Clinical, Histopathological, and Molecular Prognostic Factors Associated with Survival and Disease Progression in Adult Patients with Primary and Secondary Thyroid Lymphomas: A Scoping Review Protocol

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Abstract

Background: To identify the key prognostic factors in patients with primary and secondary thyroid lymphoma, focusing on clinical, histopathological, biological, and genetic components, as these factors remain unclear.

Objective: To analyze and synthesize the available evidence to identify factors that may influence the prognosis of patients with primary and secondary thyroid lymphoma.

Methods: This review will include indexed databases such as LILACS, MEDLINE, EMBASE, and PubMed as the primary search sources. The search will cover the period from June 1, 2024, to July 1, 2024. Eligibility criteria will include observational studies of human patients aged 18 years or older, with a diagnosis of primary and/or secondary thyroid lymphoma. We will include reports of adult cases diagnosed with primary thyroid lymphoma or secondary thyroid lymphoma and exclude studies involving patients with primary or secondary tumors of an origin other than thyroid lymphoma. Additionally, studies reporting patients who, alongside primary or secondary thyroid lymphoma, have concomitant diseases associated with high morbidity or mortality will be excluded.
A total of two independent reviewers will participate in the screening, selection, and data extraction process, all of which will be carried out blindly. Conflicts between reviewers will be resolved through discussion or by involving an additional reviewer. Results will be reported using descriptive statistics, and the information will be stored in RedCap (Electronic Research Data Capture).

Results: The literature search was conducted on August 9, 2024, using the following databases: LILACS, MEDLINE, and EMBASE, to identify observational studies. A total of 1,404 results were retrieved. The scoping review is expected to be completed by August 2025

Conclusions: This scoping review will describe the current understanding of the prognostic factors that influence the course of the disease in patients diagnosed with primary and secondary thyroid lymphoma. The review will highlight characteristics that may identify patients at risk of more aggressive disease behavior and could potentially guide therapeutic decisions. Future studies should assess the incidence of these prognostic factors across different age groups and explore their clinical correlations.

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Keywords

Thyroid lymphoma, Secondary thyroid Lymphoma, Primary thyroid lymphoma

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Introduction

Thyroid lymphoma can be classified as **primary**, in which neoplastic cells originate de novo in the thyroid gland, or **secondary**, resulting from the extension of neoplastic cells from other tissues (1). Given that both clinical entities are rare and that most information on their clinical course comes from case reports, it has not been possible to thoroughly evaluate the prognostic factors that may influence the natural progression of the disease (2). Walsh and Lowery (3), as well as Evoy et al., identified genetic characteristics and the expression of certain markers as favorable prognostic factors compared to patients who did not exhibit them. This underscores the importance of describing the population characteristics, clinical behavior, and histology of this condition, as these factors significantly impact treatment selection and survival outcomes. This was demonstrated by Matsuzuka F. et al. in their case series of 119 patients, where they reported a pre-treatment mortality rate of 35%, which decreased to 5% following the introduction of therapy in 1982 (4).

Methods

The proposed scoping review will be conducted in accordance with the JMIR methodology for scoping reviews

Review Questions

The research questions for this study are as follows:

What is the current state of knowledge regarding the clinical course of primary and secondary thyroid lymphoma?
What is the epidemiology of primary and secondary thyroid lymphoma?
What are the most frequently observed clinical characteristics in patients with primary and secondary thyroid lymphoma?
What are the most common histopathological characteristics of primary and secondary thyroid lymphoma?
What are the most common radiological features of primary and secondary thyroid lymphoma?
How do these characteristics impact mortality in primary and secondary thyroid lymphoma?
What clinical factors influence disease progression in primary and secondary thyroid lymphoma?
What are the existing knowledge gaps and future research directions regarding thyroid lymphoma?

Participants

This review will consider studies of any design reporting adult patients (+ 18 year old) with confirm diagnosis of primary or secondary thyroid lymphoma

Inclusion Criteria

The following studies will be selected for this review:

- Studies including patients with primary or secondary thyroid lymphoma describing frequency, clinical features, and complication**s.**
- Studies providing information about histopathological features
- Studies providing information about treatment strategies
- Studies providing information about characteristics that condition progression on primary and secondary thyroid lymphoma and mortality

Exclusion Criteria

The exclusion criteria were as follows:

- Studies describing neoplastic thyroid pathologies other than primary or secondary thyroid lymphoma.
- Studies including patients with primary or secondary thyroid lymphoma with associated comorbidities with high morbidity and mortality as other terminal neoplasias, reduced ejection fraction heart failure , end stage chronic kidney disease.
- We will exclude studies assessing only children, but allow inclusion of studies describing mixed populations of children and adults.

Concept

The accurate identification of prognostic factors influencing the course of the disease in patients diagnosed with primary or secondary thyroid lymphoma will enable us to determine the characteristics that may indicate a more aggressive disease behavior and even guide therapeutic decision-making. Considering that no studies have systematically compiled this information to date, addressing this gap is essential.

Context

This review will consider studies on primary or secondary thyroid lymphoma, including population characteristics and histological findings, which may influence treatment selection and survival. Additionally, prognostic factors identified in various databases and search engines will be analyzed.

Types of Sources

This scoping review will include all sources of scientific evidence, including quasi-experimental and observational studies. No restrictions will be placed on

the type of quantitative research included. The review will be conducted following the JMIR methodology for scoping reviews and aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR)

Search Strategy

The search strategy is intended to locate published scientific studies that meet the inclusion criteria. An initial search was performed by the epidemiologist on August 9, 2024, on Scopus (Elsevier), Embase, Ovid; this resulted in 1400 article references. A detailed search strategy is provided in Multimedia appendix 1.

Keywords and index terms:

“Thyroid cancer; Thyroid lymphoma; Secondary Lymphoma; Primary lymphoma, demographics and baseline characteristics in thyroid lymphoma; Radiological characteristics; Hashimoto's autoimmune thyroiditis; Wnt5a protein,receptor Ror2;monoclonal antibody rituximab; subclinical hypothyroidism; thyroid gland; thyroid cytology ;monomorphic infiltration of lymphoid cells; Lymphoma histologically; Neck mass; Dysphagia; Hoarseness; Solid, hypoechoic mass with increased vascularity; Lymph node biopsy; Thyroidectomy; Specific lymphoma subtype; Thyroid-centered mass, Monomorphic nature of lymphocytes OR monomorphic lymphoid cells OR monomorphic lymphocyte infiltration; Packing of thyroid follicle, Infiltration lymphocytes just beneath the endothelium of blood vessels; Epstein-Barr virus infection; Growing mass in the thyroid gland; Antimicrosomal antibodies ; Asymmetrical pseudocystic pattern; Fine needle aspiration biopsy ;Large needle biopsy; Thyroid scan with I-iodine ; Radiation therapy plus cyclophosphamide, adriamycin, vincristine, prednisolone(CHOP)chemotherapy ; Nitrogen mustard, vincristine, procarbazine, and prednisolone (MOPP) therapy; Extrathyroidal extension; Gallium scan; Immunohistochemical markers Ki 67; Immunohistochemical markers CD 20; VH genes associated with antithyroid antibodies in thyroid lymphoma ; t(3;14) (p14;q32) translocation with FOXP-ICH fusion; Immunohistochemical markers CD79α; Immunohistochemical markers bcl-2; Immunohistochemical markers MUM1p; Immunohistochemical markers IRTA-1; MALT lymphoma; MUM1 Diffuse

large B-cell lymphoma; Immunohistochemical markers P53; Extranodal marginal zone lymphoma; Diffuse large B-cell lymphoma; Germinal-center B-cell subtype; non Germinal-center B-cell subtype; Follicular lymphoma”

All key terms were adapted for each included database and information source. The search terms will be developed collaboratively by the entire team of reviewers, but the search itself will be conducted by a single reviewer. Additionally, the reference lists of all included sources of evidence will be screened for relevant studies. Studies published in any language will be included.

Study or Source of Evidence Selection

A total of 1,400 article references were compiled and uploaded to Rayyan. Independent researchers will screen the titles and abstracts, and potentially relevant articles will be retrieved in full, with their citation details imported into the JBI System for the Unified Management, Assessment, and Review of Information.

Articles published in languages other than Spanish and English will initially be translated using Google Translate. If they meet the inclusion criteria, they will be professionally translated. Full-text articles selected for inclusion will be evaluated against the inclusion and exclusion criteria by the same independent researchers. Reasons for exclusion will be recorded and reported in the scoping review.

Any disagreements between researchers at each stage of the selection process will be resolved through discussion or by consulting a third researcher. The search results will be fully reported in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

Data Extraction

Data will be extracted from papers included in the scoping review by 2

independent researchers using a spreadsheet to include the following variables (5):

Title, authors, year of publication, journal, DOI, origin or country of origin (where the source was published or conducted), authors, study type, aims or purpose, population characteristics (age, sex , comorbidities as history of autoimmune thyroiditis), Clinical characteristics (Presence of a painless tumor mass in the anterior cervical region, with rapid growth, with or without cervical lymphadenopathy, usually accompanied by symptoms of aerodigestive obstruction), Hormonal status (Thyroid profile), Imagenologic characteristics, Diagnostic method (fine needle aspiration, open biopsy) , Primary or secondary Thyroid lymphoma, if secondary thyroid lymphoma: site of primary lymphoma, Classification according to the World Health Organization (WHO) Classification of Tumors of Hematopoietic and Lymphoid Tissues, Immunohistochemical characteristics, presences of other malignancies, surgery (yes or no), Treatment (type of chemotherapy, radiotherapy), overall survival.

The draft spreadsheet will be modified and revised as needed throughout the data extraction process for each included paper. Any modifications will be documented in the final scoping review. Disagreements between researchers will be resolved through discussion or by consulting a third researcher. If necessary, the authors of the included papers will be contacted to request missing or additional data.

Data Analysis and Presentation

A narrative description of the findings will be discussed in the framework of the review questions. The data will be summarized and presented in tables.

Reference Searches

Citation tracking will be used to identify key articles relevant to the topic of interest. This process will involve reviewing the reference lists of relevant papers as well as identifying articles that have cited them. Any duplicate papers that have already been examined will be removed. If a paper meets the inclusion criteria, its reference list will be screened to identify additional relevant

manuscripts.

Results:

The search was conducted on August 9, 2024, using Scopus (Elsevier), Embase, and Ovid, yielding a total of 1400 results. A comprehensive review of the manuscripts is expected to be completed by August 2025. All potential manuscripts will be imported into the reference management software Rayyan QCRI 23. This scoping review aims to identify and describe the clinical, histopathological, and molecular prognostic factors associated with survival and disease progression in adult patients with primary and secondary thyroid lymphomas.

Discussion

Primary and secondary thyroid lymphomas are rare clinical entities, with most available information on their clinical course derived from case reports and only a few large case series. Due to this limitation, it has not been possible to thoroughly evaluate the prognostic factors that may influence the natural progression of the disease or to comprehensively describe the clinical, histopathological, and molecular prognostic factors associated with survival and disease progression. Understanding these factors is crucial, as it may enhance knowledge of these conditions and contribute to improved patient outcomes.

The objective of this scoping review is to assess the breadth of existing literature on primary and secondary thyroid lymphomas and identify key factors that influence better outcomes for affected individuals. Additionally, this review may help identify specific patient populations, such as those at higher risk of disease progression or those who do not respond to therapy.

Limitations of this study include the reliance on case reports, with results being primarily descriptive, which may restrict the ability to draw strong conclusions. However, this review serves as a foundational step toward a more

comprehensive systematic review and meta-analysis, ultimately guiding clinical decision-making and integrating these findings into patient care

Conflicts of Interest

None declared.

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