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REVIEW

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SARS-CoV-2-related immune dysregulation and biologically plausible pathways to lymphomagenesis: a PRISMA-ScR-based scoping review

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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related immune dysregulation has generated interest in diagnostic pathology because infection-related inflammation, long coronavirus disease (COVID)-related immune disturbance, and post-vaccination lymphoid reactions may overlap with lymphoid-biological mechanisms and complicate the distinction between reactive lymphoid proliferations and lymphoid neoplasia. *Aim*: This scoping review aimed to map biologically plausible pathways through which SARS-CoV-2-associated immune perturbation may intersect with lymphomagenesis-related mechanisms, emphasizing diagnostic implications rather than causality. *Materials and Methods*: This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR). *PubMed/MEDLINE*, *Scopus*, and *Web of Science* were searched from January 2020 to March 2026, with selected pre-2020 sources retained for mechanistic or diagnostic relevance. Sources were charted across mechanistic, immunological, virological, clinicopathological, and diagnostic domains. *Results*: After screening and eligibility assessment, 63 sources were retained for thematic synthesis. Evidence clustered around lymphoma-relevant but non-specific mechanisms, including inflammatory signaling, impaired immune surveillance, latent oncogenic viral reactivation, prolonged germinal-center activity with activation-induced cytidine deaminase (AID)-related genomic vulnerability, and lymphoid microenvironment remodeling. These mechanisms appear most relevant in predisposed hosts with chronic immune dysregulation, latent viral infection, defective deoxyribonucleic acid (DNA) repair, or occult abnormal lymphoid clones. Infection and vaccination are distinct contexts, because infection may produce broader immune disruption, whereas most post-vaccination nodal events are reactive and self-limited. *Conclusions*: Current evidence supports biological plausibility rather than a direct or generalizable causal relationship. The main diagnostic implication is careful clinicopathological correlation and distinction between reactive lymphoid proliferations and lymphoid neoplasia in post-COVID-19 and post-vaccination settings.

Keywords: SARS-CoV-2, COVID-19, lymphomagenesis, lymphoma, immune dysregulation, diagnostic pathology.

Introduction

Lymphomagenesis is a multistep process in which genetic and epigenetic alterations, disturbed apoptotic control, altered proliferative signaling, and progressive escape from immune surveillance interact with signals derived from the tissue microenvironment [1, 2]. This framework is particularly relevant in lymphoid tissues, where chronic antigenic stimulation, pathogen-associated immune activation, and persistent inflammatory signaling may lower the threshold for clonal persistence and malignant evolution in susceptible lymphoid populations [3, 4]. The close pathogenetic link between chronic microenvironmental inflammation and inflammation-associated lymphoid neoplasms, classically illustrated by mucosa-associated lymphoid tissue (MALT)-type extranodal marginal-zone lymphoma, provides a biological framework for asking whether newer forms of immune perturbation might, in selected contexts, intersect with similar pathways rather than acting as autonomous carcinogenic events [5].

Against this background, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a systemic immunological stressor, inducing acute inflammation, prolonged immune activation, perturbation of lymphocyte subsets, and features of immune exhaustion that may persist beyond the initial infection [6–8], while also intersecting with mechanisms already implicated in lymphoma biology, including dysregulated survival signaling, impaired immune surveillance, viral reactivation, and altered stromal crosstalk [9, 10].

Vaccination, however, must be considered separately from infection because, although messenger ribonucleic acid (mRNA)-based platforms are intentionally designed to generate strong adaptive immunity and persistent germinal-center responses [11–13], they do not reproduce the broader inflammatory and systemic immune-disruptive burden associated with severe coronavirus disease 2019 (COVID-19) [6–8, 14, 15], this distinction remaining essential to any balanced interpretation of the literature when biological plausibility is discussed without implying causation.

Available human data remain mixed and require cautious interpretation, Sara *et al.* [16] suggesting, in an ecological study, that COVID-19 and non-Hodgkin's lymphoma (NHL) may share a partially overlapping susceptibility-related background, Claaß *et al.* [17] finding no association between

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ipsilateral SARS-CoV-2 vaccination and malignant B-cell NHL, and Chen *et al.* [18] emphasizing that chronic immune dysregulation and autoimmune backgrounds can contribute to lymphoma development more broadly; taken together, these observations justify biological vigilance, yet fall well short of proving a causal relationship.

Aim

This scoping review examines whether SARS-CoV-2-associated immune perturbation may create, in selected biological contexts, potentially permissive conditions for lymphomagenesis, not by arguing for direct causation, but by mapping molecular, immunological, virological, clinicopathological, and diagnostic observations that intersect with pathways already implicated in lymphoma biology.

The review addressed the following questions: (*i*) which immune and microenvironmental mechanisms reported in the SARS-CoV-2 literature overlap with established pathways of lymphomagenesis; (*ii*) how infection, long COVID, and vaccination-related immune activation differ as biological contexts; and (*iii*) which findings are most relevant for diagnostic pathology, particularly for distinguishing reactive lymphoid proliferations from true lymphoid neoplasia and for guiding cautious clinicopathological interpretation in post-COVID-19 and post-vaccination settings.

Materials and Methods

Review design

This scoping review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) [19]. A scoping design was selected because the available literature is mechanistically heterogeneous and includes experimental, translational, clinical, imaging-based, virological, immunological, and pathology-oriented evidence. The purpose of the review was therefore to map concepts, identify biologically plausible mechanistic intersections, and clarify diagnostic implications rather than to estimate pooled effects or infer causality. No formal meta-analysis was planned or performed. No prospectively registered protocol was available for this review; however, the review question, population/problem, concept, and context (PCC) framework, eligibility criteria, evidence domains, and charting variables were defined before final thematic synthesis.

Conceptual framework

The review question was organized according to a PCC framework, allowing the biological substrate, the mechanistic focus, and the diagnostic setting to be separated before evidence charting. The operational definitions and rationale for each PCC component are summarized in Table 1.

Table 1 – ***Conceptual framework of the scoping review according to the PCC structure***

Framework element	Operational definition in this review	Reason for inclusion
Problem	Lymphoid tissues, lymphoid proliferations, reactive lymphadenopathy, and lymphoid neoplastic processes.	Defines the pathological substrate in which SARS-CoV-2-related immune perturbation may be interpreted.
Concept	Immune and microenvironmental mechanisms that may intersect with known pathways of lymphomagenesis.	Captures cytokine signaling, T-cell exhaustion, viral reactivation, germinal-center dysregulation, AID-related genomic injury, and stromal remodeling.
Context	COVID-19 infection, long COVID, vaccination-related immune activation, and diagnostic pathology settings.	Separates infection from vaccination and anchors the synthesis in clinicopathological interpretation rather than causal attribution.

AID: Activation-induced cytidine deaminase; COVID-19: Coronavirus disease 2019; PCC: Population/problem, concept, and context; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Information sources and search strategy

The literature search was performed in *PubMed/MEDLINE*, *Scopus*, and *Web of Science*, supplemented by manual screening of reference lists from relevant reviews, mechanistic articles, clinicopathological reports, and imaging studies. The final search was executed in March 2026. SARS-CoV-2-related evidence was searched from January 2020 to March 2026. Foundational pre-2020 sources were retained when they clarified established mechanisms of lymphomagenesis, immune surveillance, viral oncogenesis, germinal-center biology, activation-induced cytidine deaminase (AID)-related genomic injury, or lymphoid microenvironment remodeling. Older sources were not retained for historical completeness alone and were excluded when they did not provide non-redundant mechanistic, clinicopathological, or diagnostic information beyond that available in the more recent eligible literature.

The *PubMed*/*MEDLINE* search strategy was constructed around four thematic domains, operationalized through five search strings: SARS-CoV-2 infection and lymphoma, immune dysregulation and inflammatory signaling, latent oncogenic viral reactivation, and germinal-center or vaccination-related lymphoid reactions. The final *PubMed*/*MEDLINE* search strings were:

(*i*) ("SARS-CoV-2" OR "COVID-19" OR "long COVID") AND ("lymphoma" OR "lymphomagenesis" OR "lymphoid neoplasm" OR "B-cell lymphoma" OR "T-cell lymphoma");

(*ii*) ("SARS-CoV-2" OR "COVID-19" OR "long COVID") AND ("immune dysregulation" OR "inflammation" OR "cytokines" OR "T-cell exhaustion" OR "immune surveillance" OR "checkpoint");

(*iii*) ("COVID-19" OR "SARS-CoV-2") AND ("Epstein–Barr virus" OR "EBV" OR "KSHV" OR "HHV-8" OR "viral reactivation");

(*iv*) ("SARS-CoV-2 vaccination" OR "COVID-19 vaccination" OR "mRNA vaccine") AND ("lymphadenopathy" OR "lymphoma" OR "reactive lymphadenitis" OR "follicular hyperplasia");

(*v*) ("SARS-CoV-2" OR "COVID-19" OR "COVID-19 vaccination") AND ("germinal center" OR "germinal centre" OR "activation-induced cytidine deaminase" OR "AID" OR "somatic hypermutation" OR "class-switch recombination").

Equivalent combinations of keywords were adapted for *Scopus* and *Web of Science*. Searches were limited to

English-language biomedical publications. Article types considered eligible included original studies, translational studies, experimental studies, clinicopathological reports, case reports or case series, imaging studies, and selected reviews when they provided mechanistic or diagnostic information relevant to the PCC framework.

Eligibility criteria

Eligibility was determined according to the PCC framework and according to mechanistic or diagnostic relevance (Table 2). Sources were included when they contributed evidence regarding at least one of the following domains: inflammatory survival signaling, T-cell exhaustion or impaired immune surveillance, latent oncogenic viral reactivation, germinal-center dysregulation, AID-mediated genomic instability, host susceptibility, vaccine-associated lymphadenopathy, or lymphoid microenvironment remodeling. Sources based only on temporal association were included only when they provided sufficient clinicopathological, immunological, virological, or diagnostic context. Purely speculative opinion pieces, non-biomedical publications, duplicate records, inaccessible reports, and publications without usable mechanistic or diagnostic information were excluded.

Table 2 – ***Eligibility criteria applied during source selection***

Criteria	Included sources	Excluded sources
Research focus	Sources addressing SARS-CoV-2 infection, long COVID, vaccination-related lymphoid reactions, immune dysregulation, lymphoma biology, or diagnostic pathology.	Sources unrelated to lymphoid biology, lymphomagenesis, immune perturbation, or diagnostic lymphadenopathy.
Evidence type	Original studies, translational studies, clinicopathological reports, imaging studies, case reports/series, and selected reviews with mechanistic relevance.	Non-biomedical material, purely editorial opinions, and publications without substantive biological or diagnostic information.
Mechanistic relevance	Sources contributing information on inflammatory signaling, immune surveillance, viral latency/reactivation, germinal-center biology, genomic instability, or microenvironmental remodeling.	Temporal associations without interpretable biological, clinical, or pathology-relevant context.
Data usability	English-language biomedical literature with sufficient bibliographic detail and enough retrievable information for thematic charting.	Duplicate records, non-retrievable sources, and reports with insufficient data for evidence mapping.

COVID: Coronavirus disease; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Selection process and data charting

All records retrieved from database searches and supplementary screening were imported into a reference-management file and checked for duplicates. After duplicate removal, titles and abstracts were screened for relevance to the PCC framework. Potentially eligible reports were then assessed in full text. Screening was performed by the first author and discussed with the co-authors when uncertainty existed; the absence of fully independent duplicate screening was recorded as a methodological limitation. For each retained source, the following charting variables were extracted: first author, year of publication, publication type, exposure or biological context, mechanistic domain, lymphoid or pathology-relevant finding, diagnostic implication, and main interpretive limitation. Data charting was performed thematically rather than quantitatively because the review aimed to map mechanistic intersections and diagnostic implications rather than to calculate pooled estimates.

Critical appraisal of included sources

No formal critical appraisal or risk-of-bias assessment was performed, because the purpose of this scoping review was to map mechanistic, immunological, virological, clinicopathological, and diagnostic concepts across heterogeneous evidence sources rather than to estimate pooled effects, grade certainty of evidence, or generate practice recommendations based on comparative effect sizes. However, interpretive limitations related to source type, study design, indirectness, temporal association, case-report evidence, and lack of causal inference were recorded during data charting and considered during thematic synthesis.

Results

The study selection process is summarized in Figure 1. The screening process identified 267 records from database searches and supplementary reference screening, of which 197 were screened after removal of duplicates and other pre-screening exclusions. After title/abstract screening, report retrieval, and full-text eligibility assessment, 63 evidence sources were retained for thematic synthesis. The PRISMA-ScR reporting guideline [19] was cited as a methodological reference and was not counted among the 63 evidence sources retained for thematic synthesis. The included sources comprised mechanistic and translational studies, immunological studies, virological studies, lymphoma-biology reviews with direct mechanistic relevance, clinicopathological reports, imaging studies of vaccine-associated lymphadenopathy, and selected case reports or case series. Case reports were not interpreted as evidence of causality, but were retained when they illustrated diagnostic pitfalls, temporal associations requiring caution, or biologically plausible scenarios of unmasking or acceleration of pre-existing disease. The charted evidence was subsequently organized into a thematic evidence map, which synthesizes the principal mechanistic domains, main interpretive signals, and limitations of the retained literature. Because no formal source-level critical appraisal was performed, Table 3 reports thematic interpretive limitations rather than risk-of-bias judgments for individual sources.

Discussions

Biological basis of lymphomagenesis in the context of immune perturbation

Lymphomagenesis reflects the cumulative convergence of abnormalities that allow altered lymphoid clones to persist, expand, and evade normal control, with intrinsic lesions affecting proliferation, apoptosis, or differentiation interacting with extrinsic influences from the immune and stromal milieu, while chronic antigenic stimulation,

defective immune surveillance, persistent inflammatory signaling, and altered tissue architecture may all lower the threshold for malignant transformation in susceptible lymphoid populations [1, 2, 20–23].

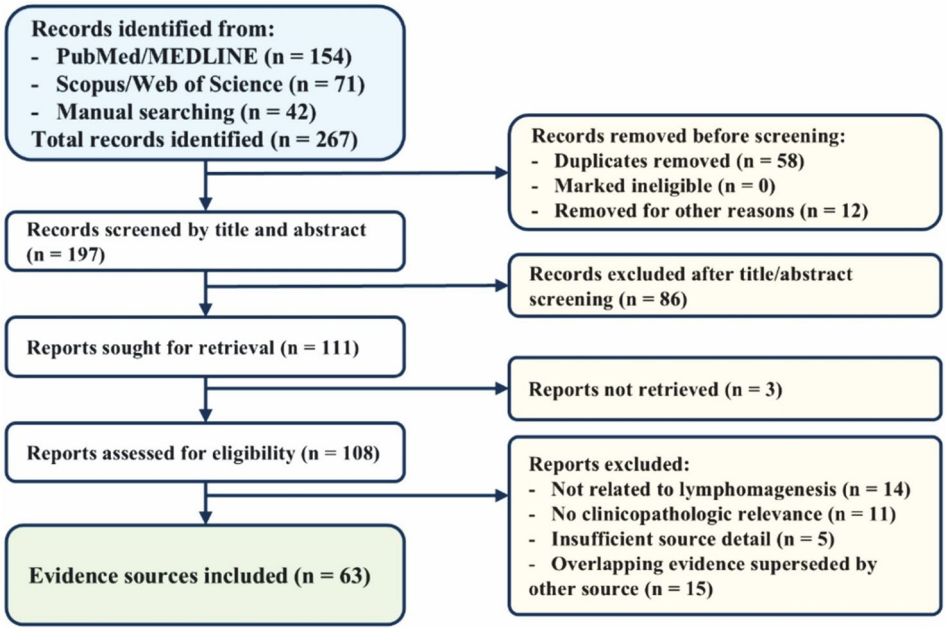

Figure 1 – ***PRISMA-ScR flow diagram for the scoping review. The diagram summarizes identification of records through PubMed/MEDLINE, Scopus, Web of Science, and supplementary reference screening, followed by duplicate removal, title/abstract screening, full-text eligibility assessment, and final inclusion of 63 evidence sources retained for thematic synthesis. The PRISMA-ScR reporting guideline was cited as a methodological reference and was not counted among the evidence sources retained for thematic synthesis. PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.***

Table 3 – ***Evidence map of the mechanistic domains included in the scoping review***

Mechanistic domain	Evidence base retained	Main synthesis signal	Principal limitation
Inflammatory survival signaling	Mechanistic, immunological, and lymphoma-biology studies.	IL-6/STAT3 and TNF-α/NF-κB pathways overlap with pro-survival programs already recognized in lymphoid neoplasia.	Supports plausibility, not proof of malignant transformation.
T-cell exhaustion and immune surveillance	Immunological and translational studies on chronic antigenic stimulation, checkpoint pathways, and cytotoxic dysfunction.	Reduced immune editing may allow abnormal lymphoid clones to persist in predisposed hosts.	Evidence is mostly indirect for SARS-CoV-2-associated lymphoma initiation.
Latent viral reactivation	Virological, clinicopathological, and immune-dysregulation studies focused mainly on EBV and KSHV/HHV-8.	Loss of viral latency control may re-engage oncogenic viral programs with established relevance in hematopathology.	Reactivation can be epiphenomenal and requires tissue-based confirmation.
Germinal-center dysregulation	Immunological and molecular studies on AID, SHM, CSR, and prolonged B-cell activation.	Sustained germinal-center activity may increase opportunities for genomic injury under permissive conditions.	Physiological immune activation and reactive follicular hyperplasia are not equivalent to neoplasia.
Microenvironment remodeling	Studies on stromal, vascular, hypoxic, myeloid, and regulatory immune compartments.	Disrupted lymphoid architecture may create a permissive niche for clonal persistence and immune escape.	Direct clinicopathological validation remains limited and heterogeneous.

AID: Activation-induced cytidine deaminase; CSR: Class switch recombination; EBV: Epstein–Barr virus; HHV-8: Human herpesvirus-8; IL-6: Interleukin-6; KSHV: Kaposi's sarcoma-associated herpesvirus; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B-cells; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SHM: Somatic hypermutation; STAT3: Signal transducer and activator of transcription 3; TNF-α: Tumor necrosis factor-alpha.

This principle is especially relevant in lymphoid tissues, where adaptive immunity already depends on inherently mutagenic processes, with germinal-center reactions requiring rapid proliferation, somatic hypermutation, class-switch recombination, and tightly regulated B-cell selection [24, 25], while elimination of dangerous clones depends on intact immune checkpoints, functional T-cell surveillance, and preserved stromal organization [26–29]; SARS-CoV-2-related immune dysregulation becomes relevant not because it proves a direct oncogenic pathway, but because persistent inflammatory activation, impaired immune control, viral reactivation, and prolonged lymphoid stimulation may, in selected individuals, act together rather than in isolation [1, 10, 30]. Figure 2 presents an integrated, hypothesis-generating overview of the biologically plausible mechanisms discussed in this review, emphasizing conditional intersections rather than a demonstrated causal sequence.

Cytokine-driven survival signaling and prolonged inflammatory activation

Severe SARS-CoV-2 infection is frequently accompanied by increased systemic levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), together with broader interferon (IFN)-related immune dysregulation [14, 15], creating a cytokine milieu with clear relevance to lymphoma

biology. IL-6 is especially important because it engages the IL-6 receptor alpha (IL-6Rα)/glycoprotein 130 (gp130) complex and activates Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling [31], thereby supporting lymphocyte survival, proliferation, and resistance to apoptosis through transcriptional upregulation of genes such as B-cell lymphoma 2 (*BCL2*), myeloid cell leukemia 1 (*MCL1*), and *MYC*, while STAT3-related survival signaling is already recognized in diffuse large B-cell lymphoma (DLBCL) biology [9].

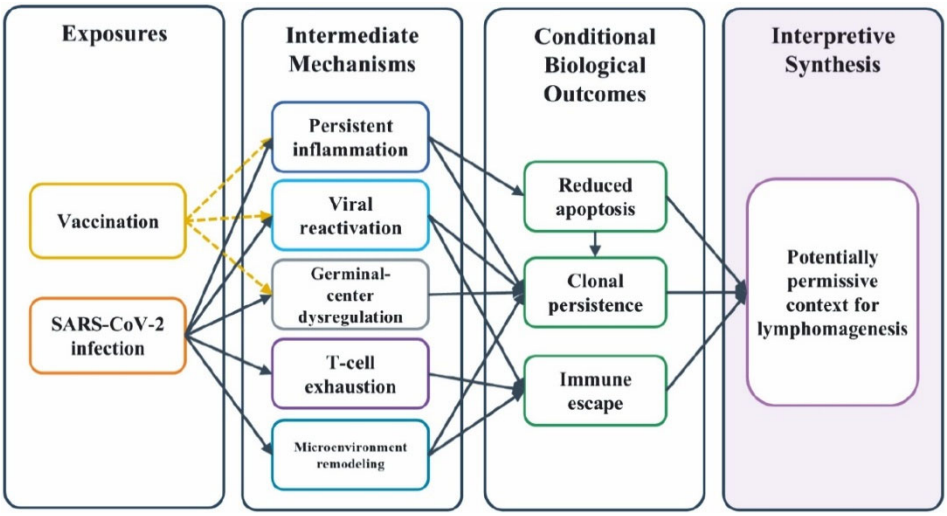

Figure 2 – ***Hypothesis-generating intersections between SARS-CoV-2-related immune perturbation and pathways relevant to lymphomagenesis. Schematic overview of biologically plausible, non-causal intersections through which severe or prolonged SARS-CoV-2-related immune dysregulation, and more limited immune stimulation related to vaccination, may overlap with mechanisms already implicated in lymphoma biology. The figure summarizes the principal intermediate domains examined in this review, including persistent inflammation, viral reactivation, germinal-center dysregulation, T-cell exhaustion, and microenvironment remodeling. The downstream elements, including reduced apoptosis, clonal persistence, and immune escape, should be interpreted as conditional processes that may become relevant mainly in predisposed hosts, rather than as direct or inevitable outcomes of infection or vaccination. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.***

TNF-α, acting through canonical nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) signaling [32], reinforces transcriptional programs centered on cell survival and resistance to cell death, and in aggressive lymphomas this pathway contributes to malignant cell survival and proliferation [9, 32]; for that reason, the inflammatory environment of severe or prolonged COVID-19 is biologically noteworthy, not because it demonstrates transformation, but because it transiently recapitulates signaling circuits already central to lymphoid neoplasia, potentially allowing abnormal clones in predisposed hosts to be less efficiently eliminated and more readily sustained [22, 23, 26].

The same caution must be maintained when vaccination is considered, because although B-cell-rich reactive or atypical lymphoid lesions have been described after vaccination [33, 34], Claaß *et al.* [17] did not identify an association between ipsilateral SARS-CoV-2 vaccination and malignant B-cell NHL, and Yamanaka *et al.* [35] emphasized the diagnostic importance of separating vaccine-related benign nodal enlargement from true malignant lymphadenopathy, the relevance of cytokine-driven signaling in the present review therefore lying in biological plausibility and diagnostic interpretation rather than in proof of a direct epidemiological effect.

T-cell exhaustion and impaired immune surveillance

Another candidate mechanism is erosion of effective T-cell-mediated immune surveillance, because during severe or prolonged immune stimulation the T-cell compartment may show loss of effector function, sustained expression of inhibitory receptors, metabolic dysfunction, and reduced capacity to eliminate abnormal or persistently stimulated cell populations [36–38], the exhausted phenotype being characterized by increased expression of programmed cell death-1 (PD-1), cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), lymphocyte-activation gene-3 (LAG-3), T-cell immunoglobulin (Ig) and mucin-domain containing-3 (TIM-3), and T-cell immunoreceptor with Ig and ITIM domains (TIGIT) together with broader transcriptional and metabolic reprogramming that progressively weakens cytotoxic competence [36–39].

Among the best-studied pathways is the PD-1/programmed cell death-ligand 1 (PD-L1) axis, persistent PD-1 expression on exhausted T-cells promoting continued interaction with PD-L1 and programmed cell death-ligand 2 (PD-L2) [40], ligands that may also be exploited within lymphoma cells and the tumor immune microenvironment [41, 42]; chronic antigenic stimulation also remodels transcriptional programs involved in T-cell fitness, including T-box transcription factor 21 (TBX21), eomesodermin (EOMES), thymocyte selection associated high mobility group box (TOX), and nuclear receptor subfamily 4A (NR4A)-family regulators [37], while additional checkpoint pathways may converge locally to weaken tumor control [42].

Even so, T-cell exhaustion does not by itself prove lymphoma initiation, its relevance in the present context being narrower, namely that it may create a more permissive immunological setting in which altered lymphoid clones that have already acquired oncogenic lesions survive longer

and continue to accumulate additional abnormalities [10, 37, 38]; post-vaccination case reports and benign reactive lymphadenopathy should therefore be interpreted cautiously [43, 44], since they do not justify any stronger causal inference.

Reactivation of latent oncogenic viruses

Another biologically relevant route involves reactivation of latent oncogenic viruses, particularly Epstein–Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV)/ human herpesvirus-8 (HHV-8), because in the setting of lymphocyte subset perturbation, sustained inflammatory activation, and cytokine imbalance [14, 15], control over latent viral reservoirs may weaken, thereby creating conditions in which reactivation may become more consequential for lymphoma biology [22, 45].

For EBV, the oncogenic relevance of reactivation lies in latent proteins that reproduce or exaggerate signaling programs involved in B-cell activation, survival, and immune escape, latent membrane protein 1 (LMP1) functioning as a constitutive mimic of cluster of differentiation 40 (CD40) signaling and activating NF-κB-dependent survival pathways [45], while latent membrane protein 2A (LMP2A) mimics tonic B-cell receptor signaling and helps sustain infected B-cells under conditions in which physiological selection would otherwise eliminate them [45]; a similar logic applies to KSHV/HHV-8, viral IL-6 being able to activate gp130 and initiate STAT3 signaling independently of the usual IL-6Rα requirement [31, 45], while viral BCL2 directly inhibits proapoptotic pathways [46].

What matters here is not the unsupported claim that SARS-CoV-2 acts as a direct transforming agent, but the narrower and biologically stronger argument that profound immune dysregulation may weaken viral latency control and permit re-engagement of oncogenic viral programs already well established in hematopathology [10, 22, 45, 46]; possible vaccine-related herpesvirus reactivation has also been reviewed [47], yet the evidence remains limited, especially for oncogenic herpesviruses, and should still be regarded as hypothesis-generating rather than demonstrative.

Germinal center dysregulation and genomic instability

The germinal center is the principal compartment in which B-cells undergo affinity maturation through somatic hypermutation and class-switch recombination, processes essential for humoral immunity yet intrinsically vulnerable to genomic error because they depend on AID [24, 25]; under physiological conditions these reactions are tightly regulated in space and time, but when germinal-center responses become unusually prolonged or insufficiently controlled, the same adaptive mechanisms that generate antibody diversity may also create conditions favorable to genomic instability and malignant transformation [48], particularly because germinal-center programs are central to the biology of several B-cell lymphomas [49].

Within the context of SARS-CoV-2 infection, and after immunization with highly immunogenic mRNA platforms, robust or sustained germinal-center activity has been described [12, 13, 50], raising the possibility that prolonged antigenic stimulation may extend the duration of B-cell proliferation and selection beyond usual physiological limits, while reactive post-vaccination lymphoid changes and lymphadenopathy, including follicular hyperplasia or prominent germinal-center reactions, have been documented [33, 34, 44], findings that underscore robust immune activation without, by themselves, indicating neoplastic transformation.

AID is central to this discussion because it initiates somatic hypermutation and drives class-switch recombination through double-stranded deoxyribonucleic acid (DNA) breaks [51], yet its activity is not perfectly restricted to Ig loci, off-target lesions affecting non-Ig genes and creating the substrate for oncogenic rearrangements when repair is incomplete or aberrant [51]. The significance of such events becomes greater when defective DNA-damage responses are superimposed on prolonged germinal-center stimulation [48], so that the evidence supports biological plausibility rather than causality, any proposed link being likely to remain conditional and most relevant in predisposed hosts with defective DNA repair, disordered immune regulation, latent oncogenic viral infection, or other cooperating abnormalities [10, 45, 48, 51, 52].

Microenvironmental remodeling and stromal alterations

Beyond direct effects on lymphoid cells, SARS-CoV-2-related immune dysregulation may also become relevant through potential disruption of the structural and functional integrity of the lymphoid microenvironment, which normally governs cellular trafficking, antigen presentation, clonal selection, and immune homeostasis [20, 21, 27–29]; under physiological conditions, secondary lymphoid organs are organized into highly specialized niches, with B-cell follicles supported by follicular dendritic cells, T-cell zones structured by fibroblastic reticular cells, and high endothelial venules regulating controlled lymphocyte entry and recirculation [27, 53, 54].

During severe COVID-19, this organization may plausibly be challenged by sustained inflammatory signaling and broader immune dysregulation [14, 15], follicular and stromal niches being particularly relevant because they maintain B-cell localization, clonal selection, and humoral immune function [27], while high endothelial venules and the vascular compartment may undergo structural and functional remodeling that alters antigen transport, lymphocyte trafficking, endothelial activation, angiogenic responses, and local oxygenation [53–55].

These alterations may be compounded by inflammatory myeloid infiltrates and by an immunosuppressive mediator profile involving interleukin-10 (IL-10) and prostaglandin E_2 (PGE_2) [56, 57], favoring regulatory T-cell expansion, suppressive myeloid cell activity, metabolic adaptation, and impaired cytotoxic control. Microenvironmental remodeling should therefore be interpreted not as an isolated cause of lymphoma initiation, but as a permissive and cooperating condition that may, in susceptible hosts, interact with chronic inflammatory signaling, impaired immune surveillance, viral reactivation, and germinal-center dysregulation to support persistence of altered lymphoid clones [20, 21, 28, 29, 55]. The structural and functional alterations affecting the germinal center and lymphoid microenvironment are summarized in Figure 3 as a conditional model of micro-environmental permissiveness, not as a proven sequence of malignant transformation.

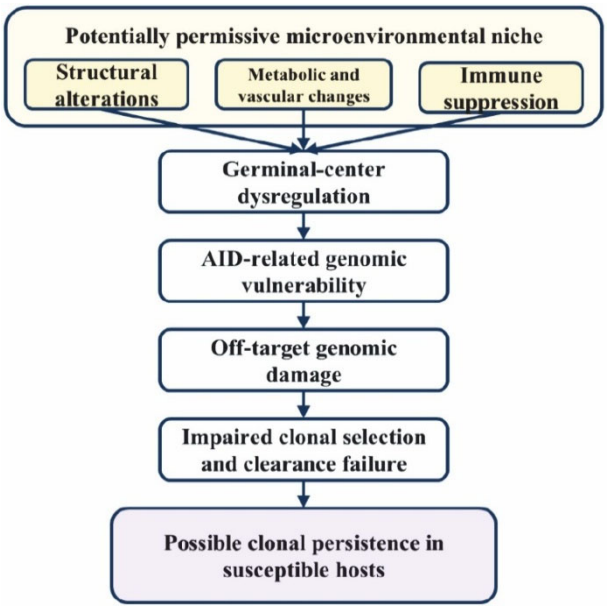

Figure 3 – ***Germinal-center dysregulation and lymphoid microenvironment remodeling in a potentially permissive lymphoid niche. Schematic representation of a conditional relationship between microenvironmental alterations and lymphoma-relevant biological processes. Structural alterations, metabolic and vascular changes, and immune suppression may interact with abnormal germinal-center dynamics, AID-mediated genomic vulnerability, and impaired clonal selection, potentially supporting clonal persistence in susceptible hosts. The model should be interpreted as hypothesis-generating and does not represent a proven sequence of malignant transformation. AID: Activation-induced cytidine deaminase.***

Host susceptibility and contributing cofactors

The mechanisms discussed so far are unlikely to carry the same biological significance across all individuals, their relevance depending heavily on host susceptibility, because persistent inflammatory signaling, immune exhaustion, viral reactivation, and microenvironmental disruption are far more likely to matter when they act upon an already vulnerable biological substrate [10, 26, 30]; host susceptibility therefore shifts the discussion away from a simple exposure-based model and toward a conditional framework in which immune perturbation acts as an accelerator, amplifier, or permissive cofactor rather than as an autonomous initiating event.

One layer of susceptibility consists of latent or subclinical clonal abnormalities that predate SARS-CoV-2 exposure but remain clinically silent until additional immune or cellular stressors alter the balance between clonal restraint and clonal persistence [2, 26, 58], while another involves latent oncogenic viral infection, EBV or KSHV introducing a preformed oncogenic potential that may become more consequential when immune control weakens in the setting of lymphocyte-subset perturbation, sustained inflammatory activation, and cytokine imbalance [14, 15, 22, 45, 46].

Autoimmune and chronic inflammatory conditions may provide a further predisposing background [3, 5, 10, 18], and genomic context matters as well, because abnormalities in DNA-damage response, repair, or checkpoint-related pathways may increase susceptibility to the consequences of prolonged germinal-center activity and AID-mediated mutagenesis [48, 51, 52, 59]; the same conditional logic applies to repeated or unusually prolonged antigenic stimulation, which remains hypothetical as a model, yet is still useful because it emphasizes that exposure alone is unlikely to be sufficient, whereas exposure superimposed on biological vulnerability may be more consequential.

Taken together, any plausible link between SARS-CoV-2-related immune dysregulation and lymphomagenesis is unlikely to be uniform, immediate, or population-wide, being more reasonably understood as a context-dependent process in which pre-existing clonal, genetic, immunological, or viral vulnerabilities determine whether transient immune perturbation resolves without consequence or instead interacts with established oncogenic programs to favor clonal persistence and malignant evolution [1, 10, 26, 45, 58, 59].

SARS-CoV-2 infection and vaccination as distinct immunological contexts

Although both SARS-CoV-2 infection and vaccination involve immune activation, they should not be treated as biologically equivalent contexts, severe infection being capable of inducing broad and dysregulated inflammation characterized by cytokine excess, lymphocyte-subset perturbation, IFN-related immune dysregulation, prolonged immune activation, and features of immune exhaustion [6–8, 14, 15], whereas vaccination is designed to generate a controlled and protective immune response and, although capable of eliciting strong germinal-center activity, generally remains self-limited and clinically beneficial [11–13, 50].

This distinction is central to the present review because infection may bring together several of the processes discussed throughout this manuscript, including persistent inflammatory signaling, impaired immune surveillance, latent viral reactivation, prolonged germinal-center stimulation, and remodeling of the lymphoid microenvironment [6–8, 10, 14, 15, 22, 45, 50], allowing them to overlap over a sustained interval, especially in predisposed hosts, while vaccination may induce strong but generally self-limited immune activation, transient lymph-node enlargement, and reactive histological changes without reproducing the broader systemic immunopathology of severe COVID-19 [11–13, 34, 35, 43, 44, 60].

Isolated reports have described lymphoid malignancies diagnosed shortly after vaccination, Khatri *et al.* [61] and Cavanna *et al.* [62] therefore keeping open the possibility that intense immune stimulation might, in rare circumstances, unmask, or less certainly accelerate, an already silent process; even so, the evidentiary weight of such reports remains limited because temporal proximity alone cannot distinguish true induction from incidental timing, diagnostic unveiling, or acceleration of pre-existing subclinical disease, and this caution is reinforced by the well-recognized phenomenon of vaccine-associated lymphadenopathy, imaging and clinico-pathological studies, including those by Samkowski *et al.* [43], Wilpert *et al.* [60], and Yamanaka *et al.* [35], indicating that most post-vaccination lymph-node enlargements are benign and reactive, although they may mimic malignancy and sometimes prompt invasive investigations, especially in oncological patients.

A balanced reading of the literature therefore supports two conclusions, namely that infection and vaccination may intersect with some overlapping immune pathways, particularly those related to antigen-driven activation and germinal-center responses [12, 13, 50, 63, 64], while the biological and clinical implications are not symmetrical, infection exposing the host to a broader and more disruptive immunological burden [6–8, 14, 15], whereas vaccination remains predominantly protective, with most investigated post-vaccination nodal events proving reactive rather than malignant [17, 34, 35, 43, 44, 60]. This distinction matters in diagnostic pathology because post-infectious and post-vaccination nodal alterations can create interpretive challenges, yet temporal association alone is never sufficient to support oncogenic attribution.

Diagnostic pathology implications

From a diagnostic pathology perspective, the reviewed evidence supports a structured and cautious approach to lymphoid lesions arising after SARS-CoV-2 infection or vaccination. The main interpretive problem is not the demonstration of a direct lymphomagenic effect, but the distinction between reactive lymphoid activation, atypical post-vaccination or post-infectious lymphoid changes, and true lymphoid neoplasia. This distinction is particularly important because vaccine-associated lymphadenopathy has repeatedly been reported as a diagnostic pitfall in oncological and hematopathological settings. Patil *et al.* [34] described atypical follicular hyperplasia with light-chain-restricted germinal centers after a COVID-19 booster, emphasizing that such lesions may mimic follicular lymphoma despite representing a reactive post-vaccination process. Yamanaka *et al.* [35], in a positron emission tomography (PET)/computed tomography (CT)-based study evaluating axillary lymphadenopathy after COVID-19 vaccination, showed that clinical-imaging parameters may help distinguish vaccine-associated axillary hypermetabolic lymphadenopathy from malignant hypermetabolic lymphadenopathy, particularly when nodal morphology, fatty hilum status, size, and clinical timing are interpreted together.

The same diagnostic caution is supported by imaging and cytopathology-oriented studies. Samkowski *et al.* [43] reviewed post-vaccination lymphadenopathy as an oncological diagnostic dilemma, noting that vaccine-related nodal enlargement can mimic metastatic or malignant disease on imaging and may prompt unnecessary invasive procedures if vaccination timing is not integrated into interpretation. Hagen *et al.* [44] reported fine-needle aspiration findings in COVID-19 vaccine-associated lymphadenopathy and emphasized that newly enlarged lymph nodes after recent vaccination should initially be considered reactive, while persistent enlargement should be re-evaluated after an appropriate interval and investigated further according to the clinical context. Wilpert *et al.* [60] similarly discussed vaccine-associated axillary lymphadenopathy as a recognized post-vaccination phenomenon that remains diagnostically relevant because it can overlap with malignant lymphadenopathy in oncological imaging and follow-up. Therefore, persistent nodal enlargement, architectural effacement, cytological atypia, aberrant immunophenotypes, light-chain restriction, or discordance between clinical timing and expected reactive evolution should prompt additional hematopathological work-up rather than immediate causal attribution to infection or vaccination [34, 35, 43, 44, 60].

The practical diagnostic implications of these observations are summarized in Table 4, which separates common reactive scenarios from features that should prompt additional hematopathological work-up. The table is intended as an interpretive framework rather than as a rigid diagnostic algorithm, because each case still requires integration of morphology, immunophenotype, molecular findings, virological data when indicated, imaging, and clinical evolution.

Table 4 – ***Diagnostic interpretation of lymphoid lesions in post-COVID-19 and post-vaccination settings***

Diagnostic setting	Findings usually supporting a reactive interpretation	Findings requiring additional hematopathological work-up	Practical diagnostic implication
Post-vaccination lymphadenopathy	▪ Recent ipsilateral vaccination; ▪ Transient nodal enlargement; ▪ Preserved or reactive architecture; ▪ Polymorphous lymphoid population; ▪ Follicular hyperplasia.	▪ Persistent or progressive enlargement; ▪ Architectural effacement; ▪ Monomorphic infiltrate; ▪ Aberrant immunophenotype; ▪ Light-chain restriction; ▪ Discordant clinical evolution.	Avoid immediate causal attribution; consider follow-up, core or excisional biopsy, immunohistochemistry, flow cytometry, or clonality testing when persistence or suspicious morphology is present.
Post-COVID-19 lymphoid enlargement	▪ Recent infection, inflammatory clinical context; ▪ Polymorphous reactive changes; ▪ Absence of clonal features.	▪ Persistent lymphadenopathy; ▪ Unexplained B symptoms; ▪ Cytological atypia; ▪ Extranodal involvement; ▪ Clonal B-cell or T-cell population.	Interpret in clinicopathological context; persistent or atypical lesions should be evaluated according to standard lymphoma diagnostic pathways.
Suspected viral contribution	▪ Clinical, serological, or tissue context suggesting viral reactivation; ▪ Mixed inflammatory background.	▪ EBV-positive atypical proliferation; ▪ HHV-8-associated morphology; ▪ Plasmablastic features; ▪ Immunodeficiency-associated patterns.	Use EBER *in situ* hybridization, HHV-8 testing when appropriate, and correlation with immune status and tissue morphology.
Equivocal follicular proliferation	▪ Preserved architecture; ▪ Reactive follicular hyperplasia; ▪ Polymorphous background; ▪ Reactive follicular dendritic-cell meshwork.	▪ Loss of germinal-center polarization; ▪ Abnormal BCL2 expression in germinal centers; ▪ Monomorphic follicular population; ▪ Clonal rearrangement.	Apply a focused follicular lymphoma work-up, including CD20, CD3, CD10, BCL6, BCL2, Ki-67, CD21/CD23, light chains, and molecular testing if needed.
Final interpretive endpoint	Self-limited reactive lymphoid activation.	True lymphoid neoplasia or possible unmasking of pre-existing subclinical disease.	Require convergent clinicopathological evidence; temporal proximity to infection or vaccination is insufficient by itself.

BCL: B-cell lymphoma; CD: Cluster of differentiation; COVID-19: Coronavirus disease 2019; EBER: Epstein–Barr encoding region; EBV: Epstein–Barr virus; HHV-8: Human herpesvirus-8.

Accordingly, the temporal relationship with SARS-CoV-2 infection or vaccination should be documented when clinically relevant, but it should not replace standard diagnostic reasoning. Reactive follicular hyperplasia, transient nodal enlargement, or increased metabolic activity on imaging may justify follow-up or tissue sampling in selected cases, especially in oncological patients, but they do not establish lymphoma in the absence of convergent morphological, immunophenotypic, molecular, virological, and clinical evidence [34, 35, 43, 60]. Conversely, persistent or progressive lymphadenopathy, tissue effacement, monomorphic cytology, aberrant antigen expression, light-chain restriction, EBV- or HHV-8-associated atypical proliferations, or demonstrable clonality should not be dismissed as reactive solely because infection or vaccination occurred recently [22, 34, 35, 45]. The diagnostic value of the present synthesis therefore lies in identifying situations in which additional work-up is justified while preventing overinterpretation of self-limited reactive lymphadenopathy as malignant transformation.

Future research directions

The principal challenge for future research is to move beyond biological plausibility and determine whether SARS-CoV-2-related immune perturbation leaves reproducible molecular, microenvironmental, or clinicopathological signatures in lymphoid neoplasia, Pjanova & Rafeeque [52] emphasizing, in the broader context of SARS-CoV-2-related immune dysregulation and cancer, that the key question is not whether immune dysregulation can be theorized, but whether it can be demonstrated in a measurable cancer-relevant context; future work should therefore combine longitudinal epidemiology with tissue-based immune profiling, viral studies, and genomic analysis rather than relying on isolated temporal associations [10, 45, 52, 59].

A first priority is well-powered longitudinal cohort studies with extended follow-up capturing lymphoma incidence, latency, host susceptibility, prior immune status, oncogenic viral carriage, and treatment-related confounders, whereas a second priority is comparative tissue-based investigation capable of determining whether the biological relevance hypothesized here becomes visible not merely as a temporal association, but as a reproducible pathological or molecular pattern distinguishing reactive lymphoid alterations from evolving neoplastic processes.

Single-cell and spatially resolved approaches are especially attractive because many of the mechanisms proposed in this review arise from altered interactions among malignant or premalignant lymphoid cells, exhausted T-cells, stromal compartments, and myeloid populations [20, 21, 27–29, 36–42, 53–57], so that such technologies may clarify whether post-infectious or post-vaccination lymphoid tissues display transient reactive programs or, in selected settings, more durable changes in checkpoint signaling, cytokine circuitry, stromal organization, or viral latency [22, 36–42, 45, 46, 53–57]; mechanistic experimental models are likewise needed in order to test whether prolonged exposure to SARS-CoV-2-related inflammatory mediators sustains survival of abnormal B-cell clones, weakens immune editing, or alters microenvironmental support in ways that are not evident from observational work alone [9, 31, 32].

A further line of inquiry should focus on viral latency and reactivation, prospective studies incorporating viral-load monitoring, serological status, and tissue-based detection of latent and lytic viral programs being particularly valuable for clarifying whether viral re-engagement functions merely as an epiphenomenon of immune stress or as a true cooperating mechanism [22, 45, 47]; post-vaccination observations, meanwhile, should be studied without alarmist assumptions and with careful separation among reactive lymphadenopathy, pseudolymphomatous lesions, unveiling of previously silent disease, and true biologically meaningful acceleration [17, 34, 35, 43, 60–62]. Ultimately, the most useful future research will be integrative rather than siloed, combining epidemiology, pathology, immunology, and molecular biology in order to determine whether the pathways reviewed here remain theoretical intersections or correspond to reproducible clinicopathological patterns.

Limitations

This scoping review has several limitations. First, no prospectively registered protocol was available, although the review question, PCC framework, eligibility criteria, evidence domains, and charting variables were defined before final thematic synthesis. Second, screening and source selection were performed by the first author and discussed with the co-authors when uncertainty existed, but fully independent duplicate screening was not performed. Third, no formal source-level critical appraisal or risk-of-bias assessment was conducted, because the purpose of the review was to map heterogeneous mechanistic, immunological, virological, clinicopathological, and diagnostic evidence rather than to estimate pooled effects or grade certainty of evidence.

Additional limitations arise from the nature of the available literature. The retained evidence includes mechanistic studies, translational studies, imaging studies, clinicopathological reports, selected reviews, and case reports or case series, which differ substantially in design, population, outcome definition, and inferential strength. Case reports and temporally associated observations were useful for identifying diagnostic pitfalls and hypothesis-generating scenarios, but they cannot establish causality. The review was also limited to English-language biomedical publications and may therefore have missed relevant non-English sources. Finally, because SARS-CoV-2-related immune dysregulation, long COVID, and post-vaccination lymphoid findings remain rapidly evolving fields, the synthesis should be interpreted as a structured map of current evidence rather than as a definitive causal model.

Conclusions

Taken together, this scoping review supports a conditional model of biological plausibility rather than a direct or generalizable causal relationship between SARS-CoV-2-related immune perturbation and lymphoma development. The pathways summarized in the review and figures should therefore be read as conceptual and hypothesis-generating models, not as sequential evidence that infection or vaccination independently induces lymphoma. In selected and predisposed hosts, persistent inflammatory signaling, impaired immune surveillance, latent viral reactivation, prolonged germinal-center activity, and microenvironmental remodeling may converge in ways that support clonal persistence or create

a potentially permissive biological context. The most defensible conclusion is therefore not that SARS-CoV-2 acts as an autonomous lymphomagenic trigger, but that severe or prolonged immune dysregulation may transiently recreate or intensify mechanisms already known to participate in lymphoma biology. From a diagnostic pathology perspective, this interpretation is relevant because reactive lymphoid alterations and true neoplastic processes may occasionally approach one another morphologically, immunophenotypically, clinically, or radiologically without being biologically equivalent. Careful clinicopathological correlation remains essential, and temporal association alone should not be used to support oncogenic attribution.

Authors' contribution

All authors have read and agreed to the published version of the manuscript.

Conflict of interests

The authors declare no conflict of interests.

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Data Availability

No new primary data were generated or analyzed in this study. All information synthesized in this scoping review was derived from previously published sources cited in the reference list. Data sharing is therefore not applicable to this article.

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