
Kelly et al. (2012) [113]	Case–control (U.S.; 950 cases/1,146 controls)	NHL	BMI at age 18; adult BMI	Higher BMI at age 18 $\rightarrow$ $\uparrow$ NHL risk (OR 1.38), particularly in females (OR 1.90); adult BMI not associated	Risk
Boyle et al. (2017) [114]	Cohort; $n = 413$ (238 DLBCL, 175 FL)	DLBCL, FL	Obese ≥ 30 ; inactive vs. active	Increased risk and reduced survival	Outcome
Teras et al. (2022) [109]	Pooled U.S. cohort (6 studies; $n \approx 568$ 717)	NHL subtypes	BMI trajectory (persistent ≥ 30)	>2-fold $\uparrow$ DLBCL risk (HR 2.67)	Risk
Aune et al. (2025) [8]	Population-based cohort (Norway; $n = 1,723,692$)	HL	BMI	Confirms positive association between obesity and HL risk (HR 1.61); HR 1.16 per +5 kg/m ²)	Risk
Hidayat et al. (2018) [110]	Systematic review/meta-analysis (22 prospective cohorts; >20,000 NHL cases)	NHL overall	BMI per 5 kg/m ²	Each 5 kg/m ² $\uparrow$ $\rightarrow$ 6% $\uparrow$ NHL risk; strongest in DLBCL	Risk
Chihara et al. (2021) [115]	Prospective cohort (U.S.; $n = 4,009$)	DLBCL, FL, CLL/SLL, other subtypes	Obesity (BMI ≥ 30)	Pre-diagnosis obesity $\rightarrow$ shorter LSS in FL (HR 3.02); no association in DLBCL or CLL/SLL	Outcome
Castillo et al. (2014) [108]	Meta-analysis (16 studies: 6 case–control, 10 cohort)	DLBCL	Overweight (BMI 25–29.9); obesity (BMI ≥ 30 kg/m ²)	Overweight $\rightarrow$ $\uparrow$ DLBCL risk (RR 1.14); obesity $\rightarrow$ $\uparrow$ DLBCL risk (RR 1.29)	Risk
Atak et al. (2023) [116]	Retrospective cohort ($n = 79$)	DLBCL	Normal (<25) vs. Overweight (25–29.9) vs. Obese (≥ 30)	No significant association between BMI and treatment response	Outcome
Hu et al. (2023)	Retrospective cohort (China; $n = 67$)	HL (ABVD-like regimen)	BMI categories	Overweight/obesity $\rightarrow$ poorer ORR and shorter PFS	Outcome
Hontecillas-Prieto et al. (2025) [30]	Translational substudy of phase II trial ($n = 75$)	R/R DLBCL (R2-GDP-GOTEL)	Overweight 25–29.9 vs. others	Excess weight $\rightarrow$ better treatment response and longer survival	Outcome
Yeo et al. (2025) [117]	National Readmission Database (U.S.; $n = 1$ 874)	DLBCL (CAR-T)	Obese ≥ 30 vs. non-obese	Increased early mortality and non-home discharge after CAR-T	Outcome
Du et al. (2025) [118]	Retrospective CAR-T cohort (China; $n = 115$)	B-cell malignancies	BMI ≥ 28 and obesity-related comorbidities	Hyperlipidemia increased severe CRS risk; no impact on efficacy	Outcome / Toxicity

Table 2 (continued)

Study (Year)	Design Setting/ <i>N</i>	Lymphoma subtype	Exposure/ Metric	Main finding	Axis
Faruqi et al. (2022) [119]	Multi-trial analysis (U.S.; <i>n</i> = 139)	B-ALL / NHL (CAR-T)	Overweight ≥ 25; Obese ≥ 30	No significant association between BMI and CAR-T response, neurotoxicity, or OS	Out- come / Toxicity
Chen et al. (2026) [120]	GBD 2021 analysis (1990–2021)	NHL (mortality)	High BMI (GBD definition)	High BMI-attributable NHL DALY burden increased with SDI, reaching 39.14% in high-income North America	Burden

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; B-ALL, B-cell acute lymphoblastic leukemia; BMI, body mass index; CAR-T, chimeric antigen receptor T-cell therapy; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; CR, complete response; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GBD, Global Burden of Disease; HBMI, high body mass index; HL, Hodgkin lymphoma; HR, hazard ratio; LSS, lymphoma-specific survival; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; OR, odds ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; RR, relative risk; SDI, Socio-demographic Index

obesity on lymphoma risk. For NHL, the obesity–risk association is largely confined to B-cell subtypes, particularly DLBCL and FL, whereas findings for marginal zone lymphoma (MZL) are less consistent and absent for T-cell lymphomas [103]. This subtype specificity aligns with broader evidence of etiologic heterogeneity across NHL entities, suggesting that metabolic exposures do not uniformly affect lymphoma subtypes [123]. Finally, while obesity appears to increase lymphoma incidence, its effect on disease biology and outcome is less uniform across different histotypes.

Such findings indicate that the impact of adiposity is highly subtype-specific, reflecting distinct biological interactions between metabolic status and lymphoma pathogenesis. These differences are critical for interpreting clinical outcomes and therapeutic responses.

Clinical implications and the obesity paradox

While previous sections addressed obesity as a risk factor, its role in clinical outcomes is more complex. In fact, beyond its role in disease risk, obesity has a complex and sometimes paradoxical impact on lymphoma outcomes. Likewise, classical HL is commonly treated with ABVD, consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine (or, in selected contexts, bleomycin-sparing variants). In current European practice, first-line therapy for diffuse large B-cell lymphoma (DLBCL) is typically based on R-CHOP, a chemoimmunotherapy regimen combining rituximab (an anti-CD20 monoclonal antibody) with cyclophosphamide, doxorubicin, vincristine, and prednisone [124]. Several retrospective analyses and clinical cohorts have described a paradoxical association between higher BMI and improved survival in patients with DLBCL treated with standard chemoimmunotherapy (e.g., R-CHOP) [30, 31, 125]. In a meta-analysis of more than 5000 patients, Wang et al. (2021) reported that overweight individuals had improved overall survival compared with normal-weight or underweight counterparts, whereas obesity itself had a neutral effect [125]. Similarly, Carson et al. (2012) found that obese DLBCL patients treated with rituximab-based therapy exhibited superior event-free and overall survival, possibly reflecting better tolerance to full-dose therapy and preserved nutritional reserves [31]. Recent studies have expanded this evidence toward treatment response. Hontecillas-Prieto et al. (2025) demonstrated that overweight and obese patients with relapsed/refractory DLBCL receiving lenalidomide-based therapy achieved higher overall response rates and longer progression-free survival, accompanied by enhanced CD8⁺ and NK-cell activity and elevated vitamin D levels [30]. Moreover, Chihara et al. (2021), analyzing more than 4,000 patients with major lymphoma subtypes, found that obesity prior to diagnosis was associated with significantly shorter lymphoma-specific survival in FL (HR 3.02), whereas no association emerged for DLBCL or CLL (chronic lymphocytic leukemia) and SLL (small lymphocytic lymphoma) [115]. Consistent with a potentially adverse prognostic effect in FL, Boyle et al. (2017) reported that obesity before diagnosis was associated with a 2.5-fold higher risk of death among

patients with FL compared with those with normal BMI (HR 2.52, 95% CI 1.27–5.00) [114]. Conversely, Hu et al. (2023) reported that higher BMI was associated with lower complete response rates in HL patients treated with ABVD-like regimens, suggesting disease- and therapy-specific effects [126]. Similar evidence is lacking for HL or T-cell lymphomas, in which BMI appears neutral or slightly unfavorable for prognosis [127]. In contrast, Atak et al. (2023) found no significant difference in complete or partial response among patients with different BMI categories in newly diagnosed DLBCL treated with R-CHOP [116]. Collectively, these findings highlight that the impact of obesity on treatment outcomes is context-dependent, varying by histology, regimen, and body-composition phenotype. Nevertheless, the obesity paradox remains controversial. Several confounders—such as reverse causality, selection bias, and unmeasured pre-diagnostic weight loss—can distort survival analyses [128]. In particular, collider bias may contribute to the apparent survival advantage observed in obese patients, as inclusion in treated cohorts can be influenced by factors related to both body weight and disease severity. Moreover, BMI alone does not differentiate between visceral adiposity and sarcopenic obesity, which might exert opposing effects on prognosis [129]. The so-called “obesity paradox” should therefore be interpreted cautiously, as it is highly susceptible to multiple sources of bias. Importantly, these findings should not be generalized across lymphoma subtypes, as the prognostic impact of obesity appears to be highly context-dependent and varies substantially between DLBCL, Hodgkin lymphoma, and other entities. Future prospective studies incorporating longitudinal body composition and metabolic biomarkers will be essential to clarify whether adiposity directly modifies lymphoma outcomes or reflects underlying metabolic resilience. These considerations highlight the complexity of interpreting the prognostic impact of obesity and underscore the need for a clearer understanding of how metabolic and body composition factors influence therapeutic response.

Mechanistic and preclinical evidence linking obesity and lymphomagenesis

Building on the systemic immunometabolic alterations described above, several obesity-associated mediators may intersect with signaling pathways relevant to lymphoma biology. However, the strength of evidence varies considerably, and many proposed mechanisms derive from obesity or solid-tumor models rather than direct experimental studies in lymphoma. In hypertrophic adipose tissue, adipocytes undergo stress, hypoxia, and cell death, which recruit macrophages and other immune cells [20, 98]. These infiltrating leukocytes, together with adipocytes themselves, secrete proinflammatory cytokines (e.g. TNF- α , IL-6, IL-1 β), chemokines (e.g. MCP-1), and reactive oxygen species, thereby activating inflammatory pathways such as those triggered by NF- κ B and STAT3 [130, 131]. Key to the immune–metabolic interface are adipokines, endocrine factors released by adipose tissue that modulate immune function [132]. Leptin, produced proportionally to adipose mass, is a potent immunoregulatory molecule: it binds to leptin receptors on immune cells, activating JAK/STAT signalling, promoting T-cell survival, proliferation, and Th1 polarization [65, 133, 134]. Leptin also supports inflammatory responses, and persistently elevated leptin levels are implicated in sustaining low-grade inflammation [135–137]. The oncogenic actions of leptin have been extensively investigated, delineating its role as a pleiotropic hormone linking metabolism, inflammation, and tumor growth in hormone-responsive cancers such as breast cancer (BC), where leptin and adipocyte-derived mediators, including IGF-1, can sustain proliferative and survival signaling [89, 91, 92, 138–140]. Whether these mechanisms operate to the same extent in lymphoma remains less well established. More recently, these metabolic and inflammatory mechanisms have been proposed to influence hematologic malignancies as well, in which chronic leptin exposure and altered adipokine balance might shape both tumor initiation and immune microenvironment remodeling. In lymphoma, available evidence is predominantly clinical and associative rather than mechanistically causal. Clinical studies have linked elevated serum leptin levels and high BMI to adverse features and poorer outcomes in NHL and DLBCL [30, 141–145]. In Egyptian cohorts, leptin concentrations correlated positively with BMI and disease stage, being significantly higher in patients with stage IV disease or B symptoms, and in those who failed to respond to R-CHOP chemotherapy [142]. Similarly, Mahmoud et al. reported that DLBCL patients with elevated leptin showed reduced response rates and shorter

disease-free survival compared to those with normal levels, suggesting that leptin may act as a prognostic biomarker associated with treatment resistance [141]. In line with these observations, a population-based case–control study by Skibola et al. demonstrated that obesity was associated with up to a threefold increased risk of NHL, including DLBCL and FL, and that genetic polymorphisms in the *LEP* (A19G, G–2548 A) and *LEPR* (Q223R) genes further enhanced this risk [146, 147]. Overall, these findings indicate that leptin represents a potential molecular link between adiposity, chronic inflammation, and lymphoma progression, potentially influencing both disease biology and therapeutic response. Further research should clarify whether targeting the leptin/Ob-R axis could mitigate obesity-associated immune dysregulation and improve outcomes in lymphoma patients. Interestingly, STAT3, NF- κ B, and PI3K/AKT signaling are well-established regulators of lymphoma-cell survival, proliferation, metabolic adaptation, and therapeutic resistance [148–152]. These pathways can also be modulated by cytokines and metabolic signals altered in obesity; however, direct evidence demonstrating that obesity-driven activation of these pathways causally promotes human lymphomagenesis remains limited [153–155]. Obesity-associated chronic immune stimulation may additionally contribute to T-cell dysfunction and exhaustion [153–155], although the extent to which these systemic alterations directly shape lymphoma-specific antitumor immunity remains incompletely defined. Importantly, JAK/STAT, PI3K/AKT/mTOR, NF- κ B, and MAPK signaling also represent central oncogenic networks in lymphoma biology [56, 156, 157]. Their convergence with pathways responsive to metabolic and inflammatory cues provides a biologically plausible, but not yet fully demonstrated, interface between obesity and lymphoma pathogenesis. Several clinical trials have investigated pharmacological inhibition of these pathways in lymphoma (Table 3). Importantly, these therapeutic strategies were developed on the basis of lymphoma-intrinsic biology rather than obesity-specific mechanisms; their relevance to obesity-associated metabolic dysregulation therefore remains indirect. Collectively, obesity-associated inflammatory and metabolic signals converge on pathways that are independently recognized as central to lymphoma biology. However, while this overlap provides a compelling biological framework, direct experimental evidence establishing obesity-driven activation of these pathways as a causal determinant of lymphomagenesis remains limited. This distinction is particularly important when interpreting mechanistic findings extrapolated from adipose tissue and solid-tumor models (Fig. 1).

In vivo evidence linking obesity and lymphomagenesis

The most compelling experimental validation derives from obesity-driven lymphoma mouse models. Wang et al. demonstrated that obesity promotes aggressive lymphoma progression through activation of the S1P–S1PR1/S1PR3–YAP signaling axis. Pharmacologic intervention with resveratrol significantly suppressed tumor growth by targeting this pathway, supporting a direct role for lipid-mediated signaling in lymphomagenesis [175]. In addition, Huang et al. showed that systemic metabolic modulation can influence lymphoma progression. In B-cell lymphoma models, the PPAR α agonist fenofibrate significantly reduced tumor growth by altering host lipid metabolism and decreasing circulating lipid availability required for tumor expansion [176]. Although limited in number, these studies consistently highlight lipid metabolism as a critical driver of lymphoma progression in obese conditions and support the concept that targeting host metabolic pathways may represent a complementary therapeutic strategy. These findings provide a biological rationale for clinical trials targeting immunometabolic pathways in lymphoma.

Immunometabolic crosstalk: T-cell activation, exhaustion, and tumor interaction

The functional state of T cells represents a critical interface between obesity-associated metabolic dysfunction and lymphoma progression. In the obese state, chronic stimulation of T cells, particularly CD8⁺ cytotoxic T lymphocytes (CTLs), can occur via adipokine influences and cytokine signaling even in the absence of pathogens [177, 178], consistent with the concept of metaflammation and obesity-driven sterile immune activation [179].

Table 3 Clinical trials on metabolic and inflammatory pathways in lymphoma

NCT ID	Target / Pathway	Drug / Intervention	Disease setting	Phase	Status	Objective	Key findings
NCT00869999 [158]	mTOR	Everolimus+ Rituximab	DLBCL (relapsed/refractory)	II	Completed	Evaluate efficacy and safety of mTOR inhibition + anti-CD20	Demonstrated clinical activity with manageable toxicity
NCT01076543 [159]	mTOR	Temsirolimus + Lenalidomide	NHL (relapsed/refractory)	I/II	Completed	Assess safety, dose, and preliminary efficacy	Combination feasible; hematologic toxicity observed
NCT00967044 [160]	mTOR	Panobinostat+ Everolimus	HL and NHL (relapsed/refractory)	II	Completed	Evaluate dual HDAC + mTOR inhibition	Limited activity; combination biologically rational
NCT00790036 [161]	mTOR	Everolimus (RAD001) adjuvant	DLBCL (high-risk)	III	Completed	Improve DFS	No significant DFS benefit (PILLAR-2 trial)
NCT01660451 [162]	PI3K	Copanlisib (BAY 80-6946)	NHL (relapsed/refractory)	II	Completed	Evaluate PI3K inhibition	Demonstrated activity, especially in indolent NHL
NCT02626455 [163]	PI3K	Copanlisib + Standard Chemotherapy	Indolent NHL (relapsed)	III	Completed	Improve PFS vs. standard therapy	No significant PFS improvement (CHRONOS-4)
NCT02049541 [164]	PI3K	Buparlisib+ Rituximab	NHL (relapsed/refractory)	I	Completed	Assess safety and dose	Limited efficacy; toxicity concerns
NCT02164006 [165]	PI3K	Umbralisib+ Brentuximab Vedotin	Hodgkin Lymphoma (relapsed)	I/II	Completed	Evaluate PI3K δ + CD30 targeting	Combination feasible with clinical activity
NCT05083208 [166]	PI3K	Parsaclisib+ Chidamide	NHL (relapsed/refractory)	Ib/II	Active	Evaluate PI3K δ + HDAC inhibition	Results pending
NCT02974647 [167]	JAK/STAT	Ruxolitinib	T/NK-cell lymphoma	II	Completed	Target STAT3 signaling	Modest activity in selected subtypes
NCT01431209 [168]	JAK/STAT	Ruxolitinib	DLBCL / PTCL (relapsed/refractory)	II	Completed	Evaluate response and biomarkers	Biomarker-driven responses observed
NCT04105010 [169]	JAK/STAT	AZD4205	NHL (relapsed/refractory)	I/II	Completed	Selective JAK1 inhibition	Favorable safety; early activity signals
NCT07032532 [170]	JAK/STAT	Golidocitinib	PTCL	II/III	Recruiting	Assess efficacy in PTCL	Early data suggest promising activity
NCT00562380 [171]	IGF-1R	Ganitumab (AMG-479)	NHL (included cohort)	I	Completed	Evaluate IGF-1R inhibition	Limited lymphoma-specific efficacy
NCT00920738 [172]	Metabolic biomarkers	Observational metabolic assessment	Pediatric leukemia/lymphoma survivors	Observational	Completed	Assess metabolic syndrome/insulin resistance and related biomarkers	Metabolic and inflammatory biomarkers evaluated
NCT03391466 [173]	CD19 / CAR-T	Axicabtagene ciloleucel	R/R LBCL	III	Completed	Evaluate CAR-T efficacy versus standard-of-care second-line therapy	Improved clinical outcomes with axi-cel versus standard care
NCT03310619 [174]	CD19 / CAR-T	Lisocabtagene maraleucel (JCAR017) $\pm$ combination agents	R/R B-cell NHL	I/II	Completed	Evaluate safety and efficacy of CAR-T-based combination strategies	Clinical activity evaluated across combination cohorts

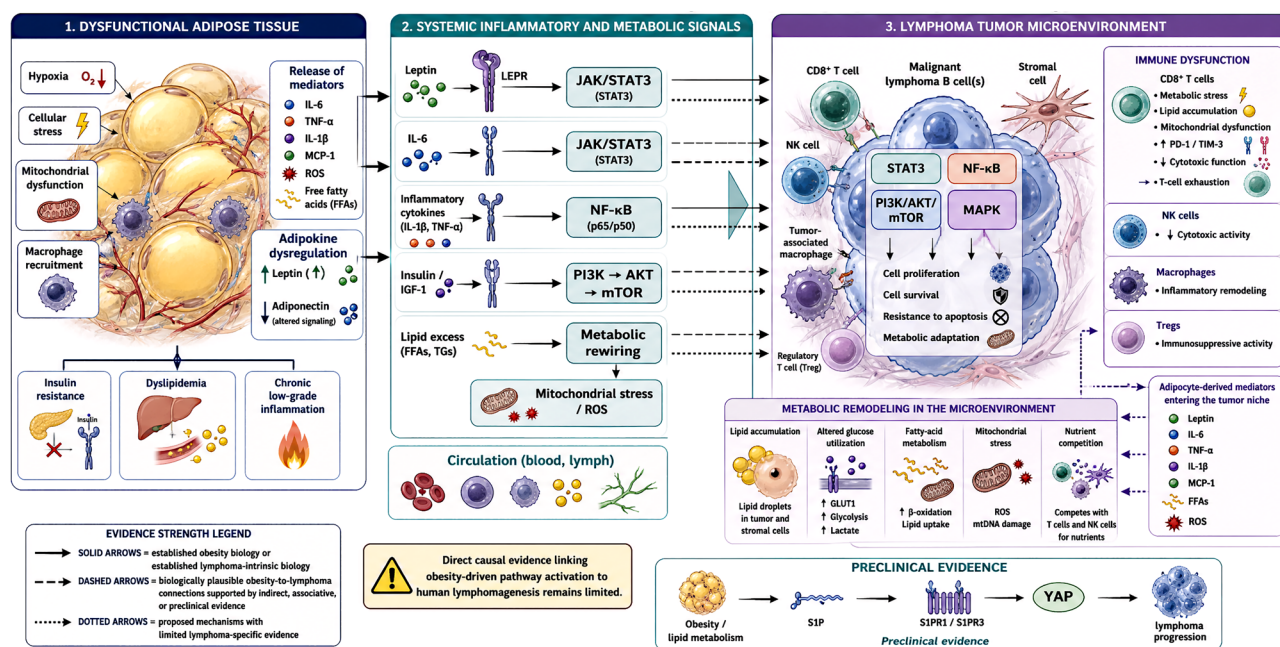


Fig. 1 Obesity promotes lymphoma progression and influences therapeutic responses through immunometabolic remodeling. Obesity-induced inflammation, adipokine imbalance, and metabolic dysregulation create a tumor-supportive microenvironment that favors lymphoma development and alters treatment response

Persistent exposure to inflammatory mediators may upregulate inhibitory “checkpoint” molecules (e.g. PD-1, TIM-3), leading to a dysfunctional or exhausted phenotype [180, 181], as described in chronic inflammatory and metabolically stressed environments [182–186]. This state has been described as a form of sterile autoimmunity or subclinical autoimmune-like activation, whereby T cells might lose tolerance or functional integrity through chronic metabolic stress rather than through classical autoantigen recognition [187–190]. The functional capacity of CD8⁺ T cells is tightly linked to their metabolic state. Activation demands increased uptake of nutrients (glucose, amino acids, fatty acids) and shifts in intracellular metabolic pathways (glycolysis, oxidative phosphorylation, fatty acid oxidation). In tumor settings, CD8⁺ T cells often differentiate into terminally exhausted phenotypes with metabolic impairments [191]. In obesity, the metabolic constraints are exacerbated: competition for nutrients, lipid overload, and mitochondrial dysfunction impair the bioenergetics of CD8⁺ T cells. Turbitt et al. (2020) discuss how obesity imposes metabolic stress, altering T-cell metabolic profiles and reducing effector function [192]. Similarly, in murine models of diet-induced obesity, tumor-infiltrating CD8⁺ T cells show reduced expression of effector genes (e.g. IFN- γ , perforin, granzyme B) and higher exhaustion signatures; these impairments are not fully reversible by pharmacologic weight loss [11, 193]. Lipid metabolism plays a pivotal role in this dysfunction. CD8⁺ T cells within tumors upregulate lipid transporters (such as CD36) and accumulate lipids, which can lead to lipotoxicity, oxidative stress, and mitochondrial impairment [29]. Some studies show that in obesity, STAT3 activation promotes fatty acid oxidation at the expense of glycolysis, blunting effector cytokine production and enhancing T-cell exhaustion underlying the predictive role of obesity in both chemotherapy and immunotherapy settings. From a translational perspective, obesity-related metabolic dysfunction may represent a modifiable factor. Potential strategies include metabolic optimization prior to CAR-T infusion, targeting systemic inflammation, and enhancing T-cell metabolic fitness, although these approaches remain investigational and require prospective validation. These findings suggest that obesity-induced metabolic stress contributes to T-cell dysfunction and exhaustion, with potential implications for both tumor progression and response to immunotherapy.

Clinical and therapeutic implications

The immunometabolic dysregulation induced by obesity has important clinical implications in lymphoma, influencing both disease progression and therapeutic response. While excessive adiposity contributes to lymphoma-genesis through chronic inflammation, cytokine imbalance, and insulin resistance, several clinical studies have shown that BMI can also influence treatment outcomes in patients with lymphoma, sometimes with paradoxical effects.

Chemotherapy and obesity

The impact of obesity on treatment outcomes in lymphoma is complex and, in some contexts, counterintuitive, particularly in patients receiving chemoimmunotherapy. Early studies suggested that excess body weight might adversely affect outcomes, particularly in high-dose chemotherapy settings. In fact, in patients with NHL receiving high-dose chemotherapy and autologous stem cell transplantation, Tarella et al. (2000) reported that overweight was an adverse prognostic factor associated with reduced overall survival [194]. Conversely, subsequent studies suggested that higher BMI might confer a protective effect. In a Swedish cohort of HL patients, Landgren et al. (2005) found that BMI was independently associated with improved cause-specific survival (CSS); the corresponding five-year overall survival (OS) rates were 100% for obese, 79% for overweight, and 70% for normal or underweight individuals [34, 195]. Similarly, Jones et al. (2010) demonstrated that BMI was an independent prognostic factor for OS in intermediate-grade B-cell NHL, with better outcomes observed in overweight and mildly obese patients [32]. These findings were confirmed in a large U.S. Veterans cohort by Carson et al. (2012), who showed that increased BMI was significantly associated with improved OS and progression-free survival (PFS) in DLBCL treated with rituximab-based chemoimmunotherapy [31]. However, most of these studies rely on BMI as a surrogate of adiposity, which may not adequately capture underlying body composition, metabolic status, or sarcopenic obesity.

Data from clinical trials reinforce this apparent paradox. In the RATHL trial, Preston et al. (2017) reported that obese patients with advanced HL had similar treatment tolerance and hematologic toxicity compared with normal-weight patients, with no significant difference in the incidence of neutropenia [196]. At the pharmacologic level, obesity alters the distribution and metabolism of lipophilic agents such as doxorubicin and cyclophosphamide, potentially influencing both efficacy and toxicity. A systematic review and meta-analysis by Hourdequin et al. (2013) demonstrated that chemotherapy dosing based on actual body weight does not increase severe toxicity compared with dosing adjusted for ideal body weight, thereby supporting the safety of full-weight dosing in obese patients [197]. Nevertheless, obesity-related metabolic dysfunction may still modulate drug bioavailability: Sheng et al. (2019) showed that adipocytes can sequester and metabolize chemotherapeutic agents, potentially reducing their intratumoral concentration [198]. Importantly, Alsharif et al. (2022) analyzed patients with hematologic malignancies receiving cytotoxic chemotherapy and demonstrated that obesity was not associated with increased toxicity or inferior outcomes; on the contrary, obese individuals tended to maintain higher treatment adherence and metabolic resilience, supporting the hypothesis that adiposity might confer a therapeutic advantage in selected contexts [199]. Moreover, De Pergola et al. (2012) reported that obese patients showed higher expression of tumor proliferation markers compared with their non-obese counterparts, suggesting that adiposity might influence tumor biology and aggressiveness [200]. Finally, Ligibel et al. (2014) reported that obesity has been associated with an increased risk of chemotherapy-related toxicities, including fatigue and peripheral neuropathy [201]. These observations should be interpreted with caution, as improved outcomes in overweight patients may reflect multiple factors, including pharmacokinetic differences, treatment adherence, physiologic reserve, or residual confounding, rather than a direct protective effect of obesity.

Collectively, these data support the complex and sometimes paradoxical role of obesity in lymphoma promoting disease initiation and progression through systemic inflammation and metabolic reprogramming, yet in

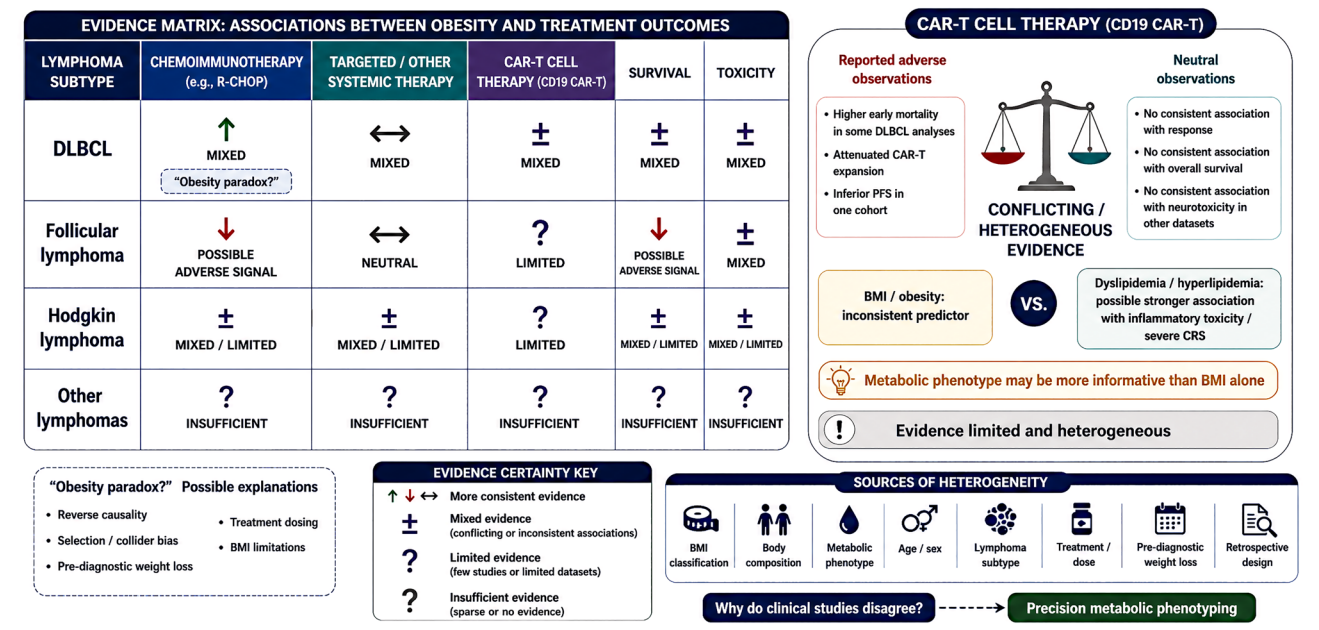


Fig. 2 Therapy-dependent impact of obesity on lymphoma outcomes. Obesity, defined by a high body mass index (BMI), exerts differential effects on treatment outcomes in lymphoma

certain clinical contexts conferring improved treatment tolerance and survival, a phenomenon often referred to as the “*obesity paradox*.”

CAR-T cell therapy and obesity

The potential impact of obesity is of particular interest in the context of advanced immunotherapies such as CAR-T cell therapy (Fig. 2). The metabolic and inflammatory milieu characteristic of obesity might influence T-cell differentiation, trafficking, and persistence, thereby affecting therapeutic outcomes. Recent reviews on the sequencing of anti-CD19 therapies highlight how antigen modulation, T-cell exhaustion, and prior CD19-directed exposure critically shape CAR-T efficacy, providing a conceptual framework to interpret metabolic and obesity-related determinants of treatment response [202]. Using the National Readmission Database, Yeo et al. [117] analyzed 1,874 patients with DLBCL who received CAR-T therapy between 2018 and 2020. After propensity score matching, patients with obesity showed significantly higher rates of early in-hospital mortality (10.6% vs. 4.4%, $p=0.03$) and non-home discharge (18.8% vs. 8.1%, $p=0.01$). However, rates of neurotoxicity, infection, acute kidney injury, and other evaluated in-hospital complications were not significantly different between groups. Conversely, a large multicenter retrospective analysis by Upadhyay et al. including 4,657 patients treated with CAR-T therapy found that, after propensity-score matching, patients with a BMI>25 kg/m² had a significantly higher 3-year survival probability than those with a BMI of 18–25 kg/m² (61% vs. 55%, $p<0.001$), while rates of CRS and ICANS did not differ significantly between groups 201. These findings further illustrate the heterogeneity of the available evidence and argue against a uniformly detrimental effect of elevated BMI on CAR-T outcomes [203]. Preclinical and translational findings reported by Maaskant et al. suggest that obesity-associated metabolic conditions may impair CAR-T-cell function, including reduced cytokine production and increased expression of exhaustion markers such as PD-1 and LAG-3 [204]. These findings align with the mechanisms of antigen modulation and T-cell exhaustion described in CD19-directed therapies, raising the possibility that metabolic and microenvironmental factors may contribute to altered CAR-T-cell persistence and function. Further supporting a metabolic contribution, Du et al. 203 retrospectively analyzed 115 patients with B-cell malignancies treated with CAR-T therapy [205]. Obesity-related conditions as a group were associated

with a higher proportion of severe CRS; however, obesity/overweight itself was not significantly associated with severe CRS or treatment efficacy. Notably, hyperlipidemia was independently associated with an increased risk of severe CRS (OR=3.73, 95% CI 1.20–11.56). Elevated total cholesterol correlated with higher IL-6 and IFN- γ levels, while overweight patients exhibited a lower proportion of CAR-T cells after infusion. These findings suggest that specific metabolic abnormalities, particularly dyslipidemia, rather than BMI alone, may influence CAR-T-associated inflammatory toxicity. Adding to these findings, Faruqi et al. [119] retrospectively evaluated CAR-T outcomes across five phase 1 trials, with the primary analysis including 139 B-ALL CAR-T infusions. No significant associations were observed between BMI and complete remission, neurotoxicity, or overall survival. A small descriptive NHL cohort ($n=23$) showed a broadly similar pattern, although its limited size precludes firm conclusions regarding BMI-related efficacy or toxicity. Nevertheless, remission and survival outcomes were comparable across BMI categories, indicating that CAR-T therapy may retain efficacy in obese and high-risk populations. These heterogeneous findings also highlight the limitations of BMI as a surrogate of metabolic health and support prospective evaluation of body composition and metabolic parameters alongside BMI. Overall, the impact of obesity on therapeutic response remains incompletely understood and should be interpreted cautiously, particularly in the absence of prospective studies incorporating detailed body composition and metabolic profiling. Collectively, these studies suggest that obesity and its metabolic sequelae may modulate both the efficacy and toxicity of CAR-T therapy, although the available evidence remains limited and heterogeneous, with partly conflicting findings across studies. Future studies should also determine whether modifiable metabolic abnormalities represent clinically actionable determinants of CAR-T toxicity or efficacy before specific metabolic interventions can be recommended.

Conclusions

Obesity is increasingly recognized as an important immunometabolic condition that may influence lymphoma development, disease biology, and therapeutic response through a complex interplay of inflammatory, endocrine, and metabolic mechanisms. Experimental and epidemiological evidence consistently supports associations between excess adiposity and increased risk of several lymphoma subtypes, particularly diffuse large B-cell lymphoma and follicular lymphoma. Mechanistically, chronic inflammation, adipokine imbalance, and activation of signaling pathways such as JAK/STAT3 and PI3K/AKT/mTOR may contribute to immune dysregulation, lymphoma cell survival, and remodeling of the tumor microenvironment [56, 156, 157]. However, many of these mechanisms have been primarily derived from preclinical or associative studies and still require prospective clinical validation. The clinical impact of obesity in lymphoma remains complex and, in some settings, paradoxical. Although obesity is generally associated with increased lymphoma incidence, several retrospective studies have reported comparable or even improved outcomes in overweight or mildly obese patients receiving standard chemoimmunotherapy [31, 36]. These observations may reflect differences in pharmacokinetics, treatment tolerance, nutritional reserve, or limitations inherent to BMI-based analyses, including reverse causality and selection bias. Importantly, BMI alone does not adequately capture body composition, visceral adiposity, metabolic dysfunction, or sarcopenic obesity, all of which may differentially influence prognosis and treatment response. Therefore, the so-called “obesity paradox” should be interpreted cautiously and not generalized across lymphoma subtypes or therapeutic settings. Emerging immunotherapies further highlight the relevance of metabolic and inflammatory status in lymphoma management. Preliminary evidence suggests that obesity-associated metabolic and inflammatory alterations may influence CAR-T-cell function and inflammatory toxicity [117, 204]. Nevertheless, available clinical data remain limited and sometimes conflicting, emphasizing the need for larger prospective studies integrating metabolic biomarkers, imaging-based body composition assessment, and longitudinal immune profiling. Such approaches may help clarify whether metabolic interventions could improve treatment efficacy or reduce toxicity in selected patients. Overall, current evidence supports the concept that obesity represents more than a simple comorbidity in lymphoma and may contribute to disease heterogeneity through systemic

immunometabolic alterations. Future research should move beyond conventional BMI classification and focus on integrated metabolic characterization, including visceral adiposity, sarcopenia, inflammatory mediators, and metabolic fitness [41]. A more comprehensive understanding of these interactions may help refine prognostic stratification and support the development of personalized therapeutic strategies, although their clinical applicability will require prospective validation in well-designed translational and clinical studies.

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Data availability No new data were generated or analyzed in support of this research.

Declarations

Ethical approval Not applicable.

Competing interests The authors declare no conflict of interest.

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