General notions on Non-Hodgkin Lymphoma and the role of Complement System

Nociones Generales Sobre el Linfoma no Hodgkin y el Papel del Sistema del Complemento

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RESUMEN

Introducción: Los linfomas son un grupo heterogéneo de neoplasias malignas originadas de la línea linfoide, que se caracterizan por un incremento en la proliferación y/o disminución de la apoptosis de los linfocitos. Estas patologías se clasifican principalmente en dos grupos: Linfoma de Hodgkin y Linfoma No Hodgkin (NHL). Estas neoplasias tienen un origen multifactorial, que involucra estados de inmunosupresión y estimulación constante del sistema inmune. Por lo cual es de interés conocer su correlación con el sistema inmune, especialmente al sistema del complemento que actúa como primera línea de defensa de la inmunidad innata. En este trabajo exploramos la interrelación entre los linfomas y cómo el sistema del complemento afecta la respuesta al tratamiento, su correlación con el pronóstico y con la progresión de la enfermedad. Objetivo: describir la relación entre el NHL y el sistema de complemento. Materiales y métodos: Esta revisión de literatura adopta un enfoque sistemático del NHL y el sistema del complemento. Siguiendo las normas PRISMA se utilizó exhaustivamente la base de datos PubMed. Los criterios de inclusión comprenden estudios centrados en el NHL, estudios sobre el sistema del complemento y artículos publicados en revistas revisadas

 https://doi.org/10.61865/j.cyfsld.2025.954t-vbhe

por pares entre 2020 y 2025 escritos en inglés, mientras que los criterios de exclusión abarcan estudios en idiomas distintos del inglés y estudios que no comprenden metaanálisis ni revisiones sistemáticas. De un total de 130,029 estudios potenciales, 58 fueron incluidos en la revisión. Conclusión: La participación del sistema del complemento en el NHL es compleja. Se necesitan más estudios para explorar el potencial del sistema del complemento para el tratamiento del NHL con el fin de mejorar la supervivencia global y la calidad de vida de estos pacientes

Palabras clave: neoplasias hematológicas, Linfoma No Hodgkin, Inmunidad, Sistema de Complemento, células linfoides.

ABSTRACT

Introduction: Lymphomas are a heterogeneous group of malignant neoplasms originated from the lymphoid lineage, characterized by an increase in proliferation and/or a decrease in apoptosis of lymphocytes. These diseases are classified into two main groups: Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL). These neoplasms have a multifactorial origin, involving states of immunosuppression and constant stimulation of the immune system. It is of interest to know the correlation with the immune system, especially the role of the complement system that acts as the first line defense of innate immunity. In this work we explore the interrelationship between lymphomas and how the complement system affects the treatment response, its correlation with the prognosis and the progression of the disease. Objective: Describe the relationship between NHL and the complement system. Methods: This literature review adopts a systematic approach to NHL and the complement system. Following PRISMA guidelines, we utilized PubMed database comprehensively. Inclusion criteria comprise studies focusing on NHL, studies about complement system and articles published in peer-reviewed journals between 2020 - 2025 written in English, while exclusion criteria encompass non-English language studies and non-meta-analysis nor systematic review studies. Of a total of 130,029 potential studies, 58 were included in the review. Conclusion: Complement system involvement in NHL is complex. Further research is needed to explore the potential of targeting the complement system for NHL treatment to improve the overall survival and quality of life of these patients.

Keywords: Hematologic neoplasms, Non-Hodgkin Lymphoma, Immunity, Complement System, lymphoid cells.

1. Introduction

Lymphomas are a heterogeneous group of malignant neoplasms originated from the lymphoid lineage, characterized by an increase in proliferation and/or a decrease in apoptosis of lymphocytes (Matsushita, 2010). These diseases can affect various tissues and are classified into two main groups: Hodgkin's lymphoma and non-Hodgkin's lymphoma (NHL, characterized by the absence of Reed – Stenberg cells). Between 80 – 95% of NHL cases derive from B lymphocytes, while the remainder originate from T lymphocytes and NK cells (Lewis, Lilly, & Jones, 2020; Shankland, Armitage, & Hancock, 2012).

These neoplasms have a multifactorial origin, involving states of immunosuppression, especially those related to T lymphocyte suppression, viral infections, and constant stimulation of the immune system (Garcia-Gutierrez, Delgado, & Leon, 2019; Salam et al., 2020; Shankland et al., 2012). It is of interest to know how this is going to affect the immune system, especially the role of the complement system that acts as the first line defense of the immune system. This system is known for its participation in the regulation of the proteolytic cascade, in pathogens opsonization, and also can interact with the adaptive immune system (Merle, Church, Fremeaux-Bacchi, & Roumenina, 2015; Ricklin, Hajishengallis, Yang, & Lambris, 2010).

2. Methodology and Materials

This literature review adopts a systematic approach to non-Hodgkin's lymphoma and the complement system. The review follows the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA). A comprehensive search strategy was implemented to identify relevant studies. Databases: PubMed.
Keywords: "Hematologic neoplasms", "Non-Hodgkin Lymphoma", "Immunity", "Complement System", "lymphoid cells". Search Filters: the search was restricted to peer- reviewed articles published between 2020 - 2025 written in English.
To ensure the quality and relevance of the studies included, the following criteria were applied. Inclusion criteria: studies focusing on non-Hodgkin's lymphoma, studies about complement system and articles published in peer- reviewed journals. Exclusion criteria: non- English language studies.
Data extraction and analysis: data were systematically extracted using a standardized data extraction form, a thematic analysis was conducted to identify non-Hodgkin lymphoma and complement system, clinical characteristics, diagnosis, staging and treatment.
Ethical considerations: as this study is a literature review, there was no new data collected, and therefore, ethical approval was not required. The review process was transparent, with detailed reporting of inclusion and exclusion criteria to maintain rigor.

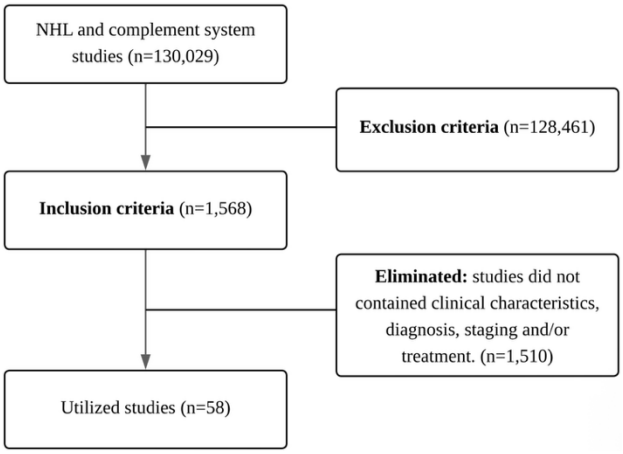

Figure 1. Flowchart explaining the selection criteria for the articles used in this work.

3. Clinical Presentation

Lymphomas are a result of malignant proliferation of lymphoid cells, presenting with a wide variety of clinical manifestations. They usually present as chronic or recurrent painless lymphadenopathy (not exclusive to the disease), and the evolution of lymphadenopathy varies depending on the type of lymphoma; the lymph node chains in the neck, axilla, and groin are the most affected (Shankland et al., 2012). Extranodal locations are common, with the main sites being the stomach, small intestine, skin, and brain, leading to clinical findings due to compression (Bowzyk Al-Naeeb, Ajithkumar, Behan, & Hodson, 2018).
The clinical presentation also depends on factors such as the site of localization and the presence or absence of B symptoms (weight loss >10%, night sweats, and fever). Indolent lymphomas are characterized by chronic, asymptomatic peripheral lymphadenopathy, unless they cause compression at some site; they are insidious, slow-growing, and may present with hepatomegaly, splenomegaly, or cytopenia. Aggressive lymphomas tend to grow rapidly and are usually symptomatic, presenting with rapid mass growth, systemic B symptoms, or elevated serum lactate dehydrogenase and uric acid levels (Ansell, 2015; Lewis et al., 2020; C. Yadav et al., 2016). Common symptoms such as fatigue, night sweats, or weight loss may also be present (Bowzyk Al-Naeeb et al., 2018). The 80% of lymphomas in adults have a B immunophenotype (IP) and are mostly characterized by nodal presentation, unlike in the pediatric age group, where most of the cases correspond to T cell

lymphoma with extranodal presentation(Bowzyk Al-Naeeb et al., 2018).
Risk factors associated with poor prognosis include age over 60 years, histological type, presence or absence of B symptoms, poor general condition, presence of an abdominal mass >10 cm, number of extranodal sites affected (more than three), serum lactate dehydrogenase concentration, and involvement of bone and bone marrow (Hermans et al., 1995; Maurer, 2023; C. Yadav et al., 2016).
The NHL are responsible for 60% of all lymphomas in children, and the main histological subtypes in this age group are Burkitt lymphoma, diffuse large B-cell lymphoma, anaplastic large cell lymphoma, and lymphoblastic lymphoma, with the latter accounting for 30% of NHLs (Lewis et al., 2020; Sandlund & Martin, 2016; Sheikh et al., 2022). Patients with this subtype of lymphoma mostly present with a mass in the intrathoracic or supradiaphragmatic mediastinal area, and it is associated with severe complications, such as symptoms due to compression of the airway or superior vena cava, and pleural effusions (Besteiro et al., 2021).

4. Epidemiology

Non-Hodgkin lymphoma represents a significant number of deaths worldwide, being the eleventh leading cause of cancer-related mortality(J. Luo et al., 2022). It has an incidence of 2.8% of new cancer diagnoses and 2.6% of deaths globally (Barreno-Rocha et al., 2023). The incidence varies from country to country; in 2020, China had the highest number of cases at 17.1%, followed by the United States with 13.5%. In 2020, 544,352 people were diagnosed with NHL, of which 259,793 resulted in deaths (J. Luo et al., 2022). In Mexico, it accounts for 3.5% of new cancer diagnoses and 3.4% of cancer-related deaths. A five-year prevalence of 19,495 cases is estimated, one-third of which corresponds to the diffuse large B-cell lymphoma (Barreno-Rocha et al., 2023). According to the most recent data published by the WHO, in 2022 there were 553 389 new cases of NHL, representing 2.8% of all cancer cases diagnosed globally, with an incidence of 5.6 every 100 000 inhabitants and a global mortality rate of 6.2 every 100 000 inhabitants (Ferlay et al., 2021).
By 2030, the incidence and mortality of NHL (non-Hodgkin lymphoma) are expected to increase by 60% in Latin America (Pavlovsky et al., 2022). In 2003, in Mexico, this pathology accounted for the third most common type of cancer in men at 7.8%, while in women it was the sixth leading cause at 3.9%; and from 2000 to 2017, the group of non-Hodgkin Lymphoma represented 2.82% of new cancers and 2.6% of all cancer related deaths (Ferlay et al., 2021).
In the general population, the lifetime risk of developing NHL is 1 in every 108 men and 1 in every 162 women. Infection with the human immunodeficiency virus (HIV) significantly increases this risk, estimated at 1 every 25 to 29 (Kimani et al., 2020). Globally, between 2007 and 2017, the number of cases of NHL increased by 39%, where 15% of this increase was due to a change in the age structure of the general population, another 13% due to population growth, and finally 11% due to changes in incidence rates (Global Burden of Disease Cancer et al., 2019).
There are distinct types of NHL classified by the World Health Organization (WHO), and the prevalence of each type depends on factors such as the age of presentation. The most common types in pediatric age are Burkitt lymphoma, diffuse large B-cell lymphoma (DLBCL), and lymphoblastic lymphoma, which are primarily observed in patients aged 1 to 9 years. As children grow older, the incidence changes, with DLBCL increasing and Burkitt lymphoma decreasing (Sheikh et al., 2022).

5. Diagnosis

The initial suspicion arises from the observed clinical signs and symptoms. Confirmatory tests involve performing a biopsy of the affected tissue, which is then analyzed using immunohistochemistry or flow cytometry to observe the characteristics of the cells involved in the neoplasm (Cho, 2022; Liu & Barta, 2019). Each subtype of the disease has a characteristic expression of markers that allows for differentiation (Cho, 2022; Glynn, Soma, Wu, Wood, & Fromm, 2019; Lewis et al., 2020).

Table 1. Immunophenotype of different types of lymphoma.

Lymphoma	Immunophenotype
DLBCL	CD20, CD3, BCL-6, CD10, BCL-2, Ki-67.
SBCL	CD20, CD5, CD23, Cyclin D1, BCL-6, CD10, Ki-67.
Classic Hodgkin	CD20, CD3, CD45, CD30, CD15, LMP-1.
T/NK Lymphoma	CD20, CD3, CD43, Ki-67, CD4, CD8, CD30, CD56, ALK-1, EMA, TIA-1, Perforin, Granzyme B, EBER.

Table 2. Flow cytometry markers of different types of NHL.

Lymphoma	Flow cytometry markers
Diffuse large B-cell lymphoma	Variable expressions of CD19, CD20 and CD45; CD10 may or may not be expressed.
Follicular lymphoma	CD4; CD19, CD20 and CD38 decreased, CD10 increased.
Chronic lymphocytic leukemia/ small lymphocytic lymphoma	CD45, CD5, CD20 dim; CD23 and CD200 positive, FMC-7 negative.
Mantle- zone lymphoma	CD45, CD5, CD20 (normal), CD23 and CD200 negative, FMC-7 positive.
Burkitt lymphoma	CD45, CD20, CD10, CD38 increased.
Hairy cell leukemia	CD20 bright, CD19, co-expression of CD11c, CD25 and CD103 without CD5 and CD10.
Marginal zona lymphoma	CD20, CD19; CD5 and CD10 negative.

6. Staging

The classification of the disease is fundamental in determining the treatment to be administered to patients. This classification can be carried out in different ways, however, the most used systems are based on physical examinations, laboratory tests, chest X-rays, CT scans or MRIs, and bone marrow analysis, such as the Ann Arbor system (Makita et al., 2020).

The classification proposed by Lugano in 2014 includes the use of more recent techniques, such as positron emission tomography. However, it has been determined that traditional methodologies, such as bone marrow biopsy, cannot be dispensed with (Makita et al., 2020).

Both systems define the presence of a lesion differently. The Ann Arbor system defines them as any nodal lesion with a diameter greater than or equal to 1.5 cm at its largest axis; while the system proposed by Lugano defines them as any lymph node with the ability to capture FDG (18Fluorodeoxyglucose) (Makita et al., 2020).

The Ann Arbor criteria classify the disease into 4 stages, according to the areas of the body that are affected, dividing it into two zones delimited by the diaphragm. According to these criteria, stage I is defined as the disease where only one nodal region is affected; stage II considers two nodal regions affected but located on the same side of the diaphragm. Stage III is where the disease affects both sides of the diaphragm. Finally, stage IV is characterized by the involvement of extranodal sites (Shankland et al., 2012).

It also considers the presence of B symptoms and extranodal disease during classification, with the suffix "A" corresponding to lymphomas that do not cause B symptoms, the suffix "B" to lymphomas that cause B or systemic symptoms; and the suffix "E" corresponds to the disease that presents extranodal infiltration (Cheson et al., 2007; Shankland et al., 2012).

A good correlation has been found between, both systems, although the Lugano system has greater sensitivity; however, it is not very common for the disease category and its treatment to change when

using either of the two systems (Makita et al., 2020; Rosenberg et al., 1971).

Table 3. Ann Arbor staging system.

Ann Arbor	
Stage	
1	Restricted to 1 lymph node affected or 1 extranodal site (1E).
2	Affects 2 or more lymph nodes on the same side of the diaphragm.
3	Lymph node injury on both sides of the diaphragm.
4	Extensive extranodal disease (liver, bone, others)
Substage	
A	Absence of B symptoms (systemic symptoms)
B	Weight loss (more than 10% of the body weight) and/or unexplainable fever and/or nocturnal diaphoresis.
E	Extranodal disease

Table 4. Lugano staging system.

Lugano	
Stage	
1	Only one lymph node affected, or only one extralymphatic lesion.
2	Multiple lymph nodes affected in the same side of the diaphragm, or with extralymphatic involvement.
3	Multiple lymph nodes affected on both sides of the diaphragm; the spleen may be involved.
4	Noncontinuous extralymphatic involvement.
Substage	
A	Absence of symptoms
B	Weight loss (more than 10% of the body weight) and/or unexplainable fever and/or nocturnal diaphoresis.

7. Prognosis

The International Prognostic Index (IPI) is a prognostic tool originated in 1993; this index is composed of the Ann Arbor staging and the following features (table 5). In this system the low-risk groups are those whose score goes from 0 – 1 point, the medium risk is assessed at 2 points, medium – high at 3 and high risk from 4 to 5 points. A higher score represents a more severe risk (Hermans et al., 1995; Maurer, 2023).

Table 5. IPI score system.

Item	**Points**
Age > 60	+ 1
ECOG performance status ≥ 2	+ 1
LDH > upper limit of reference range	+ 1
≥ 2 extranodal sites involved	+ 1
Ann Arbor stage III/IV	+ 1
IPI score	Sum of Points

ECOG: Eastern Cooperative Oncology Group Performance status; LDH: Lactate dehydrogenase.

The information provided by a prognostic tool provides guidance for treatment selection, helps to determine clinical trial eligibility and is useful for patient counseling (8,9).

8. Treatment

The most common treatment for NHL is the CHOP regimen (chemotherapy) which consists of the use of cyclophosphamide, doxorubicin, vincristine, and prednisone. A modification of this regimen includes the use of a monoclonal antibody directed against CD20 (rituximab); randomized controlled trials demonstrate that the addition of this monoclonal antibody to chemotherapy cycles improves overall disease survival however about one-third of the patients relapse (Ansell, 2015; Linschoten et al., 2020; Mondello & Mian, 2019). The treatment can be administered every 14 (condensed cycles) or 21 days (R– CHOP 14; R – CHOP 21, respectively). The first trial comparing the difference between the two forms of administration demonstrated that R-CHOP-14 had a lower relapse, however the overall survival in R-CHOP-21 was higher (78%) compared with R-CHOP-14 (67%), nevertheless further studies have shown no difference between these two regimens compared to its effectiveness and even toxicity. Therefore, because the 14-day regimen demonstrates a lower overall 3-year survival rate including all ages, older people, and risk groups, it is not as recommended for use. Cunningham et al, in its phase 3 comparison between these two regimens, 1,080 patients with recently diagnosed Diffuse Large B-cell Lymphoma were studied, and they concluded that both have similarities in terms of efficacy and toxicity results, however the differences found were centered in the group that received R-CHOP-14, who were associated with levels of thrombocytopenia, and there was a higher mortality in that group (Candelaria & Duenas-Gonzalez, 2021; Cunningham et al., 2013).

9. Complement system

The complement system consists of more than 60 proteins synthetized in the liver and other cells that work together to function as the first line defense of the immune system. This system was described for the first time in 1980. The CS has a broad variety of functions, since it participates in the regulation of the proteolytic cascade necessary for the assembly of the MAC; also participates in pathogens opsonization, induces inflammation and can interact with the adaptative immune system; as well as keeping the body homeostasis (Merle et al., 2015; Ricklin et al., 2010).

9.1 Mechanisms of the CS

The CS can be activated by three described pathways: the classical pathway, the lectin pathway and the alternative pathway (Merle et al., 2015).

9.1.1 Classical pathway

The classical pathway is initiated when the C1 complex (composed of C1q, C1r and C1s) detects a specific structure or ligand, such as IgG, IgM, phosphatidylserine, HTLV-1, C – reactive protein, calreticulin – CD91 and integrin alpha2beta1. The recognition of these structures and molecules occurs through the globular fraction of C1q (gC1q) (Gal, Ambrus, & Zavodszky, 2002; Kardos et al., 2008).
After the recognition mediated by C1q, this subunit activates the catalytic core of the C1 complex, which is composed by the C1r and C1s subunits in a tetrameric structure (C1s-C1e-C1r-C1s) (Gal et al., 2002; Gal, Dobo, Zavodszky, & Sim, 2009; Kouser et al., 2015). Once C1r is activated by C1q, C1r activates C1s that has the ability to cleave C4 and form C4a and C4b bound to C2, which leads to the formation of the C3 convertase (C4b2a); the C3 convertase leads to the formation of the C5 convertase and the proteolysis of C5 into C5a and C5b(Merle et al., 2015). Through a series of steps involving proteins such as C6, C7, C8 and C9, the membrane attack complex is assembled in a membrane. During this proteolytic cascade anaphylatoxins (C3a, C5a) and opsonins (C3b) are also

formed (M. K. Yadav et al., 2023).

9.1.2 Lectin pathway

The pattern recognition molecules of this pathway are mannose – binding lectins and ficolins H, L, and M. Mannose – binding lectin (MBL) is an innate immune system protein that can recognize and bind multiple types of pathogens (bacteria, fungi, viruses, parasites) to protect against infections caused by these agents. The recognition capacity of this protein is primarily due to its oligomeric structure, spacing and orientation of the globular recognition domains, through which it can bind to specific carbohydrates such as mannose or N – acetylglucosamine found on the surface of the aforementioned pathogens (Skjoedt et al., 2012).
This pathway is initiated by the ficolins due to their ability to recognize carbohydrates on the surface of pathogens or transformed endogenous cells (Lei et al., 2015). Ficolins are associated with mannose – binding lectin – associated serine proteases (MASPs), which have C – terminal domains capable of recognizing N – acetylglucosamine present on bacterial surfaces; after the detection of these structures, MASPs are activated and cleave C2 and C4, triggering the rest of the complement signaling cascade (Matsushita, 2010).

9.1.3 Alternative pathway

This pathway is constitutively active at low levels, allowing the system to respond when needed. The activation of this pathway occurs through the spontaneous hydrolysis of C3, forming a structure known as C3(H_2O), which acts similarly to C3b to bind factor B. This union to factor B serves as a substrate for the serine protease Factor D, and cleavage by this enzyme initiates the assembly the convertase of this pathway, C3(H_2O)Bb, which, similar to the classical pathway convertase, can cleave C3 into C3b, thus initiating the rest of the complement cascade and the cyclical amplification of the pathway (tick – over), increasing the intensity of the response if the necessary regulator (e. g., Factor H) are absent (de Boer et al., 2023; Merle et al., 2015).

9.2 CS and cancer

There is evidence that indicates the variable role of the CS with cancer, where the observed association depends on the cancer type, the CS is associated with a better prognosis, but in other cases promotes the development of the disease.
The evidence that describes components of the CS as cancer promoters shows high levels of C3a and C5a in the tumor microenvironment that interact with C3aR and C5aR1 receptors in the tumor, enhancing the cytoskeleton remodeling as well as the synthesis of matrix metalloproteases, which increases the mobility and metastatic potential of the cancerous cells (Shu et al., 2020).
Another mechanism of cancer progression is mediated by the immunosuppressor role of the C5a – C5aR1 interaction, which causes an increase in ROS and NOS, inhibiting the cytotoxic activity of CD8+ T cells, facilitating the immune evasion of the tumor (Vadrevu et al., 2014).
However, there is evidence that supports the antitumoral effects of the CS, being the most common the mechanisms known as complement dependent cytotoxicity initiated by the use of therapeutic antibodies that provide the interaction necessary for the activation of the CS by the classical pathway. This CS activation also produces opsonins that enhance the phagocytosis processes (Felberg et al., 2020; Markiewski et al., 2008; Pierpont, Limper, & Richards, 2018; Urban et al., 2022; Wang & Weiner, 2008).
The CS also is a protector factor when it is found in high concentrations (especially C3), providing a better prognosis in these patients; according to Felberg et. al., concentrations lower than 0.18 g/L are sufficient to maintain a stable complement function, however at least 40% of patients with chronic lymphocytic leukemia may have low levels of circulating complement proteins. All tumor cells can produce complement proteins, therefore, their growth is directly stimulated, which is why there are many associations that indicate that the presence of complement proteins produces a worse outcome

for patients, this being a controversy, the idea that the complement behaves in an anti-tumor defense manner is based on two reasons: the function of the immune system as a surveillance against malignant cells and the cytotoxicity of the complement of monoclonal antibody therapies (Revel, Daugan, Sautes-Fridman, Fridman, & Roumenina, 2020; Wang & Weiner, 2008).
There is also evidence suggesting that C1q acts intracellularly as a pro-apoptotic protein by enhancing the signaling and the activation of tumor – suppressor genes that impairs the survival of cancer cells (Mangogna et al., 2019). Evidence by Hong et. Al suggests a pro-apoptotic effect of C1q on prostate and ovarian cancer in vitro (Hong et al., 2009; Mangogna et al., 2019).
Nevertheless, it has been described that C1q also exerts pro – tumoral behavior, it is expressed in several malignant tumors and function as a tumor-promoting factor which causes migration and proliferation of cancer cells as well as metastasis. This protein activates WWOX, a tumor suppressor gene (50). A study done by Bulla et. Al investigated among different types of adenocarcinomas including colon, pancreatic, lung, breast and melanoma, Cq1 signaling was found in all of them, unlike other components such as C1, C3, C4 where they expressed in different cancers but not in all (Mangogna et al., 2019; Revel et al., 2020).

9.3 CS and NHL

Besides the information provided in the previous section, there are also regulators of the CS that can be found in the NHL tumors, such as CD59, CD55 and CD46 impairing the clearance of the cancer cells by the CS. It has been found that the patients with lower concentrations of these regulators (CD59) in the tumors have a better response to treatment and better prognosis in comparison with those with elevated levels of the CS regulators, who often show treatment resistance (Couves et al., 2023; Liszewski & Atkinson, 2015; Sarmoko, Ramadhanti, & Zulkepli, 2023; Shao et al., 2022)
Genetic variations of CD9, CD46 and CD55 are associated with better overall survival specifically in Follicular Lymphoma; it has been observed that the overexpression of some regulators like CD46, CD55, CD59 it is the leading cause of NHL cells evading complement (S. Luo et al., 2020), the functional failure of complement in some cases of NHL may be due to the expression of complement regulatory cells on the surface of cancer cells (Dzietczenia et al., 2010). The role of MBP (mannan binding protein) and MASP2 (mannose-binding protein-associated serine protease 2) play an important role in overall risk in NHL by inhibiting or enhancing the activation of lymphocytes (Hu et al., 2013). On the other hand, high levels of C5 have been proposed as a protective component against the development of NHL due to its role in DNA repair and apoptosis, being a potential target for treatment (Shi, Baranova, & Cao, 2024).
– The progression of tumors develops due to the interaction of tumor cells and their surrounding tumor microenvironment, which is characterized by a network of immune cells, fibroblasts, blood vessels, extracellular matrix, and matrix-associated molecules, which together provide a niche for the tumor that influences survival, tumor invasion, and metastasis. The complement system is considered an important regulator of these tumor microenvironment processes; one of its most well-known actions is the modulation of myeloid-derived suppressor cells (MDSC). In the presence of a tumor, the components of the complement system activate signaling pathways within tumor cells that lead to cell proliferation, inhibition of apoptosis, and activation of migration and invasion networks, where fragments derived from C3 and C5a are considered the main modulators of these functions. However, the impact that C5a has on the tumor microenvironment seems to depend on the type of tumor and the characteristics of the tumor microenvironment. It was found that in mice bearing lymphoma cells with low levels of C5a, they had a reduced tumor burden and showed a greater antitumor T cell response, whereas those with high C5a-producing tumor cells showed the opposite, which suggests a dose-dependent effect of C5a in tumor progression. This suggests that the variety of molecular and cellular elements within the tumor microenvironment have an impact on the growth and spread of cancer (Senent, Tavira, Pio, & Ajona, 2022).
The complement system component 1q (C1q) is a molecule of the classical pathway that, in high expression, has been associated with poor prognosis in cancer patients. The exact mechanism of how it contributes to diffuse large B-cell lymphoma is still not well clarified. Nevertheless, it has been

identified that C1q1 acts in the tumor microenvironment of this type of lymphoma, functioning as a biomarker for tumor-associated macrophage subsets and as a tumor-promoting gene (G. Gao et al., 2024).

9.4 NHL and treatment effects on the CS

As described previously, the pharmacological treatment for NHL consists in the usage of CHOP and R – CHOP, unfortunately, as every drug, the ones used in this treatment also have adverse effects, and many of them may reduce the hepatic function, which may alter the expression of components of the complement system and affect the function of this system in the clearance of cancer cells (Mohebbi et al., 2022; Thorgersen et al., 2019) (56–58).

The cellular immunophenotype of NHL varies depending on the type; however, more than 90% of NHLs are CD20+, which is why the therapy is directed at this membrane antigen (Calderín Miranda, de Castro Suárez, & Fernández, 2022).

Monoclonal antibodies (mAbs) have been associated with an improvement in the survival of patients with mature B-cell neoplasms, they target the immune system by attacking and suppressing cancer cells, mAbs once bound to the cells activate the complement cascade for the deposition of C3 activation fragments and tumor cell lysis (Baskar et al., 2025).

These monoclonal antibodies can be classified into type I (rituximab, ocrelizumab, veltuzumab, ofatumumab, and onartuzumab) and type II (obinutuzumab), both can recruit the complement system, however type I have a semisaturation level that is 10 to 1000 times lower than type II mAbs (Y. Gao, 2023).

Rituximab is an anti-CD20 monoclonal antibody that has been added to the chemotherapy management of NHL, as it has been shown to improve overall disease survival. This antibody targets the CD20 antigen, which is present on malignant B cells, and contains a human IgG1 Fc portion that has the ability to activate immune mechanisms through the activation of the complement system and complement-dependent cytotoxicity. Rituximab is capable of activating the complement system via the classical pathway, generating effector proteins that destroy tumor cells. The study observed that rituximab activates the complement system by increasing activation markers such as C4d and MAC; however, this activation does not correlate with better clinical outcomes in patients who received this antibody, as it is indicated that not all patients benefit from its use (Felberg et al., 2020).

10. Conclusion

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies with varying clinical presentations, prognoses, and treatment approaches. Complement system involvement in NHL is complex, with both pro-tumor and anti-tumor effects depending on the specific component and the context. Further research is needed to explore the potential of targeting the complement system for improved NHL treatment to improve the overall survival and quality of life of these patients, while minimizing the potential side effects.

Founding
This research received no external funding.

Conflict of interest
The authors have declared no conflicts of interest.

Ethical considerations
As this study is a literature review, there was no new data collected, and therefore, ethical approval was not required.

Author contributions

Conceptualization, P.M.R.-A., R.J.P-R. and S.G.-S.; methodology, S.G.-S., B.R.-J. and A.H.N.-Z.; writing – original draft preparation, P.M.R.-A., R.J.P-R., S.G.-S., A.V.P.-P., M.C.-R., K.E.O.-C., B.R.-J. and A.H.N.-Z.; review framework production P.M.R.-A., S.G.-S., A.V.P.-P., M.C.-R. and K.E.O.-C.; writing – review and editing, P.M.R.-A., S.G.-S., B.R.-J. and A.H.N.-Z.; visualization, B.R.-J. and A.H.N.-Z.; supervision., B.R.-J. and A.H.N.-Z.; project administration, S.G.-S., B.R.-J. and A.H.N.-Z.;. All authors have read and agreed to the published version of the manuscript.

References

Ansell, S. M. (2015). Non-Hodgkin Lymphoma: Diagnosis and Treatment. *Mayo Clin Proc*, *90*(8), 1152-1163. doi:10.1016/j.mayocp.2015.04.025

Barreno-Rocha, S. G., Guzman-Silahua, S., Cardona-Munoz, E. G., Zavala-Cerna, M. G., Munoz Gaytan, D. E., Riebeling-Navarro, C., . . . Nava-Zavala, A. H. (2023). Frequency of Autoantibodies on Non-Hodgkin Lymphoma. *Healthcare (Basel)*, *11*(15). doi:10.3390/healthcare11152210

Baskar, S., Peng, H., Gaglione, E. M., Carstens, E. J., Lindorfer, M. A., Ahn, I. E., . . . Wiestner, A. (2025). Potentiating CD20 monoclonal antibody therapy by targeting complement C3 fragments covalently deposited on lymphoma cells. *Blood*, *145*(12), 1309-1320. doi:10.1182/blood.2024024846 %J Blood

Besteiro, B., Teixeira, C., Gullo, I., Pereira, S., Almeida, M., & Almeida, J. (2021). Superior vena cava syndrome caused by mediastinal lymphoma: A rare clinical case. *Radiol Case Rep*, *m*(4), 929-933. doi:10.1016/j.radcr.2021.01.063

Bowzyk Al-Naeeb, A., Ajithkumar, T., Behan, S., & Hodson, D. J. (2018). Non-Hodgkin lymphoma. *BMJ*, *362*, k3204. doi:10.1136/bmj.k3204

Calderín Miranda, J. M., de Castro Suárez, N., & Fernández, G. R. (2022). Linfomas no Hodgkin indolentes y terapia anti-CD20: una revisión de la literatura. *J Revista Cubana de Hematología, Inmunología y Hemoterapia*, *38*(2). http://scielo.sld.cu/scielo.php?script=sci_arttext&pid=S0864-02892022000200012

Candelaria, M., & Duenas-Gonzalez, A. (2021). Rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in diffuse large B-cell lymphoma. *Ther Adv Hematol*, *12*. doi:10.1177/2040620721989579

Cheson, B. D., Pfistner, B., Juweid, M. E., Gascoyne, R. D., Specht, L., Horning, S. J., . . . International Harmonization Project on, L. (2007). Revised response criteria for malignant lymphoma. *J Clin Oncol*, *25*(5), 579-586. doi:10.1200/JCO.2006.09.2403

Cho, J. (2022). Basic immunohistochemistry for lymphoma diagnosis. *Blood Res*, *57*(S1), 55-61. doi:10.5045/br.2022.2022037

Couves, E. C., Gardner, S., Voisin, T. B., Bickel, J. K., Stansfeld, P. J., Tate, E. W., & Bubeck, D. (2023). Structural basis for membrane attack complex inhibition by CD59. *Nat Commun*, *14*(1), 890. doi:10.1038/s41467-023-36441-z

Cunningham, D., Hawkes, E. A., Jack, A., Qian, W., Smith, P., Mouncey, P., . . . Linch, D. (2013). Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. *Lancet*, *381*(9880), 1817-1826. doi:10.1016/S0140-6736(13)60313-X

de Boer, E. C., Thielen, A. J., Langereis, J. D., Kamp, A., Brouwer, M. C., Oskam, N., . . . Jongerius, I. (2023). The contribution of the alternative pathway in complement activation on cell surfaces depends on the strength of classical pathway initiation. *Clin Transl Immunology*, *12*(1), e1436. doi:10.1002/cti2.1436

Dzietczenia, J., Wróbel, T., Mazur, G., Poręba, R., Jaźwiec, B., & Kuliczkowski, K. (2010). Expression of complement regulatory proteins: CD46, CD55, and CD59 and response to rituximab in patients with CD20(+) non-Hodgkin's lymphoma. *Medical Oncology*, *27*(3), 743-746. doi:10.1007/s12032-009-9278-9

Felberg, A., Taszner, M., Urban, A., Majeranowski, A., Jaskula, K., Jurkiewicz, A., . . . Okroj, M. (2020). Monitoring of the Complement System Status in Patients With B-Cell Malignancies Treated With Rituximab. *Front Immunol*, *11*, 584509. doi:10.3389/fimmu.2020.584509

Ferlay, J., Colombet, M., Soerjomataram, I., Parkin, D. M., Pineros, M., Znaor, A., & Bray, F. (2021). Cancer statistics for the year 2020: An overview. *Int J Cancer*. doi:10.1002/ijc.33588

Gal, P., Ambrus, G., & Zavodszky, P. (2002). C1s, the protease messenger of C1. Structure, function and physiological significance. *Immunobiology*, *205*(4-5), 383-394. doi:10.1078/0171-2985-00140

Gal, P., Dobo, J., Zavodszky, P., & Sim, R. B. (2009). Early complement proteases: C1r, C1s and MASPs. A structural insight into activation and functions. *Mol Immunol*, *46*(14), 2745-2752. doi:10.1016/j.molimm.2009.04.026

Gao, G., Sun, N., Zhang, Y., Li, J., Jiang, Y., Chen, N., . . . Shi, W. (2024). Single-cell sequencing in diffuse large B-cell lymphoma: C1qC is a potential tumor-promoting factor. *Int Immunopharmacol*, *143*(Pt 1). doi:10.1016/j.intimp.2024.113319

Gao, Y. (2023). Complement system in Anti-CD20 mAb therapy for cancer: A mini-review. *Int J Immunopathol Pharmacol*, *37*. doi:10.1177/03946320231181464

Garcia-Gutierrez, L., Delgado, M. D., & Leon, J. (2019). MYC Oncogene Contributions to Release of Cell Cycle Brakes. *Genes (Basel)*, *10*(3). doi:10.3390/genes10030244

Global Burden of Disease Cancer, C., Fitzmaurice, C., Abate, D., Abbasi, N., Abbastabar, H., Abd-Allah, F., . . . Murray, C. J. L. (2019). Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol*, *5*(12), 1749-1768. doi:10.1001/jamaoncol.2019.2996

Glynn, E., Soma, L., Wu, D., Wood, B. L., & Fromm, J. R. (2019). Flow Cytometry for Non-Hodgkin and Hodgkin Lymphomas. Methods Mol Biol, *1956*, 35-60. doi:10.1007/978-1-4939-9151-8_2

Hermans, J., Krol, A. D., van Groningen, K., Kluin, P. M., Kluin-Nelemans, J. C., Kramer, M. H., . . . Wijermans, P. W. (1995). International Prognostic Index for aggressive non-Hodgkin's lymphoma is valid for all malignancy grades. *Blood*, *86*(4), 1460-1463.

Hong, Q., Sze, C.-I., Lin, S.-R., Lee, M.-H., He, R.-Y., Schultz, L., . . . Chang, N.-S. (2009). Complement C1q Activates Tumor Suppressor WWOX to Induce Apoptosis in Prostate Cancer Cells. *PLOS ONE*, *4*(6), e5755. doi:10.1371/journal.pone.0005755

Kardos, J., Harmat, V., Pallo, A., Barabas, O., Szilagyi, K., Graf, L., . . . Gal, P. (2008). Revisiting the mechanism of the autoactivation of the complement protease C1r in the C1 complex: structure of the active catalytic region of C1r. *Mol Immunol*, *45*(6), 1752-1760. doi:10.1016/j.molimm.2007.09.031

Kimani, S. M., Painschab, M. S., Horner, M. J., Muchengeti, M., Fedoriw, Y., Shiels, M. S., & Gopal, S. (2020). Epidemiology of haematological malignancies in people living with HIV. *Lancet HIV*, *7*(9), 641-651. doi:10.1016/S2352-3018(20)30118-1

Kouser, L., Madhukaran, S. P., Shastri, A., Saraon, A., Ferluga, J., Al-Mozaini, M., & Kishore, U. (2015). Emerging and Novel Functions of Complement Protein C1q. *Front Immunol*, *6*, 317. doi:10.3389/fimmu.2015.00317

Lei, X., Liu, C., Azadzoi, K., Li, C., Lu, F., Xiang, A., . . . Yang, J. (2015). A novel IgM–H-Ficolin complement pathway to attack allogenic cancer cells in vitro. *Scientific Reports*, *5*(1), 7824. doi:10.1038/srep07824

Lewis, W. D., Lilly, S., & Jones, K. L. (2020). Lymphoma: Diagnosis and Treatment. *Am Fam Physician*, *101*(1), 34-41.

Linschoten, M., Kamphuis, J. A. M., van Rhenen, A., Bosman, L. P., Cramer, M. J., Doevendans, P. A., . . . Asselbergs, F. W. (2020). Cardiovascular adverse events in patients with non-Hodgkin lymphoma treated with first-line cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or CHOP with rituximab (R-CHOP): a systematic review and meta-analysis. *Lancet Haematol*, *7*(4). doi:10.1016/S2352-3026(20)30031-4

Liszewski, M. K., & Atkinson, J. P. (2015). Complement regulator CD46: genetic variants and disease associations. *Hum Genomics*, *9*(1), 7. doi:10.1186/s40246-015-0029-z

Liu, Y., & Barta, S. K. (2019). Diffuse large B-cell lymphoma: 2019 update on diagnosis, risk stratification, and treatment. *Am J Hematol*, *94*(5), 604-616. doi:10.1002/ajh.25460

Luo, J., Craver, A., Bahl, K., Stepniak, L., Moore, K., King, J., . . . Aschebrook-Kilfoy, B. (2022). Etiology of non-Hodgkin lymphoma: A review from epidemiologic studies. *J Natl Cancer Cent*, *2*(4), 226-234. doi:10.1016/j.jncc.2022.08.003

Luo, S., Wang, M., Wang, H., Hu, D., Zipfel, P. F., & Hu, Y. (2020). How Does Complement Affect Hematological Malignancies: From Basic Mechanisms to Clinical Application. *Front Immunol*, *11*,. doi:10.3389/fimmu.2020.593610

Makita, S., Maruyama, D., Maeshima, A. M., Taniguchi, H., Yuda, S., Toyoda, K., . . . Tobinai, K. (2020). A comparison of clinical staging using the Lugano versus Ann Arbor classifications in Japanese patients with Hodgkin lymphoma. *Asia Pac J Clin Oncol*, *16*(3), 108-114. doi:10.1111/ajco.13248

Mangogna, A., Agostinis, C., Bonazza, D., Belmonte, B., Zacchi, P., Zito, G., . . . Bulla, R. (2019). Is the Complement Protein C1q a Pro- or Anti-tumorigenic Factor? Bioinformatics Analysis Involving Human Carcinomas. *Front Immunol*, *10*, 865. doi:10.3389/fimmu.2019.00865

Markiewski, M. M., DeAngelis, R. A., Benencia, F., Ricklin-Lichtsteiner, S. K., Koutoulaki, A., Gerard, C., . . . Lambris, J. D. (2008). Modulation of the antitumor immune response by complement. *Nat Immunol*, *9*(11), 1225-1235. doi:10.1038/ni.1655

Matsushita, M. (2010). Ficolins: complement-activating lectins involved in innate immunity. *J Innate Immun*, *2*(1), 24-32. doi:10.1159/000228160

Maurer, M. J. (2023). The International Prognostic Index in aggressive B-cell lymphoma. *Haematologica*, *108*(11), 2874-2879. doi:10.3324/haematol.2023.284070

Merle, N. S., Church, S. E., Fremeaux-Bacchi, V., & Roumenina, L. T. (2015). Complement System Part I - Molecular Mechanisms of Activation and Regulation. *Front Immunol*, *6*, 262. doi:10.3389/fimmu.2015.00262

Mohebbi, N., Taghizadeh-Ghehi, M., Savar, S. M., Abdi, S., Kouhsari, R., Gholami, K., & Nafissi, S. (2022). Adverse drug reactions of Rituximab in patients suffering from autoimmune neurological diseases. *Daru*, *30*(2), 323-329. doi:10.1007/s40199-022-00452-w

Mondello, P., & Mian, M. (2019). Frontline treatment of diffuse large B-cell lymphoma: Beyond R-CHOP. *Hematol Oncol*, *37*(4), 333-344. doi:10.1002/hon.2613

Pavlovsky, M., Cubero, D., Agreda-Vasquez, G. P., Enrico, A., Mela-Osorio, M. J., San Sebastian, J. A., . . . Villanova, P. (2022). Clinical Outcomes of Patients With B-Cell Non-Hodgkin Lymphoma in Real-World Settings: Findings From the Hemato-Oncology Latin America Observational Registry Study. *JCO Glob Oncol*, *8*. doi:10.1200/GO.21.00265

Pierpont, T. M., Limper, C. B., & Richards, K. L. (2018). Past, Present, and Future of Rituximab-The World's First Oncology Monoclonal Antibody Therapy. *Front Oncol*, *8*, 163. doi:10.3389/fonc.2018.00163

Revel, M., Daugan, M. V., Sautes-Fridman, C., Fridman, W. H., & Roumenina, L. T. (2020). Complement System: Promoter or Suppressor of Cancer Progression?. *Antibodies (Basel)*, *9*(4). doi:10.3390/antib9040057

Ricklin, D., Hajishengallis, G., Yang, K., & Lambris, J. D. (2010). Complement: a key system for immune surveillance and homeostasis. *Nat Immunol*, *11*(9), 785-797. doi:10.1038/ni.1923

Rosenberg, S. A., Boiron, M., DeVita, V. T., Jr., Johnson, R. E., Lee, B. J., Ultmann, J. E., & Viamonte, M., Jr. (1971). Report of the Committee on Hodgkin's Disease Staging Procedures. *Cancer Res*, *31*(11), 1862-1863.

Salam, D., Thit, E. E., Teoh, S. H., Tan, S. Y., Peh, S. C., & Cheah, S. C. (2020). C-MYC, BCL2 and BCL6 Translocation in B-cell Non-Hodgkin Lymphoma Cases. *J Cancer*, *11*(1), 190-198. doi:10.7150/jca.36954

Sandlund, J. T., & Martin, M. G. (2016). Non-Hodgkin lymphoma across the pediatric and adolescent and young adult age spectrum. *Hematology Am Soc Hematol Educ Program*, *2016*(1), 589-597. doi:10.1182/asheducation-2016.1.589

Sarmoko, Ramadhanti, M., & Zulkepli, N. A. (2023). CD59: Biological function and its potential for drug target action. *Gene Reports*, *31*. doi:https://doi.org/10.1016/j.genrep.2023.101772

Senent, Y., Tavira, B., Pio, R., & Ajona, D. (2022). The complement system as a regulator of tumor-promoting activities mediated by myeloid-derived suppressor cells. *Cancer Lett*, *549*. doi:10.1016/j.canlet.2022.215900

Shankland, K. R., Armitage, J. O., & Hancock, B. W. (2012). Non-Hodgkin lymphoma. *Lancet*, *380*(9844), 848-857. doi:10.1016/S0140-6736(12)60605-9

Shao, F., Gao, Y., Wang, W., He, H., Xiao, L., Geng, X., . . . Lu, Z. (2022). Silencing EGFR-upregulated expression of CD55 and CD59 activates the complement system and sensitizes lung cancer to checkpoint blockade. *Nat Cancer*, *3*(10), 1192-1210. doi:10.1038/s43018-022-00444-4

Sheikh, I. N., Elgehiny, A., Ragoonanan, D., Mahadeo, K. M., Nieto, Y., & Khazal, S. (2022). Management of Aggressive Non-Hodgkin Lymphomas in the Pediatric, Adolescent, and Young Adult Population: An Adult vs. Pediatric Perspective. *Cancers (Basel)*, *14*(12). doi:10.3390/cancers14122912

Shi, P., Baranova, A., & Cao, H. (2024). Integrative Genomic Analysis Identifies Novel Causal Genes of Hodgkin's and Non-Hodgkin's Lymphoma. *Discov Oncol*, *16*(1). 1 0.1007/s12672-025-03101-1.

Shu, C., Zha, H., Long, H., Wang, X., Yang, F., Gao, J., . . . Zhu, B. (2020). C3a-C3aR signaling promotes breast cancer lung metastasis via modulating carcinoma associated fibroblasts. *J Exp Clin Cancer Res*, *39*(1), 11. doi:10.1186/s13046-019-1515-2

Skjoedt, M. O., Roversi, P., Hummelshoj, T., Palarasah, Y., Rosbjerg, A., Johnson, S., . . . Garred, P. (2012). Crystal structure and functional characterization of the complement regulator mannose-binding lectin (MBL)/ficolin-associated protein-1 (MAP-1). *J Biol Chem*, *287*(39), 32913-32921. doi:10.1074/jbc.M112.386680

Thorgersen, E. B., Barratt-Due, A., Haugaa, H., Harboe, M., Pischke, S. E., Nilsson, P. H., & Mollnes, T. E. (2019). The Role of Complement in Liver Injury, Regeneration, and Transplantation. *Hepatology*, *70*(2), 725-736. doi:10.1002/hep.30508

Urban, A., Majeranowski, A., Stasilojc, G., Koszalka, P., Felberg, A., Taszner, M., . . . Okroj, M. (2022). In Silico Designed Gain-of-Function Variants of Complement C2 Support Cytocidal Activity of Anticancer Monoclonal Antibodies. *Cancers (Basel)*, *14*(5). doi:10.3390/cancers14051270

Vadrevu, S. K., Chintala, N. K., Sharma, S. K., Sharma, P., Cleveland, C., Riediger, L., . . . Markiewski, M. M. (2014). Complement c5a receptor facilitates cancer metastasis by altering T-cell responses in the metastatic niche. *Cancer Res*, *74*(13), 3454-3465. doi:10.1158/0008-5472.CAN-14-0157

Wang, S. Y., & Weiner, G. (2008). Complement and cellular cytotoxicity in antibody therapy of cancer. *Expert Opin Biol Ther*, *8*(6), 759-768. doi:10.1517/14712598.8.6.759

Yadav, C., Ahmad, A., D'Souza, B., Agarwal, A., Nandini, M., Ashok Prabhu, K., & D'Souza, V. (2016). Serum Lactate Dehydrogenase in Non-Hodgkin's Lymphoma: A Prognostic Indicator. *Indian J Clin Biochem*, *31*(2), 240-242. doi:10.1007/s12291-015-0511-3

Yadav, M. K., Maharana, J., Yadav, R., Saha, S., Sarma, P., Soni, C., . . . Gati, C. (2023). Molecular basis of anaphylatoxin binding, activation, and signaling bias at complement receptors. *Cell*, *186*(22), 4956-4973. doi:10.1016/j.cell.2023.09.020