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CD3, CD15, and CD30: An Integrated Immunohistochemical Panel for the Diagnosis of Hodgkin Lymphoma and Its Mimics: A Narrative Review

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Abstract

Classic Hodgkin lymphoma (cHL) shares overlapping histologic features with several morphologic mimics, most notably anaplastic large cell lymphoma (ALCL), peripheral T-cell lymphoma (PTCL), and several large B-cell lymphomas. Immunohistochemistry is therefore indispensable for accurate diagnosis. Three markers form the practical core of this process. CD3 confirms or excludes T-cell lineage, CD15 supports the classic Hodgkin and Reed-Sternberg (HRS) cell phenotype, and CD30 is the most sensitive marker of both HRS cells and ALCL cells. Each marker has recognized limitations when used alone. CD15 has imperfect sensitivity and specificity, CD3 can be aberrantly expressed in B-cell neoplasms and lost in ALCL, and CD30 can show low or discordant expression. Interpreted together, the three markers generate a characteristic immunophenotypic signature. This signature helps distinguish cHL from nodular lymphocyte-predominant Hodgkin lymphoma, ALCL, PTCL, T-cell/histiocyte-rich large B-cell lymphoma, mediastinal gray zone lymphoma, and reactive processes. This narrative review summarizes the biology, diagnostic performance, and combined interpretation of CD3, CD15, and CD30 within the 2022 World Health Organization and International Consensus classifications. It presents a pattern-based comparison and a stepwise algorithm across major lymphoma subtypes. It also discusses diagnostic pitfalls, the limits of the available evidence, and the prognostic and therapeutic relevance of the panel, including CD30-directed brentuximab vedotin.

Categories: Pathology, Oncology, Allergy/Immunology
Keywords: anaplastic large cell lymphoma, cd15, cd3, cd30, hodgkin lymphoma, immunohistochemistry

Introduction And Background

Classic Hodgkin lymphoma (cHL) is a B-cell lymphoma that typically affects young adults, with a second peak in older age. It is defined by Hodgkin and Reed-Sternberg (HRS) cells, which are large neoplastic cells, often binucleated or multinucleated with prominent nucleoli, that usually make up only a small minority of the cells in the affected tissue [1]. They lie within an inflammatory background of non-neoplastic lymphocytes, histiocytes, eosinophils, and plasma cells. However, HRS-like cells also occur in other lymphomas that can therefore imitate, or mimic, cHL: anaplastic large cell lymphoma (ALCL), a subset of peripheral T-cell lymphomas (PTCL), and several large B-cell lymphomas. Morphology alone is thus insufficient for reliable subclassification. Immunohistochemistry, which uses labeled antibodies to show which proteins a cell expresses in a tissue section, can separate lesions that look alike because each entity has a characteristic protein profile. Contemporary practice relies on a small, targeted panel, with CD3, CD15, and CD30 forming its practical core alongside CD20 and PAX5 [2].

This diagnostic work-up now takes place within two current classification systems: the fifth edition of the World Health Organization Classification of Haematolymphoid Tumours (WHO-HAEM5) and the International Consensus Classification (ICC), both published in 2022 [3,4]. Both systems retain cHL as a distinct entity defined by its HRS-cell immunophenotype. They differ in the nomenclature of nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), which the ICC renamed nodular lymphocyte-predominant B-cell lymphoma to reflect its B-cell nature and its distinct biology [4]. This review uses the term NLPHL, as retained in WHO-HAEM5 [3].

Each of the three markers addresses a distinct diagnostic question. CD3 is a component of the T-cell receptor complex and marks T-cell lineage; in cHL, it is absent from HRS cells but strongly expressed by the numerous reactive T cells that surround them. CD15 is a carbohydrate antigen normally expressed by granulocytes; it is aberrantly expressed by HRS cells in most, but not all, cases, while the background granulocytes are also positive. CD30 is an activation-associated receptor of the tumor necrosis factor receptor superfamily that is expressed by only occasional activated lymphocytes (immunoblasts) in reactive tissue but strongly and uniformly by HRS cells and ALCL cells. Correct interpretation therefore depends on reading each marker on the large neoplastic cells rather than on the reactive background.

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None of the three markers is fully sensitive or specific. CD15 is negative in a substantial minority of cHLs, CD30 is shared by ALCL and by subsets of other T- and B-cell lymphomas, and CD3 can be lost in ALCL. The three-marker pattern alone cannot always establish the lineage of the neoplastic cells, which is why complementary markers such as PAX5 and CD20 are needed in challenging cases to confirm B-cell origin and to separate cHL from large B-cell lymphoma mimics [2]. Accurate distinction matters because these lymphomas are treated with different regimens and have different outcomes, and because CD30 status affects eligibility for the CD30-directed agent brentuximab vedotin. The objectives of this review are to summarize the biology and diagnostic performance of CD3, CD15, and CD30, to present their combined interpretation as a pattern-based comparison and a stepwise algorithm across cHL and its principal mimics, and to outline the associated pitfalls and the prognostic and therapeutic implications. The review centers on these three markers because their combined pattern separates cHL from its T-cell and null-phenotype mimics and because they carry the main interpretive pitfalls; CD20 and PAX5, which chiefly confirm B-cell lineage, are discussed as complementary markers. Whereas the existing literature largely addresses these markers individually, this review integrates them into a single practical framework aligned with the 2022 classifications.

Review

Methods

This narrative review was based on a targeted, non-systematic literature search of PubMed/MEDLINE, Scopus, and Google Scholar, supplemented by hand-searching the reference lists of retrieved articles. The search covered the period from 1982, the year of the original description of the Ki-1 (CD30) antigen, to August 2026, in order to capture both foundational immunophenotyping studies and the most recent classifications, consensus statements, and reviews on Hodgkin lymphoma and its mimics. The representative PubMed search string was (“CD3” OR “CD15” OR “CD30”) AND (“Hodgkin lymphoma” OR “Reed-Sternberg” OR “anaplastic large cell lymphoma” OR “peripheral T-cell lymphoma” OR “gray zone lymphoma”) AND (“immunohistochemistry” OR “immunohistochemistry panel” OR “immunophenotype”). Equivalent terms were adapted to the syntax of Scopus and Google Scholar.

Articles were considered for inclusion if they were published in English, reported original data or a structured review on the biology, diagnostic performance, or combined interpretation of CD3, CD15, or CD30 in lymphoid neoplasms, and were accessible as full text. Classification documents and expert-consensus statements on immunohistochemical panel selection were included, given their direct relevance to routine diagnostic practice. Studies were excluded if they addressed these markers exclusively outside the lymphoma context or were available only as conference abstracts.

Study selection was performed in two stages. Titles and abstracts were first screened for relevance by the authors, and potentially relevant articles were then assessed in full text against the eligibility criteria above; any uncertainty regarding inclusion was resolved by discussion among the authors. Priority was given to classification documents, expert-consensus statements, foundational immunophenotyping studies, large clinicopathological series, and pivotal clinical trials. A total of 33 publications were included in the final review: two classification documents, one expert-consensus statement, 15 original studies and case series, 10 review articles, and five clinical trials. Because the search was targeted rather than exhaustive, the number of records screened was not formally recorded, and a PRISMA flow diagram was not produced. Because this is a narrative rather than a systematic review, no formal risk-of-bias assessment or meta-analytic synthesis was performed. Where studies reported differing estimates, the range is given, and greater weight was placed on classification documents, expert-consensus statements, and larger series; statements that rest on single or older studies are identified as such in the text. From each included publication, the entity studied, the markers assessed, the sample size where applicable, and the key findings were extracted and summarized narratively; no standardized data-extraction form was used. The manuscript was checked against the items of the Scale for the Assessment of Narrative Review Articles (SANRA). The literature was organized thematically around the biology of each marker, their combined diagnostic pattern across major entities, recognized pitfalls, and prognostic and therapeutic implications.

Rationale for a three-marker panel

Current expert-consensus recommendations propose a core panel of CD3, CD20, CD15, CD30, and PAX5 for the primary immunohistochemical identification of cHL, with additional markers reserved for cases showing pattern discordance or a differential diagnosis extending to large B-cell lymphoma variants or ALCL [2]. Within this panel, CD3, CD15, and CD30 play complementary roles. CD3 confirms or excludes T-cell lineage, both to recognize reactive T-cell-rich backgrounds and PTCL, and to identify ALCL cases that retain T-cell marker expression. CD15 supports the classic HRS-cell phenotype, although with acknowledged sensitivity limitations. CD30 is the most sensitive and reproducible marker of both HRS cells and ALCL cells, and it also serves as the direct biomarker for CD30-directed antibody-drug conjugate therapy. Because none of these markers is both fully sensitive and fully specific, their combined interpretation is what allows a confident distinction between cHL, NLPHL, ALCL, PTCL, and reactive or other neoplastic mimics.

CD30: The anchor marker of the panel

CD30 was first identified in 1982 as the Ki-1 antigen, recognized by a monoclonal antibody raised against a Hodgkin lymphoma-derived cell line [5], and was later cloned and shown to be a member of the tumor necrosis factor receptor superfamily (TNFRSF8) [6]. Under normal conditions, it is expressed only weakly and focally on a small subset of activated T and B lymphocytes, but it is strongly and uniformly overexpressed on HRS cells [7] and ALCL cells [7,8]. This restricted normal distribution, combined with strong expression on both target entities, makes CD30 the anchor marker of the panel: a strongly CD30-positive population of large atypical cells is the starting point from which the CD3 and CD15 results are used to distinguish cHL from ALCL and other mimics [7].

Conventional immunohistochemical protocols may under-detect low levels of CD30 expression. A 2024 study using a staining protocol optimized for low-expression detection and an Allred-like scoring system found that 10% of cHL cases had low CD30 scores and 3% were CD30-negative [9]. CD30 negativity therefore does not absolutely exclude the diagnosis, and low-expression-sensitive protocols may be warranted in borderline cases.

CD15: Historical role and sensitivity limitations

CD15, a carbohydrate epitope also known as Lewis X or SSEA-1, has been used since the 1980s, together with CD30, to support the diagnosis of cHL. HRS cells typically show a characteristic membranous and paranuclear (Golgi-pattern) staining [10,11]. A 1987 review of the published literature, encompassing 571 cases of Hodgkin disease and 386 cases of non-Hodgkin lymphoma, found that CD15 sensitivity was 80% overall (91% when lymphocyte-predominant cases were excluded), whereas specificity was only about 81%, since nearly one in five non-Hodgkin lymphomas also showed CD15 positivity [10]. Large clinicopathological series have since confirmed that a substantial minority of cHL cases are CD15-negative [12].

Recent comprehensive reviews describe CD15 positivity in roughly 75% of cHL cases, at least in a fraction of HRS cells, and note that its absence does not exclude the diagnosis when CD30 and PAX5 findings are supportive [11]. Conversely, CD15 expression is not restricted to HRS cells: a subset of CD30-positive PTCL co-expresses CD15 and can closely mimic cHL [13]. CD15 therefore functions best not as a stand-alone diagnostic marker but as a supportive, pattern-confirming component of the panel.

CD3: The lineage-exclusion marker and its pitfalls

CD3 is the most consistently expressed pan-T-cell marker and, within this panel, serves primarily to exclude T-cell lineage in HRS cells, which are typically CD3-negative, while confirming T-cell lineage in PTCL and reactive T-cell-rich backgrounds [14]. A modern framework for the diagnosis of T- and NK-cell lymphomas emphasizes that demonstration of T-cell markers is required to distinguish these entities from CD30-positive mimics, notably cHL [15]. The same framework cautions that some ALCL cases show a "null" phenotype, lacking T-cell markers despite their T-cell origin [15]. CD3 in particular is negative in a large proportion of ALK-positive ALCL [16], so CD3 negativity alone cannot exclude ALCL.

Conversely, CD3 positivity is not restricted to T-cell neoplasms. Rare but well-documented B-cell lymphomas, including plasmablastic neoplasms and Epstein-Barr virus (EBV)-negative diffuse large B-cell lymphoma (DLBCL), have shown aberrant CD3 expression, which can create a diagnostic pitfall if CD3 positivity is interpreted without confirmatory B-lineage markers such as PAX5 or CD79a [17,18]. These exceptions reinforce why CD3 functions best as one component of an integrated panel rather than as a definitive, stand-alone lineage marker.

Integrated diagnostic algorithm

Table *1* summarizes the combined immunophenotypic pattern generated by CD3, CD15, and CD30 across the principal entities in the differential diagnosis of Hodgkin lymphoma. In practice, large atypical lymphoid cells are first assessed for CD30, since strong uniform positivity is the most sensitive starting point for both cHL and ALCL. The CD15 and CD3 results are then used together to separate these entities and to flag cases requiring additional markers, such as PAX5, CD20, ALK, epithelial membrane antigen (EMA), and EBV-encoded RNA (EBER), when the pattern is discordant or incomplete. Weak nuclear PAX5 expression in HRS cells is particularly useful, as it confirms their B-cell origin despite the frequent loss of other B-cell markers [19].

Entity	CD3 (neoplastic cells)	CD15 (neoplastic cells)	CD30 (neoplastic cells)	Reactive background	Typical additional findings
Classic Hodgkin lymphoma (HRS cells)	Negative	Positive in ~75%, often in only a fraction of cells (membranous and Golgi)	Strong, uniform (membranous and Golgi); low or negative in a minority	Numerous CD3+ T cells, often rosetting around HRS cells; CD15+ granulocytes; occasional CD30+ immunoblasts	PAX5 weak positive; CD20 negative or variable; CD45 negative
NLPHL (LP cells)	Negative	Negative	Negative	CD3+ T cells rosetting around LP cells within small B-cell nodules; scattered CD30+ immunoblasts	CD20 strong positive; OCT-2 positive
T-cell/histiocyte-rich large B-cell lymphoma	Negative	Negative	Negative	Predominantly CD3+ T cells and histiocytes; few small B cells	CD20 positive; no small B-cell nodules
ALK+/ALK− ALCL	Often negative (null phenotype possible)	Usually negative	Strong, uniform in all tumor cells (membranous and Golgi)	Variable; small CD3+ reactive T cells	ALK positive or negative; EMA often positive
Peripheral T-cell lymphoma, NOS	Usually positive; may be weak or lost	Usually negative (subset positive)	Variable, focal, in a proportion of cells	Reactive CD3+ T cells admixed with and difficult to separate from the neoplastic cells	Other pan-T-cell markers positive, with frequent antigen loss
Mediastinal gray zone lymphoma	Negative	Variable	Often positive	CD3+ T cells; inflammatory background usually sparser than in cHL	CD20 often strong positive; transitional morphology
EBV-positive large B-cell lymphoma	Negative	Occasionally positive	Often positive	CD3+ T-cell- and histiocyte-rich	CD20 positive; EBER positive
DLBCL (CD30-positive subset)	Negative	Negative	Variable, focal	Variable numbers of CD3+ reactive T cells	CD20 positive; high Ki-67
Reactive paracortical hyperplasia	No neoplastic cells	No neoplastic cells	No neoplastic cells	Predominant CD3+ paracortical T cells; scattered CD30+, CD15− immunoblasts	Polytypic; no HRS cells

TABLE 1: CD3, CD15, and CD30 expression in neoplastic cells and in the reactive background across classic Hodgkin lymphoma and its principal differential diagnoses

Sources by row: classic Hodgkin lymphoma [2,7,9,11,19]; NLPHL and T-cell/histiocyte-rich large B-cell lymphoma [2-4,20]; ALCL [8,15,16]; peripheral T-cell lymphoma, NOS [13,15]; mediastinal gray zone lymphoma [21]; EBV-positive large B-cell lymphoma [22]; CD30-positive DLBCL and reactive hyperplasia [2,7].

ALCL: anaplastic large cell lymphoma; cHL: classic Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; EBER: Epstein-Barr virus-encoded RNA; EBV: Epstein-Barr virus; EMA: epithelial membrane antigen; HRS: Hodgkin and Reed-Sternberg; LP: lymphocyte-predominant; NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma; NOS: not otherwise specified.

This approach can be summarized as a stepwise algorithm. Step 1 assesses CD30 on the large atypical cells and separates three groups: strong uniform expression, variable or focal expression, and absence of expression. In step 2, lineage is established with PAX5 and CD3, supplemented by CD20. In step 3, complementary markers resolve each group. Strongly CD30-positive cells that are PAX5-positive and CD3-negative proceed to CD15, CD20, CD45, and EBER, which distinguish cHL from mediastinal gray zone lymphoma and EBV-positive large B-cell lymphoma, whereas PAX5-negative cells proceed to ALK, EMA, and additional T-cell markers to identify ALK-positive and ALK-negative ALCL. Variable or focal CD30 expression

directs attention to PTCL when CD3 is positive, and to CD30-positive DLBCL or EBV-positive large B-cell lymphoma when CD20 and PAX5 are strongly positive, with EBER separating the latter two. When the large cells are CD30-negative, CD20 and the architecture distinguish NLPHL from T-cell/histiocyte-rich large B-cell lymphoma and from reactive hyperplasia. The algorithm is a guide to interpretation rather than a substitute for morphology.

Diagnostic pitfalls and discordant results

Each marker in this panel carries recognized pitfalls that argue against single-marker interpretation. CD30 can be falsely low or negative without dedicated low-expression-sensitive staining protocols [9], and responses to brentuximab vedotin have been described in patients with low or undetectable CD30 expression by routine immunohistochemistry [7]. CD15 has imperfect sensitivity (75-80% in some series) and imperfect specificity, with a meaningful minority of non-Hodgkin lymphomas, including CD30-positive PTCL, also showing positivity [10,13]. CD3 can be falsely negative in ALCL with a null phenotype and falsely positive in rare aberrant B-cell neoplasms, so in either direction it cannot be relied upon without confirmatory markers [15,17,18].

Three B-cell entities deserve particular attention because the CD3/CD15/CD30 pattern alone may not resolve them. First, the diffuse, T-cell-rich variant patterns of NLPHL closely resemble T-cell/histiocyte-rich large B-cell lymphoma (THRLBCL): both show scattered large CD30-negative, CD15-negative B cells in a CD3-positive T-cell-rich background, and recognition of the NLPHL variants depends on residual follicular dendritic meshworks and small B-cell nodules [20]. Second, mediastinal gray zone lymphoma shows features intermediate between cHL and primary mediastinal large B-cell lymphoma, often with CD30 and variable CD15 expression together with preserved, strong B-cell programme markers such as CD20 [21]. Third, EBV-positive large B-cell lymphoma, as characterized in a series of young patients, can contain HRS-like cells that express CD30 and occasionally CD15, so EBER in situ hybridization and a full B-cell panel are needed [22].

A further source of error is failure to separate staining of the neoplastic cells from that of the reactive background. All three markers should be read on the large atypical cells only. In cHL, the abundant CD3-positive T cells that surround and often rosette HRS cells can simulate membranous CD3 positivity of the tumor cells; CD15-positive granulocytes serve as an internal positive control but must not be counted as tumor-cell staining, and scattered CD30-positive reactive immunoblasts can be mistaken for HRS cells or, in NLPHL, for LP cells. Staining is also frequently heterogeneous: CD15 is often expressed in only a fraction of HRS cells [11], CD30 intensity varies between cells and cases [9], and CD30 in PTCL and DLBCL is typically focal rather than uniform. Finally, aberrant and overlapping immunophenotypes are common enough to be anticipated: CD30 and CD15 can be co-expressed in PTCL [13], CD3 can be lost in ALCL [15,16] or aberrantly gained in B-cell neoplasms [17,18], and gray zone and EBV-positive large B-cell lymphomas can reproduce part of the cHL pattern [21,22]. Table *1* therefore reports the expected staining of the neoplastic cells and of the reactive background separately.

Recent reviews illustrate how morphologic variants of cHL and deviations of HRS cells from the expected pattern of antigen expression complicate routine diagnosis [23], and how reactive conditions and other lymphoid neoplasms can imitate Hodgkin lymphoma and vice versa [24]. Table *2* summarizes the complementary markers that should be considered whenever the CD3/CD15/CD30 pattern is incomplete, discordant, or ambiguous.

Marker	Primary association	Diagnostic notes	Typical use
PAX5	B cells (nuclear; weak in HRS cells)	Weak nuclear staining in HRS cells, in contrast to strong staining in background small B cells (internal control); confirms the B-cell origin of HRS cells despite CD20 loss	cHL confirmation
CD20	B cells	Strong and uniform in NLPHL LP cells and gray zone lymphoma; variable, weak, or heterogeneous in HRS cells; background small B cells are strongly positive	cHL vs. NLPHL and gray zone lymphoma
ALK	Kinase fusion protein	Positive in ALK-positive ALCL only; prognostic subclassifier	ALCL subtyping
EMA	Epithelial membrane antigen	Frequently positive in ALCL	ALCL confirmation
EBER (in situ hybridization)	Epstein-Barr virus	Positive in the neoplastic cells in a subset of cHL and in EBV-positive large B-cell lymphoma; rare positive bystander small lymphocytes should not be over-interpreted	EBV-positive large B-cell lymphoma vs. cHL
CD79a	B cells, including plasma cells	Backup B-lineage marker when CD20/PAX5 are ambiguous	Aberrant CD3-positive B-cell pitfall
CD45 (LCA)	Leukocytes	Usually negative in HRS cells against a positive background of reactive lymphocytes; variable in ALCL	Supports the cHL phenotype

TABLE 2: Complementary immunohistochemical markers to resolve incomplete or discordant CD3/CD15/CD30 results

Sources by row: PAX5 [2,19]; CD20 [2,20,21]; ALK and EMA [8,16]; EBER [22]; CD79a [17,18]; CD45 [2,14].

ALCL: anaplastic large cell lymphoma; cHL: classic Hodgkin lymphoma; EBER: Epstein-Barr virus-encoded RNA; EBV: Epstein-Barr virus; EMA: epithelial membrane antigen; HRS: Hodgkin and Reed-Sternberg; LCA: leukocyte common antigen; LP: lymphocyte-predominant; NLPHL: nodular lymphocyte-predominant Hodgkin lymphoma.

Prognostic considerations

Among the three markers, CD15 has the most direct historical link to prognosis. In a large cohort of classic Hodgkin disease, lack of CD15 expression was an independent negative prognostic factor for both relapse and overall survival on multivariate analysis, alongside age, sex, histologic subtype, stage, and B symptoms [12]. This finding derives from a single retrospective cohort and requires confirmation in patients treated with contemporary regimens, so CD15 status should not at present be used for risk stratification. CD30 expression intensity, by contrast, has not been consistently linked to the natural disease course, and most prognostic research has instead examined whether expression level predicts response to CD30-directed therapy [9]. CD3 functions primarily as a lineage marker rather than a prognostic one, although unexpected positivity or negativity can indirectly affect prognosis by leading to diagnostic misclassification if not interpreted alongside CD15 and CD30 [15,17,18].

Therapeutic relevance

Of the three markers, only CD30 currently has a direct and validated therapeutic correlate. Brentuximab vedotin, an antibody-drug conjugate combining an anti-CD30 monoclonal antibody with monomethyl auristatin E, produced a 75% objective response rate, with 34% complete remissions, in a pivotal phase II study of relapsed or refractory cHL after autologous stem-cell transplantation [25]. It subsequently improved outcomes in combination with chemotherapy for previously untreated stage III or IV cHL [26] and for CD30-positive PTCL, including ALCL [27]. More recently, the phase III SWOG S1826 trial in newly diagnosed stage III or IV cHL showed longer progression-free survival and a better side-effect profile with nivolumab plus doxorubicin, vinblastine, and dacarbazine (AVD) than with brentuximab vedotin plus AVD [28]. The first-line role of brentuximab vedotin is therefore evolving, although CD30 remains central to diagnosis. Neither CD3 nor CD15 has an equivalent direct therapeutic role in current standard practice. A confirmed CD30-positive result therefore carries treatment-eligibility implications that a CD3 or CD15 result alone does not, reinforcing the importance of correctly establishing CD30 status even when the overall panel pattern is otherwise clear. CD30 positivity should nevertheless be regarded as a criterion for treatment eligibility rather than a validated quantitative predictor of benefit, since the observation that patients with low or undetectable expression can still respond rests on limited data [7].

Synthesis, research gaps, and future directions

Summary of Findings

Taken together, the reviewed literature supports a clear conclusion: no single marker among CD3, CD15, and CD30 is sufficient on its own to diagnose cHL reliably or to distinguish it from its principal mimics, but their combined interpretation generates a characteristic and clinically useful immunophenotypic signature, although the reproducibility and combined diagnostic accuracy of the three-marker panel have not yet been formally validated in prospective studies.

Limitations and Research Gaps

Several research gaps follow from this synthesis. Prospective, multi-institutional studies are needed to evaluate the combined diagnostic accuracy of the three-marker panel, rather than the performance of each marker in isolation, since much of the published data, including the classic CD15 analysis, predates the routine combined use of CD30 and PAX5. The relationship between panel pattern and treatment outcome also warrants study, given that CD30 status alone does not reliably predict response to CD30-directed therapy.

Regional data are also limited. A Sudanese cross-sectional study of 82 patients with palpable lymphadenopathy characterized lymphoma subtypes using an immunohistochemical panel that included CD3 alongside CD5, CD10, CD19, and CD20, and found a significant relationship between CD3 and lymphoma subtype [29]. Because this study did not evaluate CD15 or CD30, it provides only indirect support for the three-marker approach, and a single study cannot establish regional practice patterns. To our knowledge, and within the limits of a non-systematic search, published combined CD3/CD15/CD30 panel data from Saudi Arabia and the broader Middle East and North Africa are scarce, which represents an opportunity for local programmes to generate population-specific diagnostic and outcome data.

The evidence base has further limitations. The quantitative estimates of CD15 sensitivity and specificity derive from a 1987 literature review [10] and the prognostic data from a 1997 cohort [12]; both predate the routine combined use of CD30 and PAX5, and we identified no contemporary series of comparable size. On the therapeutic side, long-term follow-up of ECHELON-1 showed an overall survival advantage for brentuximab vedotin plus chemotherapy over standard chemotherapy [30], but PD-1 blockade is now reshaping first-line treatment [28], so the therapeutic weight of CD30 status continues to evolve. Several subtype-specific topics lie beyond the scope of a three-marker review but bear on interpretation: CD30 is expressed in approximately 14% of de novo DLBCL, where it identifies a subgroup with a more favorable outcome [31], and ALK-negative ALCL is genetically heterogeneous, with DUSP22 and TP63 rearrangements associated with markedly different outcomes [32]. Treatment guidelines and recent studies of gray zone lymphoma and PTCL were not reviewed systematically.

All quantitative figures cited in this review are descriptive values taken from individual studies or from earlier literature summaries; none is a pooled estimate. We report point estimates as published and refer readers to the original studies for measures of uncertainty. These figures are also subject to between-study heterogeneity: antibody clones, antigen retrieval and detection systems, thresholds for scoring positivity, and patient populations differ across studies and over time, which probably accounts for part of the variation in reported CD15 positivity (75-91%) and in the frequency of low or negative CD30 expression. The diagnostic accuracy of the combined three-marker panel has not been measured directly against a reference standard and should not be inferred from the performance of the individual markers.

Future Directions

Artificial intelligence applied to lymphoma histopathology shows promise for diagnosis and prognosis, although its biases and clinical utility remain to be established [33]. Combined with multiplexed immunohistochemistry, such tools may allow simultaneous, quantitative assessment of all three markers on a single slide, potentially improving the detection of low or heterogeneous expression.

Conclusions

CD3, CD15, and CD30 form a complementary diagnostic panel whose combined interpretation, rather than any single result, helps distinguish cHL from NLPHL, ALCL, PTCL, large B-cell lymphoma mimics, and reactive processes. The diagnostic roles of the individual markers and the efficacy of CD30-directed brentuximab vedotin are well established. By contrast, the reproducibility of the three markers as a combined panel has not been validated prospectively, the adverse prognostic significance of CD15 negativity rests mainly on a single retrospective cohort, and CD30 expression level is not a validated predictor of response to CD30-directed therapy. Within these limits, panel-based interpretation of CD3, CD15, and CD30, supported where necessary by PAX5, CD20, ALK, EMA, and EBER, remains a sound foundation for the diagnostic work-up of Hodgkin lymphoma and its morphologic mimics.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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