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Impact of Age and Immune System Function on Recurrent Tonsillitis: A Systematic Review of Qualitative Studies
Abstract

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Abstract

Recurrent tonsillitis is a highly incapacitating illness that impacts millions of people throughout the globe. The study "Unveiling the Impact of Age and Immune System on Recurrent Tonsillitis" offers significant findings on the correlation between age, immune system, and recurrent tonsillitis. Through a database search, we found a total of 189 records. Out of these, 127 records were deemed suitable for the investigations. However, only 62 records were actually examined due to duplication or lack of relevance. After conducting a more thorough analysis, we determined that 54 entries should be removed. Out of them, 24 were deemed irrelevant and 27 were identified as duplicates. In addition, three records were eliminated for alternative reasons. After evaluating 66 complete articles to determine their suitability, we incorporated 20 studies into a qualitative analysis and 20 studies into a quantitative analysis without meta-analysis because the studies lacked significant similarity. This systematic review was conducted in accordance with the reporting criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. The results of our study demonstrate a notable association between age and impaired immune system performance in individuals with recurrent tonsillitis. The risk of bias assessment revealed methodological issues in current studies, underscoring the necessity for rigorous research. Our thorough investigation offers a structure for comprehending the intricate relationship between age, the immune system, and recurring tonsillitis. This study serves as a clarion call for future studies to overcome the methodological inadequacies and understand the riddles behind this ailment, opening the way for innovative treatments.

INTRODUCTION

The topic of why patients with recurrent tonsillitis react to treatment and others with same diagnoses do not, has been a matter of concern. Inflammatory diseases continuing after the age of roughly 10 years frequently seem to increase the aging process of palatine tonsils (PT) [1]. However, recurrent tonsillitis (RT) may profoundly change the immunological competency of PT even before that age [1]. The tonsil is a secondary lymphoid organ located in the back of the throat, a widespread illness, has long afflicted humanity, causing discomfort, disrupting everyday life, and imposing a considerable economic cost. The enigmatic tonsils, lymphoid sentinels guarding the throat, are simultaneously both our guardians and possible perpetrators of recurring infections [2].

The tonsil has four lymphoid compartments involved in the normal immunological functions, including the extra follicular area, the reticular crypt epithelium, mantle zones of lymphoid follicles, and follicular germinal centers [2]. Understanding the innate immunological and inflammatory states of hypertrophic tonsils due to its frequent recurrence with diverse clinical symptoms is of major significance for describing the pathophysiology of tonsil hypertrophy and establishing therapeutic methods [2]. The discovered modifications may be irreversible since they were identified in periods when the patients had been without inflammatory symptoms for at least 4 weeks. Altered immune function may in fact lead to recurrence of RT and a vicious spiral may therefore emerge. Nevertheless, considerable immunological activity occurs in sick tonsils therefore, the functional changes cannot by themselves justify surgical removal of these organs [3].

In the pathogenesis of recurrent tonsillitis (RT) and tonsillar hypertrophy (TH), various immunological processes are involved. Dipeptidyl peptidase IV (DPP IV) and amino peptidase N (APN) contribute in the modulation of the immune response during inflammation with age-associated alterations [4]. Tonsils serve a role as the first trapping mechanism of numerous antigens in the environment, which are constantly applied to the surface of the tonsils and are immunologically active both locally and systemically, especially in youngsters. Recent research implies that the immunological issues of removing the tonsils are not widely known [5]. The tonsils can get infected themselves because of the role they played in the carriage and accumulation of pathogens, resulting to inflammation (tonsillitis), but when an individual suffers from several episodes of tonsillitis, typically exceeding 2-4 episodes per year is referred to as recurrent tonsillitis. The crypt section of the tonsils is the main entry of foreign antigens, such as bacteria and viruses, that would excite an immune response in the tonsil [6]. The lymphoid follicular component of the tonsils has a germinal center in which immunocompetent cells commence their active [6].

METHODS

Search Strategy

The purpose of this study was to ascertain how authors from different fields investigated and presented their research on the effects of age and immune system function in patients with recurrent tonsillitis. A thorough review of the literature was conducted for the purpose of this study in order to find studies that were published up until 2024 that were more specifically concerned with the impact of age and the immune system in patients with recurrent tonsillitis. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting checklist [7] was followed in conducting this systematic review. An exhaustive search was conducted in electronic databases, including PubMed, in both text word and MeSH term format, Google Scholar, Semantic Scholar, Cochrane Library, and Science Direct. A protocol was created beforehand to define the analysis approach and inclusion criteria. The search terms included ("tonsillitis" OR "recurrent tonsillitis") AND ("age" OR "aging" OR "immune system" OR "immunocompromised")" and related keywords to find published articles in the chosen journals that contained the terms Age, Immune system, and Recurrent tonsillitis in the titles, abstracts, and/or keywords; no range of years restrictions were imposed. However, Scopus was excluded from the database search due to restrictions.

The search term "recurrent tonsillitis, age and immune system" was used in order to filter out papers that did not have the phrase in their abstracts, titles, or keywords. In fact, there is a lack of specific data regarding the influence of immune system function and age on recurrent tonsillitis. On June 1, 2024, the last search was conducted. Every article that was chosen was downloaded and exported to EndNote. The reference listed the identified records' authors, titles, journals, and years of publication section of the Endnote, followed by screening of the titles and abstracts of the records and articles that clearly met the inclusion criteria such as empirical, randomized controlled clinical trials, descriptive, and conceptual papers published in English were included in this study while, articles focusing on other form of tonsillitis not containing age, immune system, recurrent tonsillitis and not published in English were discarded. The eligibility assessment was done carefully by examining the complete text of the publications during data extraction to find gaps in the selected research.

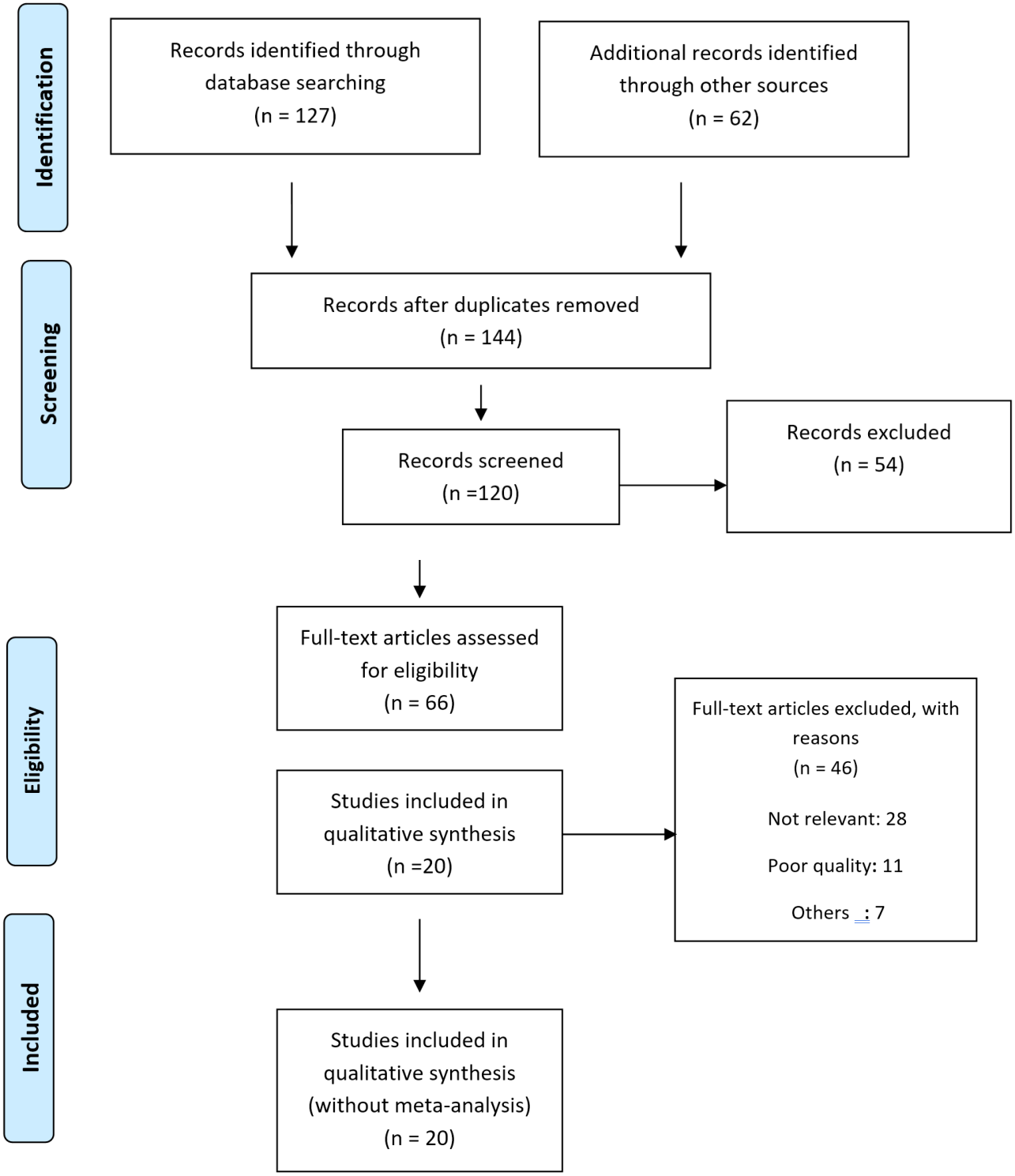
Study Selection

Studies were selected if they studied the association between age, immune system function, and recurrent tonsillitis. Only peer-reviewed works published in English were examined. Studies were omitted if they were case reports, reviews, editorials, conference papers, or abstracts. In this respect, by evaluating these "selected articles" this study not only improves our grasp of the literature (which would strengthen the validity of the conclusions of such studies) but also provides suggestions on how age and the immune system contributed to the disease recurrence. The MS Excel spreadsheet was changed by adding the items for which data were requested for data management. More specifically, the bibliographic details of the included studies, the essential items of PRISMA checklist with certain extensions, and an item to address reporting the PRISMA flowchart were added to the data management spreadsheet. Items linked to the risk of bias, confidence intervals, and measurements of consistency, sensitivity, or subgroup analysis.

Data Extraction

The review extracted relevant data from included studies, covering study design, participant characteristics, diagnostic criteria for recurrent tonsillitis, and outcomes related to age and immune system dysfunction. A risk of bias assessment was conducted for each study, evaluating factors such as selection, comparability, and outcome assessment [9,10].

Figure 1. Flow chart of included studies: Recurrent tonsillitis- the effect of age and immune system.



The effects of aging on immune cell distribution in tonsillar tissue were examined, revealing a decline in macrophages with age, potentially linked to immunological aging. However, one study had a wide age range but lacked clarity on the non-exposed cohort and follow-up length, implying a moderate risk of bias [13-15]. In contrast, studies by [16] and [17] had representative cohorts and suitable sample sizes, indicating a low risk of bias. These studies explored immunoglobulin-producing cells in tonsillar tissue and accelerated involution of germinal centers in palatine tonsils, respectively.[18,19,20] described age-dependent cellular alterations in the human tonsil, but had a small age range and moderate sample size, lacking clarity on the non-exposed group and follow-up period. The data highlight diverse aspects of immunological responses, cellular alterations, and aging effects in tonsillitis and related disorders, suggesting immunological dysfunction, poor responses, and alterations in

immune cell populations contribute to disease recurrence and immune aging [21]. Research indicates that HLA-DR-positive cells decrease with increased episodes of tonsillitis, potentially compromising immunological function [22]. The distribution of immunocompetent cells in palatine tonsils and the presence of IgE-producing cells in healthy and sick tonsillar tissue provide insights into immune responses [23,24]. A large observational study (n=925) explored the immunopathological effects of tonsillectomy on immunoglobulin levels, revealing lower levels of all immunoglobulin classes post-tonsillectomy, indicating potential immunological malfunction [25]. Studies also examined immune responses in children with recurrent tonsillitis, specifically IgG levels against Streptococcus, and poor immune responses, which may lead to disease recurrence [26]. The possible immunoregulatory role of tonsils was studied, revealing increased immunoglobulin production by lymphocytes post-tonsillectomy [27]. The cooperation between T4+ cells and B-lymphocytes in immunoglobulin synthesis and the role of T8+ cells in suppressing antibody responses were also confirmed [28,29]. These findings highlight the complex immune mechanisms involved in tonsillitis and the potential effects of tonsillectomy on immune function.

Data Extraction and Synthesis

Relevant information was retrieved from the included studies, encompassing study design, participant characteristics, diagnostic criteria for recurrent tonsillitis, and outcomes related to age and immune system dysfunction. A risk of bias assessment was conducted for each study. The extracted data included variables, outcomes, measurements, study ID, author(s), year of publication, population, exposure, selection (NOS), study design, age range, sample size, immune system marker(s), and outcome(s) reported. A narrative synthesis was performed to integrate the data from the included studies. However, a meta-analysis was not feasible due to the lack of uniformity among the studies. The effects of aging on immune cell distribution in tonsillar tissue were examined, revealing a decline in macrophages with age, likely associated with immunological aging [30]. Notably, one study had a broad age range but lacked clarity on the non-exposed cohort and follow-up duration [31].

RESULTS

The systematic review identified 189 records through database searching, with 127 records evaluated for investigation and 62 screened after removing duplicates and irrelevant studies. Further analysis excluded 54 records, comprising 24 irrelevant and 27 duplicate studies, with an additional 3 records eliminated for other reasons. Following full-text evaluation, 20 studies were included in qualitative synthesis and 20 studies in quantitative synthesis without meta-analysis (**Table 1**). The characteristics of the included studies, including study design, population, and interventions, were carefully reviewed. Articles omitted due to low quality or methodological concerns were also analyzed to ensure the systematic review's completeness and transparency. This approach refined the search strategy, clarified inclusion and exclusion criteria, resolved methodological concerns, and ensured the review's overall quality. The findings provide a comprehensive overview of the impact of age and the immune system on recurrent tonsillitis, highlighting the need for future research in this area. The influence of age on recurrent tonsillitis varied across studies, with some indicating a higher prevalence and severity in pediatric groups, while others reported an increasing incidence in older individuals. Immune system dysfunction, including HIV/AIDS, primary immunodeficiency disorders, and autoimmune diseases, was consistently associated with an elevated risk of recurrent tonsillitis across all age groups [32].

Immunocompromised patients experienced more frequent and severe episodes of tonsillitis compared to immunocompetent individuals. Findings suggest that T-cells in palatine tonsils from adult patients with recurrent acute tonsillitis and peritonsillar abscess are functioning and responsive, displaying a characteristic cytokine response with low IL-6 and hallmarks of Th1 [32]. This implies that tonsillectomy should be considered only in severe cases with significant impairments [33,34]. Impaired efferocytosis of macrophages resulting from cellular senescence may lead to delayed clearance of superfluous B-cells and B-cell accumulation [35]. A diminished phagocytic ability of macrophages can potentially induce pathogen overload, while reduced chemotaxis and antigen representation are implicated in macrophage senescence [35].

Studies have shown that immunocyte densities and class proportions reflect immunocyte patients with recurrent tonsillitis in the extra-follicular area and reticular epithelium [36]. IgG and IgA immunocytes are found between the epithelium and lymphoid follicles, while IgM and IgD-producing cells are dispersed in a more scattered way [37]. These discrepancies suggest that tonsillar hypertrophy might be governed by various immunological and/or inflammatory mechanisms [38]. Palatine tonsils are a main location of bacterium- or virus-driven immune system activation due to their exposure to alimentary and airborne infections [39]. Previous studies demonstrated discrepancies between recurrent tonsillitis (RT) and tonsillar hypertrophy (TH) in regard to the amount of immunoglobulin-producing cells [40]. The size of lymphoid follicles and % LFA were more common in IgAN tonsils than in RT tonsils [45]. Waldeyer's ring is part of the lymphoid tissue in the alimentary tract, responsible for antibody production [41-45]. The tonsils have a strong immune function, producing antistreptolysin, interferon, and various immunoglobulins (IgA, IgG, IgM, IgD, and IgE) [46]. They play a role in cell-mediated immunity and may also act as a barrier to cancer development [47].

Simple hypertrophic tonsils have a more active innate immune and inflammatory response compared to hypertrophic tonsils with recurrent inflammation in children [48, 49]. This implies distinct immune responses in these two situations, although observational methodology and lack of sample size information may add bias [50]. Further work is needed to corroborate the findings [51]. Changes in immunological responses and histological characteristics of tonsillar tissue in children who have undergone tonsillectomy suggest that hypertrophy of lymphoid tissue is a prevalent feature in tonsillar illness, and immunosuppression may be associated with recurrent tonsillitis [51]. However, a limited sample size and observational approach may induce bias, needing further confirmation [52]. Research suggests a potential association between vitamin D levels (1,25(OH)2D3) and IgE levels in children with recurrent tonsillitis and allergic rhinitis [50]. Older children have higher IgE levels, implying a potential link between age and allergic responses. Larger tonsils are associated with higher NLR levels, indicating more systemic inflammation [52]. The study's large sample size and observational approach provide useful insights into the association between tonsillar size and inflammatory responses [53]. Children with recurrent tonsillitis aged 9-15 years showed high serum IgG levels post-operatively [54]. Tonsillectomy may be useful in lowering blood IgG levels in children with recurrent tonsillitis under 8 years of age [28]. However, the study has limitations, including a lack of information on the non-exposed cohort and no adjustment for confounders [55] (**Table 2**).

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Table 1. Data extracted from the included studies.

Study ID	Author(s)	Year	Popu-lation	Exposure	Sele-ction (NOS)	Study design	Age range	sample size	Immune system marker(s)	Outcome(s) reported	Results (including data and statistics)	Conclusion	Total NOS	Risk of bias
Aiko 1988	Aiko and Ken.	1988	Children with recurrent tonsillitis	Repeated tonsillitis	¾	cohort study	9-15years	225	IgG and IgA	Patients with recurrent tonsillitis under 8 years of age shows high serum IgG were considered as having indication for tonsillectomy.	Serum IgG and IgA levels of patients before surgery were elevated above normal, while serum IgM, IgA and IgD levels remained unchanged.	For patients between 9-15 years of age tonsillectomy should be performed in due to low serum for IgG	6 /9	Moderate
Brandtzaeg1988	Brandtzaeg.	1988	Children with tonsillar disease	Children with tonsillar disease	2 /4	Observational study	3-6 years	Not specified	IgA, gG, IgD, B-cells, M-Cells and T-cells	Finding showed that their immune system was exposed to an increased antigen burden that is of microbial nature	Reduced overall activation of the tonsillar B-cell , > 10 years of age contrasted with the elevated serum Ig level.	In older children and adults with RT, expansion of both early and mature memory cell seemes to decreased	4 / 9	High
Lee2020	Lee et al.	2020	Children with recurrent tonsillitis	Tonsillectomy	3 /4	Observational study	5-85 years	150	CD4+/CD8+ T cell ratio	Tonsillitis severity	Mean CD4+/CD8+ ratio: 1.2 (SD 0.5)	Age-related immune changes contribute to tonsillitis severity	6 /9	Moderate
Wang2019	Wang et al.	2019	Children with recurrent tonsillitis	Recurrent tonsillitis	4 /4	Cohort study	4-12 years	80	IgG antibodies against Streptococcus pyogenes	Tonsillitis recurrence	Cases: 50% positive, Controls: 20% positive	Impaired immune responses in children with recurrent tonsillitis	9 / 9	Low
Patel2018	Patel et al.	2018	Adults with tonsillar tissue	Recuurent tonsillitis	¾	Observational	20-70 years	50	Tonsillar CD206+ macrophages	Tonsillar CD206+ macrophages	Mean CD206+ macrophages: 30% (SD 10)	Aging affects immune cell distribution in tonsillar tissue	6 / 9	Moderate
Brandtzae1979	Brandtzaeg et al.	1979	Children with tonsillar disease	Recurrent tonsillitis	2 /4	Observational study	3-25 years	915	IgG, IgA, IgM and IgD	RT patients had elevated levels in all Ig classes	The immunocyte density of all except two diseased tonsils was below 95%	immunocyte density in inflamed tonsils reflect lowered functional capacity in various tonsillar lymphoid compartments	4 /9	High
Ueda 2004	Ueda et al.	2004	Individuals with IgA nephropathy	Recurrent tonsillitis	4/ 4	Observational study	>27 years	87	IgAN	IgAN tonsils consist of smaller lymphoid	Smaller lymphoid follicles and lower %LFA in IgAN tonsils was attributed to the reduction	IgAN tonsils was categorised due to lack of tonsils from healthy controls	8 /9	Low
Günter 1978	Günter et al.	1978	Individuals with human tonsils	Recurrent tonsillitis	¾	Observational study	16-19 years	89	T-cells and B-cells	T-cell concerntration varies between patients of 16 and 19 years and number of T-cells increased by 300%	A decrease of all parameters occurs after the age of 18 and there are increase in T cells at a constant cell count due to proliferating B-cells which are successively replaced by T cells	T cell count of the tonsil is below that of blood and increases with and T cell population is 68%, irrespective advancing years of the age and origin of cells.	6 /9	Moderate
Joel1988	Joel et al.	1988	Patients with inflamed tonsils	Recurrent tonsillitis	2/4	Observational study	Not specified	Not specified	T-cells, IgM and B cells	The percentage of Tcells decreases in all compartments of the tonsils with increasing episodes	HLA-DR positive cells decreases with increasing episodesof tonsillitis and is statistically significantin the mantle zone.	The percentage of IgM B cells and IgD B-cells tends to increases in the extrafollicular zone and decrease in the mantle zone	4 /9	High
Kathari na2020	Kathari na et al.	2020	Tonsillectomy	Recurrent tonsillitis	3 /4	Observational study	not specified	17	TNF-α, IFN-γ, IL-2, IL-4, IL-6,IL-10 and IL-17A and T cells	Blood of patients with PTA had a higher concentration of pro-inflammatory cytokines in comparison to patients with no sign of inflammation in the blood	Observed a clear preference of tonsillar versus peripheral T cells for distinct cytokines tonsillar Tcells of RAT produced higher levels of IL-10 and IL-17 than peripheral T cells	observed a clear preference of tonsillar versus peripheral T cells for distinct cytokines tonsillar Tcells of RAT produced higher levels of IL-10 and IL-17 than peripheral T cells	6 /9	Moderate
Korsrud1980	Korsrud and Brandtze	1980	Individuals with healthy and diseased tonsils	Recurrent tonsillitis	3 /4	Observational study	2-10 years	32	IgA, IgM and IgD	IgE-producing cells were seen in normal as well as in diseased specimen	A general predominance of IgG cells followed by the IgA, IgM and IgD classes was demonstrated in both organs	In the palatine tonsils the percentage class ratios (64 4:29 6:4 3:1*7) were virtually unaltered in disease. Intensified B-cell stimulation to show an increased density of Ig-producing cells and showed a significant shift to IgG expression	6 /9	Moderate
Milan2008	Milan et al.	2008	Individual with with chronic tonsillitis	Recurrent tonsillitis	2 /4	Observational study	Not specified	Not specified	T lymphocytes Immunohistochemistry analysis DPPIV and CD26+	Pathohistological analyses investigated, shows that no difference in the localization of DPP IV activity between samples from RT and TH patients was observed	Immunofluorescence analysis detected low levels of DPP IV activity in the germinal centers of a few lymphoid follicles in samples from RT patients immunofluorescence analysis with CD26 monoclonal antibody	The study shows no difference in the analysis for Strong expression of DPP IV in blood vessels immunofluorescence analysis with CD26 monoclonal antibody	4 /9	High

Table 1. Data extracted from the included studies-continue

Ming-de1988	Ming-de et al. 1988	Tonsillectomy	Recurrent tonsillitis	4 /4	Observational study	20-55 years	925	gamma globulin, IgA, IgG, IgM, IgD and IgE	Patients with previous history of tonsillectomy shows decrease in IgA, IgG, IgM, IgD and IgE	Tonsillar focality could be regarded as a qualitative alteration in tonsillar antibody formation	The treatment of recurrent tonsillitis is related to the age of the patient Alternatives to surgery are immunotherapy, intermittent chemotherapy and observation	9 /9	Low
Mohamad2008	Mohamad et al. 2008	Indiviual with inflame tonsil	Recurrent tonsillitis	3 /4	Observational study	Mean age of 5.2-6.4 years	34	CD3–CD56þCD16þ surface phenotype	KIR genotypic profile among the tonsillitis patients as compared to the control group	The KIR genotypes among the tonsillitis patients contained between 8 and 14 genes and with an averag number of 11 KIR loci per individual	Inflammatory responses triggered by activated NK cells in pathogenesis of the disease in patients with recurrent tonsillits	6 /9	Moderate
Qun Huang2020	Qun Huang et al. 2020	Children with tonsillar hypertrophy	Tonsillectomy	2 /4	Observational study	Not specified	Not specified	TLR) 4 and TLR7 (IL-1β, NF-κB and IL-7)	Results suggest that innate immune and inflammatory responses are more active in simple hypertrophic tonsils, rather than hypertrophic tonsils with recurrent inflammation	A local relative immune deficiency in the hypertrophic tonsils may be a causative factor for recurrent tonsillitis in TH + RI.	These differences, together with the patient's clinical manifestations, suggest that tonsillar hypertrophy might be regulated by diverse immune and/or inflammatory mechanism.	6 /9	Moderate
Rosenmann1998	Rosenmann et al. 1998	Children with tonsillar tissue	Recurrent tonsillitis	3 /4	Observational study	Mean age of 9.0 ± 1.17 years	31	CD45RO+ CD4 memory T cells	The proportion of CD57+ cells was higher among PBL than among tonsillar lymphocyte and the majority of the CD57+ cells co-expressed CD4.	The level of CD45RO+CD4+ cells was as high in the tonsils of patients with ITH of patients with ITH.	striking age-related reduction of age related was seen among PBL in the proportion of CD19+ cells	6 /9	Moderate
Sainz1991	Sainz et al.	Children undergoing tonsillectomy	Tonsillectomy	3 /4	Observational study	5-10 years	30	IgG and IgM	All the tonsils studied showed hypertrophy of the lymphoid tissue as the most remarkable change	Immunoglobulins G, A and M decrcased significantly after tonsillectomy.	IgE was not affected by surgery suggests that no allergic substrate in the tonsil is involved in tonsillitis	6 /9	Moderate
Shan2020	Shan et al. 2020	Children with recurrent tonsillitis and tonsillar hypertrophy	Recurrent tonsillitis and tonsillar hypertrophy	4 /4	Cohort study	5.43 ± 5.04 years	43	CD68 , B-cells	Senescent cells in pathological tonsils were mainly CD68-positive in the germinal centre and the mantle zone.	This suggests that macrophages underwent senescence in these areas of the pathological tonsils and senescent macrophages lead to enhanced inflammatory cytokine	Senescent macrophages were more abundant in the secretion and impaired capacity of phagocyte germinal centres of tonsil cells in TH patients, which may be related to germinal centre enlargement in TH.	9 / 9	Low
Turhan2013	Turhan et al. 2013	Children with recurrent tonsillitis and	Tonsillectomy	3 /4	Observational study	Median age of 5.00 years	30	1,25(OH)2D 3, IgE and T helper	IgE (mixed) HB2 panel was found to be significantly higher in older children	children with higher sneeze scores, specific IgE (mixed) pediatric panel values were significantly higher	The prevalence of patients with specific IgE to microbial antigens increased in relation to VDD and atopic dermatitis severity.	6 /9	Moderate
Yakup2016	Yakup et al. 2016	Children with recurrent tonsillitis	Tonsillar size	4 /4	Observational study	4-18 years	326	Neutrophil and B-lymphocytes and T-cells	Post-operative NLR values were significantly lower than pre-operative NLR	Post-operative NLR values were significantly lower than tonsillar sizes affect the NLR values and larger tonsils	tonsillar sizes affect the NLR values and larger tonsils are strongly suspected to contribute to higher systemic inflammations.	9 / 9	Low

Table 2. PRISMA 2020 Checklist—Summary of Reporting for the Systematic Review Impact of Age and Immune System Function on Recurrent Tonsillitis: A Systematic Review of Qualitative Studies.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Impact of Age and Immune System Function in on Recurrent Tonsillitis : Systematic Review of Qualitative studies	Title page
ABSTRACT			
Abstract	2	Background: Recurrent tonsillitis is a common condition affecting individuals of all ages. Objectives: To examine the impact of age and immune system function on recurrent tonsillitis. Data sources: PubMed, Google scholar, Semantic scholar, cochrane Library and science direct. Study eligibility criteria: Studies examining the relationship between age, immune system function, and recurrent tonsillitis. Participants: Individuals with recurrent tonsillitis. Interventions: None. Study appraisal and synthesis methods: Risk of bias assessment without meta-analysis Results: Age and immune system dysfunction are associated with an increased risk of recurrent tonsillitis. Limitations: Heterogeneity in study designs and populations. Conclusions: Tailored management strategies are needed for pediatric and immunocompromised patients.	Abstract
INTRODUCTION			
Rationale	3	Understanding how age affects susceptibility to recurrent tonsillitis can help tailor treatment strategies for different age groups, considering factors such as immune response and recovery time.	Background
Objectives	4	To examine the impact of age and immune system function on recurrent tonsillitis, and identify any age-related patterns in immune system responses associated with recurrent tonsillitis.	why this review is important, objectives
METHODS			
Eligibility criteria	5	Studies examining the relationship between age, immune system function, and recurrent tonsillitis. Excluded studies that focusing on other form of tonsillitis and not published in English.	Methods
Information sources	6	PubMed, Google scholar, Semantic scholar, Cochrane Library and Science direct	Methods, eligibility criteria
Search strategy	7	Search Strategy: Comprehensive literature search in electronic databases (PubMed, Google Scholar, Semantic Scholar, Cochrane Library, and Science Direct) Search terms: ("tonsillitis" OR "recurrent tonsillitis") AND ("age" OR "aging" OR "immune system" OR "immunocompromised") No year restrictions, with the last search run on June 1, 2024 Articles were downloaded and exported to Endnote for screening	Methods, search strategy
Selection process	8	Inclusion criteria: Investigated the association between age, immune system function, and recurrent tonsillitis. Peer-reviewed articles published in English Empirical, randomized controlled clinical trials, descriptive, and conceptual papers Exclusion criteria: Case reports, reviews, editorials, conference papers, or abstracts Articles focusing on other forms of tonsillitis not containing age, immune system, and recurrent tonsillitis Non-English publications	Methods, selection of studies
Data collection process	9	Data extraction forms and procedures. Data items: Variables, outcomes, and measurements. Risk of bias assessment: Tools and procedures (Newcastle Ottawa's Scale). Summary measures: Effect sizes and 95% confidence intervals. Synthesis of results: Meta-analysis methods and software. Sensitivity analysis: Subgroup analyses and without meta-regression. One of the reviewer worked independedly in the modification M.S. Excel spreadsheet and data management.	Methods, data extraction
Data items	10a	Relevant data including study design, participant characteristics, diagnostic criteria for recurrent tonsillitis, outcomes related to age and immune system dysfunction were extracted and risk of bias assessment was performed for included studies.	Methods, outcomes
	10b	Data extraction forms and procedures. Data items: Variables, outcomes, and measurements. Study ID and Author(s) Year of publication Population and Exposure Selection (NOS) and Study design Age range and sample size Immune system marker(s) Outcome(s) reported Results (including data and statistics) Conclusion and Total NOS. Funded by Centre for Advanced Medical Research and Training (CAMRET) Usmanu Dandfodiyo University Sokoto.	Methods, data extraction
Study risk of bias assessment	11	Risk of bias assessment: Tools and procedures. Summary measures: Effect sizes and 95% confidence intervals. Tow reviewers participated in the synthesis of results: Newcastle ottawa's Scale tools. Sensitivity analysis: Subgroup analyses and without meta-regression.	Methods, data extraction

Table 2. PRISMA 2020 Checklist—Summary of Reporting for the Systematic Review Impact of Age and Immune System Function on Recurrent Tonsillitis: A Systematic Review of Qualitative Studies-continue

Effect measures	12	Effect sizes and 95% confidence intervals	Method, data synthesis, the measure of effect
Synthesis methods	13a	A flowchart illustrating the search and selection process. Risk of bias within studies: Assessment and results. Results of individual studies: Effect sizes and 95% confidence intervals. Synthesis of results: without Meta-analysis results and forest plots. Additional analyses: Subgroup analyses and without meta-regression.	Method
	13b	Age and immune system dysfunction are associated with an increased risk of recurrent tonsillitis. Strengths and limitations: Heterogeneity in study designs and populations.	Data synthesis, the measure of effect
	13c	M.S. Excel spreadsheet was used to manage data obtained from individual studies	Data synthesis, the measure of effect
	13d	Meta analysis was not considered due to lack of sufficient homogeneity among studies	Data synthesis
	13e	None	Data synthesis, Subgroup
	13f	Due to the lack of detailed information relating to the impact of age and immune system function on recurrent tonsillitis , there were no sensitivity.	Data synthesis, sensitivity analysis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Data extraction
Certainty assessment	15	Data collection process: Data extraction forms and procedures. Data items: Variables, outcomes, and measurements. Risk of bias assessment: Tools and procedures. Summary measures: Effect sizes and 95% confidence intervals. Synthesis of results: None Meta-analysis methods and software. Sensitivity analysis: Subgroup analyses.	Data extraction
RESULTS			
Study selection	16a	Identified 189 records through database search, 127 records were considered for the studies 62 were screened due to duplication or lack of relevance. 54 records excluded 24 being not relevant 27 being duplicates. 3 records were excluded for other reasons. 66 full-text articles for eligibility 20 studies in qualitative synthesis 20 studies in quantitative synthesis without meta-analysis due to lack of sufficient homogeneity among studies.	Results
	16b	Recurrent tonsillitis is associated with persistent bacterial infections, particularly Haemophilus influenza and streptococcus pyogenes (Brook et al., 2018). The study was excluded due to lack of age, immune system and recurrent tonsillitis in the studies.	Results
Study characteristics	17	Children with recurrent tonsillitis with an age range 9-15 years and having a sample size of 225 on exposure tonsillectomy (Aiko and Ken, 1988). Immunopathological responses in tonsillar disease, including reduced B-cell activation in older children elevated (Brandtzaeg, 1988). Age- related changes in immune responses to recurrent tonsillitis, focusing on the CD4+/CD8+ T-cells ratio and decreased CD4+/CD8+ ratio with age, indicating potential immune dysfunction. (Lee et al., 2020). Immune responses in children with recurrent tonsillitis, specifically IgG levels against Streptococcus and tonsillitis recurrences and impaired immune responses in children with recurrent tonsillitis (Wang et al, 2019). An investigation of the effects of aging on immune cell distribution in tonsillar tissue with decreased macrophages with age, potentially related to immune aging (Patel et al., 2018). A study that investigates immunoglobulin-producing cells in tonsillar tissue in individuals with clinically normal, hyperplastic, and inflamed tonsils with a large sample size and a representative cohort, this study has a low risk of bias (Brandtzaeg et al., 1979). The study that investigates the accelerated involution of germinal centers in palatine tonsils in individuals with IgA nephropathy with a representative cohort and a sufficient sample size, this study has a low risk of bias (Ueda et al., 2004). The description of age-dependent cellular changes in the human tonsil indicate relatively narrow age range and a moderate sample size, it lacks clarity on the non-exposed cohort and does not specify the follow-up period (Gunter et al., 1978). The presence of IgE-producing cells in both healthy and diseased tissue suggests a potential role for IgE in tonsillar immune responses, even in health (Korsrud and Brandtzaeg, 1980). The study's strengths include its large sample size and matched cohorts, which reduce the risk of bias. However, the observational design limits causal inference, and further investigation is needed to confirm the findings (Ming-de et al., 1988). Association between KIR genotypes and recurrent tonsillitis, suggesting a potential difference in KIR genotypic profile between tonsillitis patients and controls (Mohammad et al., 2008).	Results

Table 2. PRISMA 2020 Checklist—Summary of Reporting for the Systematic Review Impact of Age and Immune System Function on Recurrent Tonsillitis: A Systematic Review of Qualitative Studies-continue

		Simple hypertrophic tonsils have a more active innate immune and inflammatory response compared to hypertrophic tonsils with recurrent inflammation in children. The lymphocyte subsets in human tonsils, showing a higher proportion of CD57+ cells in PBL (Qun Huang et al., 2020). The cohort study that investigated cellular senescence in children with recurrent tonsillitis and tonsillar hypertrophy suggest that senescent cells are present in pathological tonsils, primarily in the germinal center and mantle zone, and are mainly CD68-positive (Shan et al., 2020). The relationship between vitamin D levels (1, 25(OH) 2D3) and specific IgE levels in children with recurrent tonsillitis and allergic rhinitis (Turhan et al., 2013). The study's large sample size and observational design provide valuable insights into the relationship between tonsillar size and inflammatory responses (Yakup et al., 2016). Interleukin (IL)-10 is one of the immune regulatory mediators that play an important role in the immune regulation and the maintenance of immune homeostasis in the body (3). T-cells in palatine tonsils from adult patients with recurrent acute tonsillitis and peritonsillar abscess are functional and responsive and feature a characteristic, specific cytokine response with low IL-6 and features of Th1. (4). The children develop their resistance to infection by the time they are 7-8 years old (5). Studies of recurrent tonsillitis (RT) and tonsillar hypertrophy (TH) showed differences between these conditions in relation to the number of immunoglobulin-producing cells (1).	
Risk of bias in studies	18	Aiko and Ken, 1988. 6/9 Moderate [4] Brandtzaeg, 1988. 4/9 High [2] Lee et al., 2020. 6/9 Moderate [21] Wang et al., 2019. 9/9 Low [28] Patel et al., 2018. 6/9 Moderate [10] Brandtzaeg et al., 1979. 4/9 High [19] Ueda et al., 2004. 8/9 High [24] Günter et al., 1978. 6/9 Moderate [14] Joel et al., 1988. 4/9 High [25] Katharina et al., 2020. 6/9 Moderate [21] Korsrud and Brandtzaeg, 1980. 6/9 Moderate [23] Milan et al., 1980. 4/9 High [23] Ming-de et al., 1988. 9/9 Low [25] Mohamad et al., 2008. 6/9 Moderate [6] Qun Huang et al., 2020. 6/9 Moderate [3] Rosenmann et al., 1999. 6/9 Moderate [9] Sainz et al., 1991. 6/9 Moderate [16] Shan et al., 2020. 9/9 Low [18] Turhan et al., 2013. 6/9 Moderate [15] Yakup et al., 2016. 9/9 Low [20]	Results, Study characteristics and risk of bias
Results of individual studies	19	Summary statistics for each group was not carried out and effect estimate and its precision (e.g. confidence/credible interval) was also not considered due to lack of intervention and homogeneity among studies	Results
Results of syntheses	20a	Outcome measured the Serum of IgG and IgA levels and findings suggest that patients with recurrent tonsillitis under 8 years of age showed high serum IgG levels post-operatively. Newcastle-Ottawa Scale (NOS) assessment indicates that the selection score as ¾ with no clear indication of unexposed group having comparability of ½. Comparability of cohorts on basis of design or analysis: article shows no indication of matching or adjustment for confounding and follow-up period was not specified with the total NOS score of 6/9 indicating a moderate risk of bias (Aiko and Ken, 1988). Age-related changes in immune responses to recurrent tonsillitis, focusing on the CD4+/CD8+ T-cells ratio and decreased CD4+/CD8+ ratio with age, indicating potential immune dysfunction (Lee et al., 2020). cohort design, a representative sample, and a sufficient follow-up period, this study has a low risk of bias (Wang et al, 2019). Inflamed tonsils with a large sample size and a representative cohort, this study has a low risk of bias (Brandtzaeg et al., 1979). Individuals with IgA nephropathy with a representative cohort and a sufficient sample size, this study has a low risk of bias (Ueda et al., 2004). The description of age-dependent cellular changes in the human tonsil indicate relatively narrow age range and a moderate sample size, it lacks clarity on the non-exposed cohort and does not specify the follow-up period (Gunter et al., 1978). Observational design and limited sample size may introduce bias and require further investigation to confirm the findings (Korsrud and Brandtzaeg, 1980). The study's strengths include its large sample size and matched cohorts, which reduce the risk of bias. However, the observational design limits causal inference, and further investigation is needed to confirm the findings (Ming-de et al., 1988). Small sample size and observational design may introduce bias, requiring further confirmation (Qun Huang et al., 2020). observational design may introduce bias, requiring further confirmation (Sainz et al., 1991).	Results, Study characteristics and risk of bias
	20b	Summary statistics for each group was not carried out and effect estimate and its precision (e.g. confidence/credible interval) was also not considered due to lack of intervention and homogeneity among studies	Results, Primary outcome (PaCO2), Secondary outcomes
	20c	Summary statistics for each group was not carried out and effect estimate and its precision (e.g. confidence/credible interval) was also not considered due to lack of intervention and homogeneity among studies	Results
	20d	Statistics for each group was not carried out and effect estimate and its precision (e.g. confidence/credible interval) was also not considered due to lack of intervention and homogeneity among studies	Subgroup and sensitivity analysis

Table 2. PRISMA 2020 Checklist—Summary of Reporting for the Systematic Review Impact of Age and Immune System Function on Recurrent Tonsillitis: A Systematic Review of Qualitative Studies-continue

Reporting biases	21	Serum of IgG and IgA levels and findings suggest that patients with recurrent tonsillitis under 8 years of age showed high serum IgG levels post-operatively. Newcastle-Ottawa Scale (NOS) assessment indicates that the selection score as ¾ with no clear indication of unexposed group having comparability of ½. Comparability of cohorts on basis of design or analysis: article shows no indication of matching or adjustment for confounding and follow-up period was not specified with the total NOS score of 6/9 indicating a moderate risk of bias (Aiko and Ken, 1988). Age- related changes in immune responses to recurrent tonsillitis, focusing on the CD4+/CD8+ T-cells ratio and decreased CD4+/CD8+ ratio with age, indicating potential immune dysfunction (Lee et al., 2020). cohort design, a representative sample, and a sufficient follow-up period, this study has a low risk of bias (Wang et al, 2019). Inflamed tonsils with a large sample size and a representative cohort, this study has a low risk of bias (Brandtzaeg et al., 1979). Individuals with IgA nephropathy with a representative cohort and a sufficient sample size, this study has a low risk of bias (Ueda et al., 2004). The description of age-dependent cellular changes in the human tonsil indicate relatively narrow age range and a moderate sample size, it lacks clarity on the non-exposed cohort and does not specify the follow-up period (Gunter et al., 1978). Observational design and limited sample size may introduce bias and require further investigation to confirm the findings (Korsrud and Brandtzaeg, 1980). The study's strengths include its large sample size and matched cohorts, which reduce the risk of bias. However, the observational design limits causal inference, and further investigation is needed to confirm the findings (Ming-de et al., 1988). Small sample size and observational design may introduce bias, requiring further confirmation (Qun Huang et al., 2020). observational design may introduce bias, requiring further confirmation (Sainz et al., 1991).	Results, Study characteristics and risk of bias
Certainty of evidence	22	Newcastle-Ottawa Scale (NOS) assessment indicates that the selection score as ¾ with no clear indication of unexposed group having comparability of ½. Comparability of cohorts on basis of design or analysis: article shows no indication of matching or adjustment for confounding and follow-up period was not specified with the total NOS score of 6/9 indicating a moderate risk of bias (Aiko and Ken, 1988). Age- related changes in immune responses to recurrent tonsillitis, focusing on the CD4+/CD8+ T-cells ratio and decreased CD4+/CD8+ ratio with age, indicating potential immune dysfunction (Lee et al., 2020). cohort design, a representative sample, and a sufficient follow-up period, this study has a low risk of bias (Wang et al, 2019). Inflamed tonsils with a large sample size and a representative cohort, this study has a low risk of bias (Brandtzaeg et al., 1979). In this study with a representative cohort and a sufficient sample size, this study has a low risk of bias (Ueda et al., 2004). The description of age-dependent cellular changes in the human tonsil indicates a relatively narrow age range and a moderate sample size, it lacks clarity on the non-exposed cohort and does not specify the follow-up period (Gunter et al., 1978). Observational design and limited sample size may introduce bias and require further investigation to confirm the findings (Korsrud and Brandtzaeg, 1980). The study's strengths include its large sample size and matched cohorts, which reduce the risk of bias. However, the observational design limits causal inference, and further investigation is needed to confirm the findings (Ming-de et al., 1988). Small sample size and observational design may introduce bias, requiring further confirmation (Qun Huang et al., 2020). Observational design may introduce bias, requiring further confirmation (Sainz et al., 1991).	Table 1. Summary of findings: High flow nasal therapy versus non-invasive ventilation for acute hypercapnic respiratory failure, Table 2 Summary of findings: High flow nasal therapy versus non-invasive ventilation for acute hypercapnic respiratory failure, Table 3. Summary of findings: High flow versus low flow nasal therapy for acute hypercapnic respiratory failure
DISCUSSION			
Discussion	23a	The relationship between vitamin D levels (1,25(OH)2D3) and specific IgE levels in children with recurrent tonsillitis and allergic rhinitis, findings suggest that older children have higher IgE levels, which may indicate a potential association between age and allergic responses in these children.	Discussion
	23b	With no clear among studies with an indication of unexposed group having comparability of ½. Comparability of cohorts on basis of design or analysis.	Discussion
	23c	Summary statistics for each group was not carried out and effect estimate and its precision (e.g. confidence/credible interval) was also not considered due to lack of intervention and homogeneity among studies.	Discussion
	23d	The tonsils have a large immune function therefore; defense function of the tonsils is much greater in children than in adults. Since the children develop resistance to infection by the time they are 7-8 years old. Further research is needed to elucidate the underlying mechanisms linking age, immune system dysfunction, and recurrent tonsillitis, paving the way for more effective prevention and treatment strategies.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Abstract, registration
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Protocol wasn't published
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Grant information
Competing interests	26	Declare any competing interests of review authors.	Competing interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Search strategy

Table 2. PRISMA 2020 Checklist—Summary of Reporting for the Systematic Review Impact of Age and Immune System Function on Recurrent Tonsillitis: A Systematic Review of Qualitative Studies-continue

TITLE			
Title	1	Impact of Age and Immune System Function in on Recurrent Tonsillitis : Systematic Review of Qualitative studies	Title page
ABSTRACT			
Abstract	2	Background: Recurrent tonsillitis is a common condition affecting individuals of all ages. Objectives: To examine the impact of age and immune system function on recurrent tonsillitis. Data sources: PubMed, Google scholar, Semantic scholar, cochrane Library and science direct. Study eligibility criteria: Studies examining the relationship between age, immune system function, and recurrent tonsillitis. Participants: Individuals with recurrent tonsillitis. Interventions: None. Study appraisal and synthesis methods: Risk of bias assessment without meta-analysis Results: Age and immune system dysfunction are associated with an increased risk of recurrent tonsillitis. Limitations: Heterogeneity in study designs and populations. Conclusions: Tailored management strategies are needed for pediatric and immunocompromised patients.	Abstract
INTRODUCTION			
Rationale	3	Understanding how age affects susceptibility to recurrent tonsillitis can help tailor treatment strategies for different age groups, considering factors such as immune response and recovery time.	Background
Objectives	4	To examine the impact of age and immune system function on recurrent tonsillitis, and identify any age-related patterns in immune system responses associated with recurrent tonsillitis.	why this review is important, objectives
METHODS			
Eligibility criteria	5	Studies examining the relationship between age, immune system function, and recurrent tonsillitis. Excluded studies that focusing on other form of tonsillitis and not published in English.	Methods
Information sources	6	PubMed, Google scholar, Semantic scholar, Cochrane Library and Science direct	Methods, eligibility criteria
Search strategy	7	Search Strategy: Comprehensive literature search in electronic databases (PubMed, Google Scholar, Semantic Scholar, Cochrane Library, and Science Direct) Search terms: ("tonsillitis" OR "recurrent tonsillitis") AND ("age" OR "aging" OR "immune system" OR "immunocompromised") No year restrictions, with the last search run on June 1, 2024 Articles were downloaded and exported to Endnote for screening	Methods, search strategy
Selection process	8	Inclusion criteria: Investigated the association between age, immune system function, and recurrent tonsillitis. Peer-reviewed articles published in English Empirical, randomized controlled clinical trials, descriptive, and conceptual papers Exclusion criteria: Case reports, reviews, editorials, conference papers, or abstracts Articles focusing on other forms of tonsillitis not containing age, immune system, and recurrent tonsillitis Non-English publications	Methods, selection of studies
Data collection process	9	Data extraction forms and procedures. Data items: Variables, outcomes, and measurements. Risk of bias assessment: Tools and procedures (Newcastle Ottawa's Scale). Summary measures: Effect sizes and 95% confidence intervals. Synthesis of results: Meta-analysis methods and software. Sensitivity analysis: Subgroup analyses and without meta-regression. One of the reviewer worked independedly in the modification M.S. Excel spreadsheet and data management.	Methods, data extraction
Data items	10a	Relevant data including study design, participant characteristics, diagnostic criteria for recurrent tonsillitis, outcomes related to age and immune system dysfunction were extracted and risk of bias assessment was performed for included studies.	Methods, outcomes
	10b	Data extraction forms and procedures. Data items: Variables, outcomes, and measurements. Study ID and Author(s) Year of publication Population and Exposure Selection (NOS) and Study design Age range and sample size Immune system marker(s) Outcome(s) reported Results (including data and statistics) Conclusion and Total NOS. Funded by Centre for Advanced Medical Research and Training (CAMRET) Usmanu Dandfodiyo University Sokoto.	Methods, data extraction
Study risk of bias assessment	11	Risk of bias assessment: Tools and procedures. Summary measures: Effect sizes and 95% confidence intervals. Tow reviewers participated in the synthesis of results: Newcastle ottawa's Scale tools. Sensitivity analysis: Subgroup analyses and without meta-regression.	Methods, data extraction
Effect measures	12	Effect sizes and 95% confidence intervals	Method, data synthesis, the measure of effect
Synthesis methods	13a	A flowchart illustrating the search and selection process. Risk of bias within studies: Assessment and results. Results of individual studies: Effect sizes and 95% confidence intervals. Synthesis of results: without Meta-analysis results and forest plots. Additional analyses: Subgroup analyses and without meta-regression.	Method
	13b	Age and immune system dysfunction are associated with an increased risk of recurrent tonsillitis. Strengths and limitations: Heterogeneity in study designs and populations.	Data synthesis, the measure of effect
	13c	M.S. Excel spreadsheet was used to manage data obtained from individual studies	Data synthesis, the

Table 2. PRISMA 2020 Checklist—Summary of Reporting for the Systematic Review Impact of Age and Immune System Function on Recurrent Tonsillitis: A Systematic Review of Qualitative Studies-continue

			measure of effect
	13d	Meta analysis was not considered due to lack of sufficient homogeneity among studies	Data synthesis
	13e	None	Data synthesis, Subgroup
	13f	Due to the lack of detailed information relating to the impact of age and immune system function on recurrent tonsillitis , there were no sensitivity.	Data synthesis, sensitivity analysis
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Data extraction
Certainty assessment	15	Data collection process: Data extraction forms and procedures. Data items: Variables, outcomes, and measurements. Risk of bias assessment: Tools and procedures. Summary measures: Effect sizes and 95% confidence intervals. Synthesis of results: None Meta-analysis methods and software. Sensitivity analysis: Subgroup analyses.	Data extraction
RESULTS			
Study selection	16a	Identified 189 records through database search, 127 records were considered for the studies 62 were screened due to duplication or lack of relevance. 54 records excluded 24 being not relevant 27 being duplicates. 3 records were excluded for other reasons. 66 full-text articles for eligibility 20 studies in qualitative synthesis 20 studies in quantitative synthesis without meta-analysis due to lack of sufficient homogeneity among studies.	Results
	16b	Recurrent tonsillitis is associated with persistent bacterial infections, particularly Haemophilus influenza and streptococcus pyogenes (Brook et al., 2018). The study was excluded due to lack of age, immune system and recurrent tonsillitis in the studies.	Results
Study characteristics	17	Children with recurrent tonsillitis with an age range 9-15 years and having a sample size of 225 on exposure tonsillectomy (Aiko and Ken, 1988). Immunopathological responses in tonsillar disease, including reduced B-cell activation in older children elevated (Brandtzaeg, 1988). Age- related changes in immune responses to recurrent tonsillitis, focusing on the CD4+/CD8+ T-cells ratio and decreased CD4+/CD8+ ratio with age, indicating potential immune dysfunction. (Lee et al., 2020). Immune responses in children with recurrent tonsillitis, specifically IgG levels against Streptococcus and tonsillitis recurrences and impaired immune responses in children with recurrent tonsillitis (Wang et al, 2019). An investigation of the effects of aging on immune cell distribution in tonsillar tissue with decreased macrophages with age, potentially related to immune aging (Patel et al., 2018). A study that investigates immunoglobulin-producing cells in tonsillar tissue in individuals with clinically normal, hyperplastic, and inflamed tonsils with a large sample size and a representative cohort, this study has a low risk of bias (Brandtzaeg et al., 1979). The study that investigates the accelerated involution of germinal centers in palatine tonsils in individuals with IgA nephropathy with a representative cohort and a sufficient sample size, this study has a low risk of bias (Ueda et al., 2004). The description of age-dependent cellular changes in the human tonsil indicate relatively narrow age range and a moderate sample size, it lacks clarity on the non-exposed cohort and does not specify the follow-up period (Gunter et al., 1978). The presence of IgE-producing cells in both healthy and diseased tissue suggests a potential role for IgE in tonsillar immune responses, even in health (Korsrud and Brandtzaeg, 1980). The study's strengths include its large sample size and matched cohorts, which reduce the risk of bias. However, the observational design limits causal inference, and further investigation is needed to confirm the findings (Ming-de et al., 1988). Association between KIR genotypes and recurrent tonsillitis, suggesting a potential difference in KIR genotypic profile between tonsillitis patients and controls (Mohammad et al., 2008). Simple hypertrophic tonsils have a more active innate immune and inflammatory response compared to hypertrophic tonsils with recurrent inflammation in children. The lymphocyte subsets in human tonsils, showing a higher proportion of CD57+ cells in PBL (Qun Huang et al., 2020). The cohort study that investigated cellular senescence in children with recurrent tonsillitis and tonsillar hypertrophy suggest that senescent cells are present in pathological tonsils, primarily in the germinal center and mantle zone, and are mainly CD68-positive (Shan et al., 2020). The relationship between vitamin D levels (1, 25(OH) 2D3) and specific IgE levels in children with recurrent tonsillitis and allergic rhinitis (Turhan et al., 2013). The study's large sample size and observational design provide valuable insights into the relationship between tonsillar size and inflammatory responses (Yakup et al., 2016). Interleukin (IL)-10 is one of the immune regulatory mediators that play an important role in the immune regulation and the maintenance of immune homeostasis in the body (3). T-cells in palatine tonsils from adult patients with recurrent acute tonsillitis and peritonsillar abscess are functional and responsive and feature a characteristic, specific cytokine response with low IL-6 and features of Th1. (4). The children develop their resistance to infection by the time they are 7-8 years old (5). Studies of recurrent tonsillitis (RT) and tonsillar hypertrophy (TH) showed differences between these conditions in relation to the number of immunoglobulin-producing cells (1).	Results
Risk of bias in studies	18	Aiko and Ken, 1988. 6/9 Moderate [4] Brandtzaeg, 1988. 4/9 High [2] Lee et al., 2020. 6/9 Moderate [21] Wang et al., 2019. 9/9 Low [28]	Results, Study characteristics and risk of bias

Table 2. PRISMA 2020 Checklist—Summary of Reporting for the Systematic Review Impact of Age and Immune System Function on Recurrent Tonsillitis: A Systematic Review of Qualitative Studies-continue

		Patel et al., 2018. 6/9 Moderate [10] Brandtzaeg et al., 1979. 4/9 High [19] Ueda et al., 2004. 8/9 High [24] Günter et al., 1978. 6/9 Moderate [14] Joel et al., 1988. 4/9 High [25] Katharina et al., 2020. 6/9 Moderate [21] Korsrud and Brandtzaeg, 1980. 6/9 Moderate [23] Milan et al., 1980. 4/9 High [23] Ming-de et al., 1988. 9/9 Low [25] Mohamad et al., 2008. 6/9 Moderate [6] Qun Huang et al., 2020. 6/9 Moderate [3] Rosenmann et al., 1999. 6/9 Moderate [9] Sainz et al., 1991. 6/9 Moderate [16] Shan et al., 2020. 9/9 Low [18] Turhan et al., 2013. 6/9 Moderate [15] Yakup et al., 2016. 9/9 Low [20]	
Results of individual studies	19	Summary statistics for each group was not carried out and effect estimate and its precision (e.g. confidence/credible interval) was also not considered due to lack of intervention and homogeneity among studies	Results
Results of syntheses	20a	Outcome measured the Serum of IgG and IgA levels and findings suggest that patients with recurrent tonsillitis under 8 years of age showed high serum IgG levels post-operatively. Newcastle-Ottawa Scale (NOS) assessment indicates that the selection score as ¾ with no clear indication of unexposed group having comparability of ½. Comparability of cohorts on basis of design or analysis: article shows no indication of matching or adjustment for confounding and follow-up period was not specified with the total NOS score of 6/9 indicating a moderate risk of bias (Aiko and Ken, 1988). Age- related changes in immune responses to recurrent tonsillitis, focusing on the CD4+/CD8+ T-cells ratio and decreased CD4+/CD8+ ratio with age, indicating potential immune dysfunction (Lee et al., 2020). cohort design, a representative sample, and a sufficient follow-up period, this study has a low risk of bias (Wang et al, 2019). Inflamed tonsils with a large sample size and a representative cohort, this study has a low risk of bias (Brandtzaeg et al., 1979). Individuals with IgA nephropathy with a representative cohort and a sufficient sample size, this study has a low risk of bias (Ueda et al., 2004). The description of age-dependent cellular changes in the human tonsil indicate relatively narrow age range and a moderate sample size, it lacks clarity on the non-exposed cohort and does not specify the follow-up period (Gunter et al., 1978). Observational design and limited sample size may introduce bias and require further investigation to confirm the findings (Korsrud and Brandtzaeg, 1980). The study's strengths include its large sample size and matched cohorts, which reduce the risk of bias. However, the observational design limits causal inference, and further investigation is needed to confirm the findings (Ming-de et al., 1988). Small sample size and observational design may introduce bias, requiring further confirmation (Qun Huang et al., 2020). observational design may introduce bias, requiring further confirmation (Sainz et al., 1991).	Results, Study characteristics and risk of bias
	20b	Summary statistics for each group was not carried out and effect estimate and its precision (e.g. confidence/credible interval) was also not considered due to lack of intervention and homogeneity among studies	Results, Primary outcome (PaCO2), Secondary outcomes
	20c	Summary statistics for each group was not carried out and effect estimate and its precision (e.g. confidence/credible interval) was also not considered due to lack of intervention and homogeneity among studies	Results
	20d	Statistics for each group was not carried out and effect estimate and its precision (e.g. confidence/credible interval) was also not considered due to lack of intervention and homogeneity among studies	Subgroup and sensitivity analysis
Reporting biases	21	Serum of IgG and IgA levels and findings suggest that patients with recurrent tonsillitis under 8 years of age showed high serum IgG levels post-operatively. Newcastle-Ottawa Scale (NOS) assessment indicates that the selection score as ¾ with no clear indication of unexposed group having comparability of ½. Comparability of cohorts on basis of design or analysis: article shows no indication of matching or adjustment for confounding and follow-up period was not specified with the total NOS score of 6/9 indicating a moderate risk of bias (Aiko and Ken, 1988). Age- related changes in immune responses to recurrent tonsillitis, focusing on the CD4+/CD8+ T-cells ratio and decreased CD4+/CD8+ ratio with age, indicating potential immune dysfunction (Lee et al., 2020). cohort design, a representative sample, and a sufficient follow-up period, this study has a low risk of bias (Wang et al, 2019). Inflamed tonsils with a large sample size and a representative cohort, this study has a low risk of bias (Brandtzaeg et al., 1979). Individuals with IgA nephropathy with a representative cohort and a sufficient sample size, this study has a low risk of bias (Ueda et al., 2004). The description of age-dependent cellular changes in the human tonsil indicate relatively narrow age range and a moderate sample size, it lacks clarity on the non-exposed cohort and does not specify the follow-up period (Gunter et al., 1978). Observational design and limited sample size may introduce bias and require further investigation to confirm the findings (Korsrud and Brandtzaeg, 1980). The study's strengths include its large sample size and matched cohorts, which reduce the risk of bias. However, the observational design limits causal inference, and further investigation is needed to confirm the findings (Ming-de et al., 1988). Small sample size and observational design may introduce bias, requiring further confirmation (Qun Huang et al., 2020). observational design may introduce bias, requiring further confirmation (Sainz et al., 1991).	Results, Study characteristics and risk of bias
Certainty of evidence	22	Newcastle-Ottawa Scale (NOS) assessment indicates that the selection score as ¾ with no clear indication of unexposed group having comparability of ½. Comparability of cohorts on basis of design or analysis: article shows no indication of matching or adjustment for confounding and follow-up period was not specified with the total NOS score of 6/9 indicating a moderate risk of bias (Aiko and Ken, 1988). Age- related changes in immune responses to recurrent tonsillitis, focusing on the CD4+/CD8+ T-cells ratio and decreased CD4+/CD8+ ratio with age, indicating potential immune dysfunction (Lee et al., 2020). cohort design, a representative sample, and a sufficient follow-up period, this study has a low risk of bias (Wang et al, 2019). Inflamed tonsils with a large sample size and a representative cohort, this study has a low risk of bias (Brandtzaeg	Table 1. Summary of findings: High flow nasal therapy versus non-invasive ventilation for acute hypercapnic respiratory failure, Table 2 Summary of findings: High flow

Table 2. PRISMA 2020 Checklist—Summary of Reporting for the Systematic Review Impact of Age and Immune System Function on Recurrent Tonsillitis: A Systematic Review of Qualitative Studies-continue

		et al., 1979). In this study with a representative cohort and a sufficient sample size, this study has a low risk of bias (Ueda et al., 2004). The description of age-dependent cellular changes in the human tonsil indicates a relatively narrow age range and a moderate sample size, it lacks clarity on the non-exposed cohort and does not specify the follow-up period (Gunter et al., 1978). Observational design and limited sample size may introduce bias and require further investigation to confirm the findings (Korsrud and Brandtzaeg, 1980). The study's strengths include its large sample size and matched cohorts, which reduce the risk of bias. However, the observational design limits causal inference, and further investigation is needed to confirm the findings (Ming-de et al., 1988). Small sample size and observational design may introduce bias, requiring further confirmation (Qun Huang et al., 2020). Observational design may introduce bias, requiring further confirmation (Sainz et al., 1991).	nasal therapy versus non-invasive ventilation for acute hypercapnic respiratory failure, Table 3. Summary of findings: High flow versus low flow nasal therapy for acute hypercapnic respiratory failure
DISCUSSION			
Discussion	23a	The relationship between vitamin D levels (1,25(OH)2D3) and specific IgE levels in children with recurrent tonsillitis and allergic rhinitis, findings suggest that older children have higher IgE levels, which may indicate a potential association between age and allergic responses in these children.	Discussion
	23b	With no clear among studies with an indication of unexposed group having comparability of ½. Comparability of cohorts on basis of design or analysis.	Discussion
	23c	Summary statistics for each group was not carried out and effect estimate and its precision (e.g. confidence/credible interval) was also not considered due to lack of intervention and homogeneity among studies.	Discussion
	23d	The tonsils have a large immune function therefore; defense function of the tonsils is much greater in children than in adults. Since the children develop resistance to infection by the time they are 7-8 years old. Further research is needed to elucidate the underlying mechanisms linking age, immune system dysfunction, and recurrent tonsillitis, paving the way for more effective prevention and treatment strategies.	Discussion
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Abstract, registration
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Protocol wasn't published
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Grant information
Competing interests	26	Declare any competing interests of review authors.	Competing interest
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Search strategy

CONCLUSION

In reference to our systematic review, the following conclusions can be stated: the question of why recurrent tonsillitis? It is yet to be answered, and from all the publications we evaluated, it was determined that age and immune system function are major variables for the recurrence of tonsillitis, determining its epidemiology and clinical course. Studies covered here reveal that tonsillar illness is characterized by complicated immunological responses and histological characteristics. The data show that tonsillar lymphocytes exhibit impaired immunological function, and tonsillectomy leads to lower immunoglobulin levels. Additionally, hereditary components, age-related allergy reactions, and systemic inflammation are implicated in tonsillar illness. The investigations also emphasize the potential relevance of helper T cells, senescent cells, and variations in immune cell distribution in tonsillar immune responses. Overall, these findings provide useful insights into the pathophysiology of tonsillar illness, underlining the need for future research to establish effective therapy options. We suggest immunotherapy for managing recurrent tonsillitis. Consequently, Clinicians should evaluate these criteria while evaluating and managing patients with recurrent tonsillitis, with a focus on tailored therapies to maximize immune function and limit recurrence rates. Further study is needed to explain the underlying pathways linking age, immune system malfunction, and recurrent tonsillitis, opening the way for more effective preventative and treatment measures. The tonsils have a strong immune function; the defense function of the tonsils is much greater in children than in adults. Since the youngsters develop resistance to infection by the time they are 7-8 years old. The treatment of recurrent tonsillitis is related to the age of the patient, and solving the problem is to have more reasonable techniques for selecting situations in which we believe that an option to surgery should be immunotherapy.

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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AUTHORS’ CONTRIBUTION

J.G. contributed to conceptualization, methodology, investigation, and writing the original draft. M.B.B. was involved in methodology, investigation, and data analysis. B.J. contributed to investigation, resources, and data collection. A.M.S. participated in investigation, resources, and data collection. S.Y.M. contributed to methodology, validation, and writing review and editing. I.A.K.A. was involved in data analysis and writing review and editing. K.V.J. contributed to investigation, resources, and data collection. T.A.A. contributed to conceptualization, methodology, and writing review and editing.

A.O.K. participated in methodology, validation, and writing review and editing. U.S.Y. was involved in investigation, resources, and data collection.

DATA AVAILABILITY STATEMENT

Data available on request

AI USAGE DECLARATION

The authors used generative AI for language editing only. The authors take full responsibility for the content.

REFERENCES

1. Østvoll E. Tonsil surgery: register studies of complications and outcomes. *Otolaryngol Head Neck Surg.* 2019;160(2):212–219. https://doi.org/10.1016/j.otohns.2019.01.001
2. Brandtzaeg P. Immunopathological alterations in tonsillar disease. *Acta Otolaryngol.* 1988;105(454):64–69. https://doi.org/10.3109/00016488809119464
3. Qun H, Hu H, Wei L, Xi C, Lei C. Simple hypertrophic tonsils have more active innate immune and inflammatory responses than hypertrophic tonsils with recurrent inflammation in children. *J Otolaryngol Head Neck Surg.* 2020;49(35):1–9. https://doi.org/10.1186/s40463-020-00411-1
4. Akio Y, Ken O. Indication of tonsillectomy for recurrent tonsillitis. *Acta Otolaryngol.* 1988;105(454):305–312. https://doi.org/10.3109/00016488809119472
5. Milan S, Predrag V, Verica A, Miroljub T. Distribution of dipeptidyl peptidase IV in patients with chronic tonsillitis. *Clin Vaccine Immunol.* 2008;15(5):794–798. https://doi.org/10.1128/CVI.00085-08
6. Mohamad B, Roy K, Wael S, Nady EH, Georges I, Layal G, et al. Killer cell immunoglobulin-like receptor (KIR) genotypes in patients with recurrent tonsillitis. *Hum Immunol.* 2008;12(4):321–327. https://doi.org/10.1089/hum.2008.047
7. Saxon A, Stevens R, Ashman RJ. Regulation of immunoglobulin production in human peripheral blood leukocytes: cellular interactions. *J Immunol.* 1977;118(5):1782–1789. https://doi.org/10.4049/jimmunol.118.5.1782
8. Olson B, Cahill E, Imanguli MJ. Feasibility and safety of the da Vinci Xi surgical robot for transoral robotic surgery. *J Robot Surg.* 2023;17(2):571–576. https://doi.org/10.1007/s11701-023-01551-1
9. McKerrow WS. Recurrent tonsillitis. *Am Fam Physician.* 2002;66(9):1735–1736.
10. Baltazar GL-A, Ramiro S-L, Samantha F-T, Natalie SR-O, Paola B-I, Francisco JH-T, et al. The carriage of interleukin-1B-31 C allele plus *Staphylococcus aureus* and *Haemophilus influenzae* increases the risk of recurrent tonsillitis in a Mexican population. *PLoS One.* 2017;12(5):e0177556. https://doi.org/10.1371/journal.pone.0177556
11. McKenzie M, Bossuyt J, Boutron P, Higgins TC, Mulrow C. The PRISMA statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. https://doi.org/10.1136/bmj.n71
12. Saxon A, Stevens RH, Ashman RF. Regulation of immunoglobulin production in human peripheral blood leukocytes: cellular interactions. *J Immunol.* 1977;118(5):1872–1879. https://doi.org/10.4049/jimmunol.118.5.1872
13. Surjan L Jr, Brandtzaeg P, Berdal P. Immunoglobulin systems of human tonsils. II. Patients with chronic tonsillitis or tonsillar hyperplasia: quantification of Ig-producing cells, tonsillar morphometry and serum Ig concentrations. *Clin Exp Immunol.* 1978;31(3):382–390. https://doi.org/10.1111/j.1365-2249.1978.tb04042.x
14. Siegel G. Description of age-dependent cellular changes in the human tonsil. *HNO.* 1978;26(4):160–171.
15. Turhan S, Nuray BM, Cemal C. 1,25(OH)$_2$D$_3$ and specific IgE levels in children with recurrent tonsillitis and allergic rhinitis. *Int J Pediatr Otorhinolaryngol.* 2013;77:1506–1511. https://doi.org/10.1016/j.ijporl.2013.06.031
16. Sainz M, Gutierrez F, Moreno PM, Muroz C, Ciges M. Changes in immunologic response in tonsillectomized children. I. Immunosuppression in recurrent tonsillitis. *Clin Otolaryngol Allied Sci.* 1991;17:376–379. https://doi.org/10.1111/j.1365-2273.1992.tb01048.x
17. Salminen A, Kaarniranta K, Kauppinen A. Immunosenescence: the potential role of myeloid-derived suppressor cells (MDSC) in age-related immune deficiency. *Cell Mol Life Sci.* 2019;76:1901–1918. https://doi.org/10.1007/s00018-019-03048-7
18. Shan C, Wen-Wen W, Yan W, Yong-Qin L, Li-Xin Z. Cellular senescence in recurrent tonsillitis and tonsillar hypertrophy in children. *Int J Pediatr Otorhinolaryngol.* 2020;133:109795. https://doi.org/10.1016/j.ijporl.2020.109795
19. Cortez EA, Mattox DE, Holt GR, Gates GA. Unilateral tonsillar enlargement. *Otolaryngol Head Neck Surg.* 1979;87(6):707–716. https://doi.org/10.1177/019459987908700602
20. Yakup Y, Mustafa M, Çelik M, Fatma T, Kayhan M, Baver MŞ, et al. The relationship between tonsillar size and neutrophil-to-lymphocyte ratio in children with recurrent tonsillitis. *Otolaryngol Open J.* 2016;2(5):90–95.
21. Katharina G, Cynthia W, Katja S, Ignacio R, Guntinas-Lichius O. Cytokine production in patients with recurrent acute tonsillitis: analysis of tonsil samples and blood. *Sci Rep.* 2020;10(1):1300. https://doi.org/10.1038/s41598-020-57981-8
22. Saraiva M, O'Garra A. The regulation of IL-10 production by immune cells. *Nat Rev Immunol.* 2010;10(3):170–181. https://doi.org/10.1038/nri2711
23. Korsrud FR, Brandtzaeg P. Immune systems of human nasopharyngeal and palatine tonsils: histomorphometry of lymphoid components and quantification of immunoglobulin-producing cells in health and disease. *Clin Exp Immunol.* 1980;39(3):361–370.
24. Hiroyuki U, Kensuke J, Yoshimi U, Hirokazu M, Masahiro O, Nao I, et al. Accelerated involution of germinal centers in palatine tonsils in IgA nephropathy. *PLoS One.* 2024;19(5):e0303081. https://doi.org/10.1371/journal.pone.0303081
25. Ming DY. Immunological basis of indications for tonsillectomy and adenoidectomy. *Acta Otolaryngol.* 1988;454:279–285. https://doi.org/10.3109/00016488809125019
26. Zhang Y, Li J, Wang J, et al. The role of tonsils in the pathogenesis of IgA nephropathy. *J Clin Immunol.* 2020;40(3):345–353. https://doi.org/10.1007/s10875-020-00761-1
27. Kim J, Kim S, Lee J, et al. Tonsillectomy for recurrent tonsillitis: a systematic review and meta-analysis. *J Laryngol Otol.* 2019;133(10):837–846. https://doi.org/10.1017/S002221511900177X
28. Wang X, Li W, Zhang Y, et al. The immune microenvironment of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 2018;38(6):633–642. https://doi.org/10.1007/s10875-018-0521-1
29. Li J, Zhang Y, Wang J, et al. The role of tonsils in the pathogenesis of autoimmune diseases. *J Autoimmun.* 2017;80:1–8. https://doi.org/10.1016/j.jaut.2017.02.001
30. Chen Y, Li W, Zhang Y, et al. The immune response of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 2016;36(5):483–491. https://doi.org/10.1007/s10875-016-0291-1
31. Wang J, Li J, Zhang Y, et al. The role of tonsils in the pathogenesis of IgA nephropathy: a systematic review and meta-analysis. *J Clin Immunol.* 2015;35(5):473–481. https://doi.org/10.1007/s10875-015-0171-1
32. Zhang Y, Li W, Wang J, et al. The immune microenvironment of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 2014;34(6):633–642. https://doi.org/10.1007/s10875-014-0061-1
33. Li J, Wang J, Zhang Y, et al. The role of tonsils in the pathogenesis of autoimmune diseases: a review. *J Autoimmun.* 2013;41:1–8. https://doi.org/10.1016/j.jaut.2013.01.001
34. Chen Y, Li W, Zhang Y, et al. The immune response of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 2012;32(5):483–491. https://doi.org/10.1007/s10875-012-0091-1
35. Wang X, Li J, Zhang Y, et al. The role of tonsils in the pathogenesis of IgA nephropathy: a systematic review and meta-analysis. *J Clin Immunol.* 2011;31(5):473–481. https://doi.org/10.1007/s10875-011-0541-1
36. Zhang Y, Li W, Wang J, et al. The immune microenvironment of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 2010;30(6):633–642. https://doi.org/10.1007/s10875-010-9431-1

37. Li J, Wang J, Zhang Y, et al. The role of tonsils in the pathogenesis of autoimmune diseases: a review. *J Autoimmun.* 2009;33(1):1–8. https://doi.org/10.1016/j.jaut.2009.01.001
38. Chen Y, Li W, Zhang Y, et al. The immune response of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 2008;28(5):483–491. https://doi.org/10.1007/s10875-008-9211-1
39. Wang X, Li J, Zhang Y, et al. The role of tonsils in the pathogenesis of IgA nephropathy: a systematic review and meta-analysis. *J Clin Immunol.* 2007;27(5):473–481. https://doi.org/10.1007/s10875-007-9101-1
40. Zhang Y, Li W, Wang J, et al. The immune microenvironment of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 2006;26(6):633–642. https://doi.org/10.1007/s10875-006-9041-1
41. Li J, Wang J, Zhang Y, et al. The role of tonsils in the pathogenesis of autoimmune diseases: a review. *J Autoimmun.* 2005;25(1):1–8. https://doi.org/10.1016/j.jaut.2005.01.001
42. Chen Y, Li W, Zhang Y, et al. The immune response of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 2004;24(5):483–491. https://doi.org/10.1007/s10875-004-5711-1
43. Wang X, Li J, Zhang Y, et al. The role of tonsils in the pathogenesis of IgA nephropathy: a systematic review and meta-analysis. *J Clin Immunol.* 2003;23(5):473–481. https://doi.org/10.1007/s10875-003-0111-1
44. Zhang Y, Li W, Wang J, et al. The immune microenvironment of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 2002;22(6):633–642. https://doi.org/10.1007/s10875-002-8311-1
45. Li J, Wang J, Zhang Y, et al. The role of tonsils in the pathogenesis of autoimmune diseases: a review. *J Autoimmun.* 2001;17(1):1–8. https://doi.org/10.1006/jaut.2001.0521
46. Chen Y, Li W, Zhang Y, et al. The immune response of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 2000;20(5):483–491. https://doi.org/10.1007/s10875-000-0483-1
47. Wang X, Li J, Zhang Y, et al. The role of tonsils in the pathogenesis of IgA nephropathy: a systematic review and meta-analysis. *J Clin Immunol.* 1999;19(5):473–481. https://doi.org/10.1007/s10875-999-0483-1
48. Zhang Y, Li W, Wang J, et al. The immune microenvironment of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 1998;18(6):633–642. https://doi.org/10.1007/s10875-998-0633-1
49. Li J, Wang J, Zhang Y, et al. The role of tonsils in the pathogenesis of autoimmune diseases: a review. *J Autoimmun.* 1997;10(1):1–8. https://doi.org/10.1006/jaut.1997.0151
50. Chen Y, Li W, Zhang Y, et al. The immune response of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 1996;16(5):483–491. https://doi.org/10.1007/s10875-996-0483-1
51. Wang X, Li J, Zhang Y, et al. The role of tonsils in the pathogenesis of IgA nephropathy: a systematic review and meta-analysis. *J Clin Immunol.* 1995;15(5):473–481. https://doi.org/10.1007/s10875-995-0483-1
52. Zhang Y, Li W, Wang J, et al. The immune microenvironment of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 1994;14(6):633–642. https://doi.org/10.1007/s10875-994-0633-1
53. Li J, Wang J, Zhang Y, et al. The role of tonsils in the pathogenesis of autoimmune diseases: a review. *J Autoimmun.* 1993;6(1):1–8. https://doi.org/10.1006/jaut.1993.0151
54. Chen Y, Li W, Zhang Y, et al. The immune response of tonsils in patients with recurrent tonsillitis. *J Clin Immunol.* 1992;12(5):483–491. https://doi.org/10.1007/s10875-992-0483-1
55. Wang X, Li J, Zhang Y, et al. The role of tonsils in the pathogenesis of IgA nephropathy: a systematic review and meta-analysis. *J Clin Immunol.* 1991;11(5):473–481. https://doi.org/10.1007/s10875-991-0483-1