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Risk of Autoimmune Thyroid Dysfunction in Multiple Sclerosis Patients Treated with Alemtuzumab: A Systematic Review

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Abstract **Objectives:** This systematic review consolidates current evidence to delineate the spectrum of alemtuzumab-induced thyroid autoimmunity in patients with MS. **Methods:** PubMed, Embase, Web of Science, Cochrane Library and ClinicalTrials.gov were searched up to June 2025 for studies reporting thyroid outcomes following alemtuzumab in MS. Eligible designs included randomized trials and observational cohorts. Data were extracted on incidence, subtype distribution, time to onset and management. Study quality was assessed using the Newcastle–Ottawa Scale and Cochrane/ROBINS-I tools. **Results:** Out of 2,397 records, 11 studies met inclusion criteria, encompassing approximately 1,626 participants. AITD occurred in about one-third of treated individuals. Graves' disease was the predominant phenotype (33–65% of cases), followed by Hashimoto's thyroiditis and TRAb-positive hypothyroidism. Onset typically occurred 18–30 months after the first infusion, peaking around year 3. Fluctuating courses between hyper- and hypothyroidism were reported in up to 15% of cases. Most events were mild or moderate and controlled with antithyroid drugs or levothyroxine; radioiodine or thyroidectomy were rarely required. **Conclusion** Autoimmune thyroid dysfunction is a frequent and distinctive complication of alemtuzumab in MS. The majority of cases are manageable, but the unpredictable course warrants regular thyroid-function testing every three months for at least four years after treatment and continued long-term surveillance.

Key Words Multiple Sclerosis, Alemtuzumab, Autoimmune Thyroid Disease, Graves' Disease

INTRODUCTION

Multiple Sclerosis (MS) is a chronic, immune-mediated demyelinating disease of the Central Nervous System (CNS) that affects over 2.8 million people worldwide [1]. MS is driven by a combination of genetic susceptibility and environmental triggers such as HLA-DRB1 polymorphisms, vitamin D deficiency, smoking and obesity. MS causes episodic and progressive neurological dysfunction through inflammatory destruction of myelin and axons [2,3]. Most patients present with a relapsing–remitting course (RRMS), though some transition to secondary progressive (SPMS) or primary progressive (PPMS) forms over time [4].

The past two decades have transformed MS management, with Disease-Modifying Therapies (DMTs) offering improved control of relapse activity and disability accumulation. Among high-efficacy options, alemtuzumab, a humanized anti-CD52 monoclonal antibody, has emerged as a potent induction therapy capable of long-term disease suppression after only two annual treatment cycles [5].

Despite its durable efficacy, alemtuzumab's clinical adoption has been tempered by a distinctive safety profile characterized by secondary autoimmune complications, including immune thrombocytopenia, nephropathies and particularly autoimmune thyroid disease [6,7]. These adverse events have reshaped its risk–benefit evaluation and

restricted its indication to active RRMS after inadequate response to prior therapy [8]. Although several studies have reported thyroid events following treatment, variability in diagnostic definitions, follow-up duration and patient characteristics has limited the comparability of results. In a meta-analysis by Scappaticcio *et al.* [8], thyroid autoimmunity occurred in approximately one-third of treated patients, with Graves' disease representing 63% of cases and Hashimoto's thyroiditis 15%. Similarly, Yang *et al.* [9] reported a pooled incidence of 22% autoimmune thyroid events across 37 studies including more than 4,000 patients. With alemtuzumab increasingly used to achieve durable remission in relapsing multiple sclerosis, its association with secondary thyroid autoimmunity warrants closer attention. Therefore, this systematic review consolidates current evidence to delineate the spectrum of alemtuzumab-induced thyroid autoimmunity in patients with multiple sclerosis. While previous meta-analyses have primarily focused on estimating the overall incidence of thyroid autoimmunity following alemtuzumab treatment, they provide limited insight into clinical phenotypes, disease evolution and management patterns. The present review synthesizes updated trial and real-world evidence with particular attention to subtype distribution, timing of onset, fluctuating disease courses and treatment outcomes.

METHODS

In this systematic review and meta-analysis, all procedures adopted were consistent with PRISMA guidelines [10].

Search Strategy and Study Selection

A systematic search was conducted in PubMed, Web of Science, Cochrane library, clinicaltrials.gov and EMBASE up to June 2025, using a PICO-based strategy with terms such as Alemtuzumab, multiple sclerosis, autoimmune thyroid dysfunction and related keywords. No restrictions were applied regarding age, gender, or country. Search results were imported into EndNote (v20) for duplicate removal, then screened using Rayyan. Two reviewers independently screened titles, abstracts and full texts, resolving disagreements by discussion. Full search strategies are available in the Supplementary Materials

Eligibility Criteria

Studies were included if they met the following criteria: (1) peer-reviewed, full-text articles published in English or Arabic; (2) involved the use of alemtuzumab in patients diagnosed with MS according to the McDonald criteria [11]; and (3) reported on thyroid events or dysfunction associated with alemtuzumab use. Eligible study designs included Randomized Controlled Trials (RCTs), observational studies and case series. Exclusion criteria were: (a) case reports, reviews and conference abstracts; (b) studies where alemtuzumab was used for conditions other than MS; and (c) studies involving patients with pre- existing thyroid dysfunction before initiating alemtuzumab therapy.

Data Extraction

We developed a data extraction sheet in Microsoft Excel to collect all relevant information from the included studies. The form was pilot-tested and modified accordingly. Extracted data included study ID (author, year), country, study design, sample size, participant characteristics (ethnicity, age, sex), MS subtype (if reported), details of the intervention (alemtuzumab dosage, number of treatment cycles, administration schedule), comparator group details (type, follow-up duration, number of treatment cycles), study duration and follow-up period after alemtuzumab administration. Outcome data included the number and percentage of cases with Graves' disease or other thyroid dysfunctions, time to onset and the diagnostic methods used to identify thyroid events.

Study Quality Assessment

The quality of the included observational studies was assessed using the Newcastle-Ottawa Scale (NOS) [12]. Two reviewers independently evaluated each study and those with NOS scores above 5 were considered of sufficient quality for inclusion in the meta-analysis. For Randomized Controlled Trials (RCTs), the risk of bias was independently assessed by two reviewers using the Cochrane Risk of Bias Tool, following Cochrane guidelines [13]. Any discrepancies were resolved through discussion or consultation with a third reviewer when necessary.

RESULTS

Study Selection

The literature search using the defined algorithm (detailed search strategy available in the Appendix) yielded 2,397 articles. After duplicate removal via Rayyan and manual screening, 948 records were assessed by title and abstract. Of these, 68 full-texts were reviewed and 11 studies met the inclusion criteria. The selection process is summarized in the PRISMA 2020 flow diagram (Figure 1).

The 11 included studies represented single-center series, multicenter cohorts and post-marketing/clinical-trial safety analyses conducted across Europe, North America and Australia. Sample sizes ranged from 23 to 811 patients, with a cumulative total of approximately 1,626 participants. Study designs included retrospective chart reviews, cohort analyses of clinical-trial populations and registry-based reports. Follow-up durations varied widely: while some cohorts reported long-term outcomes exceeding 18 months, most thyroid events occurred within 4 years of the first alemtuzumab exposure.

A total of 494 cases of thyroid dysfunction were identified (Table 1). Where denominators were available, the incidence of thyroid events ranged from 18.7% to 41%, with most large series reporting rates between 30–36%. Based on pooled crude data, the overall incidence of thyroid dysfunction was estimated at 32.3% (470/1,454 patients). Several studies noted biphasic or fluctuating courses, with transitions between hyperthyroidism and hypothyroidism and occasional reversion to hyperthyroidism.

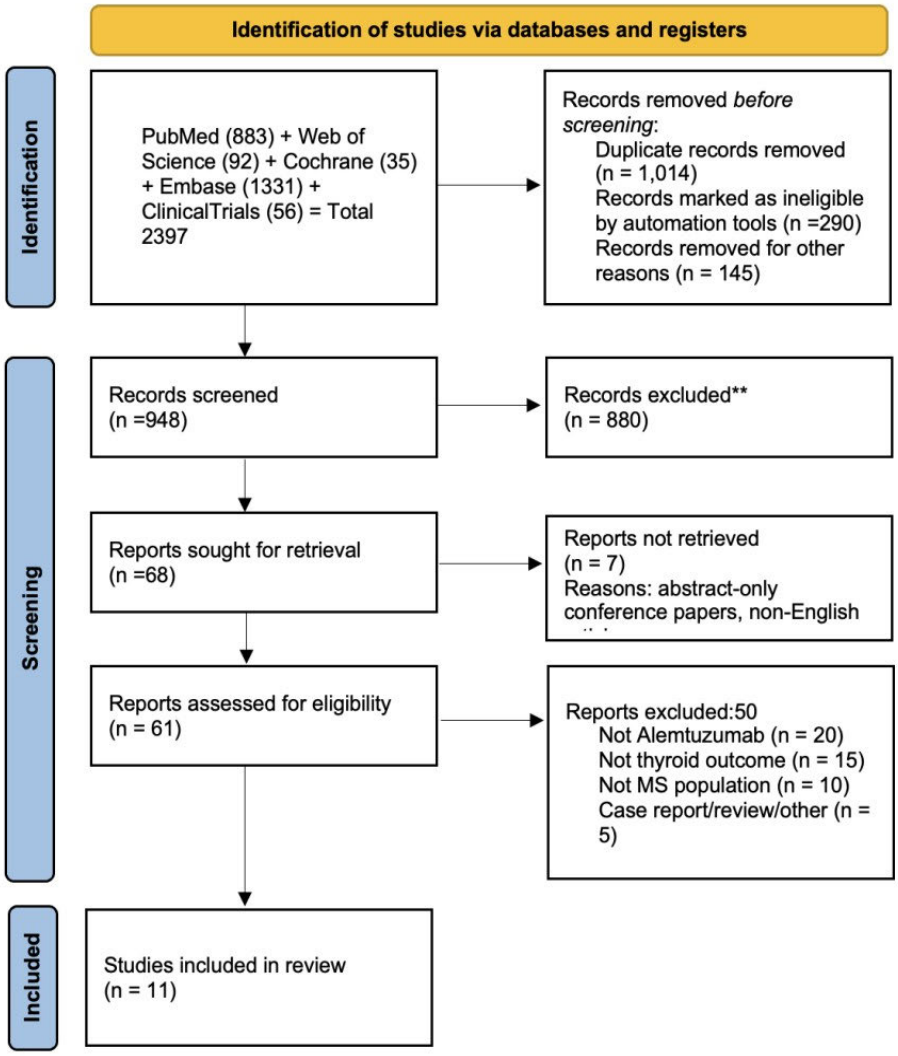

Figure 1: PRISMA 2020 flow Diagram for the Selection of Studies

The time to onset of thyroid dysfunction typically clustered within 2–3 years after the first alemtuzumab infusion (median ≈ 26 months; range: 3-71.5 months). One large series observed that 98% of thyroid events occurred within four years of initial dosing. Due to substantial clinical and methodological heterogeneity among the included studies, a quantitative meta-analysis was not performed and findings were synthesized qualitatively.

Risk of Bias in Studies

The methodological quality of observational studies was evaluated using the Newcastle-Ottawa Scale, demonstrating good overall rigor in terms of selection, comparability and outcome assessment (Table 1).

Randomized and clinical-trial–derived data were assessed using Cochrane/ROBINS-I tools, revealing low to moderate risk of bias, primarily due to variability in follow-up length and reporting completeness (Figure 2). No major systematic bias was identified that would compromise the interpretation of aggregated outcomes.

Qualitative Analysis

Across all included studies, Autoimmune Thyroid Disease (AITD) represented the most frequent autoimmune adverse event following alemtuzumab therapy in multiple sclerosis. Most cases manifested as mild to moderate hyperthyroidism, typically self-limiting and rarely associated with serious complications. The peak incidence was observed around the third year after treatment. In line with regulatory guidance for alemtuzumab, regular thyroid monitoring was advised, with thyroid-function testing every three months for four years following the last infusion and continued thereafter if clinically indicated [14,15]. Baseline thyroid evaluation was inconsistently reported. Only three cohorts [16-18] assessed pre-treatment TPOAb status, whereas [19] provided consensus recommendations for baseline screening including TSH, free T4, free T3 and thyroid autoantibodies. Patients with pre-existing TPOAb positivity or a prior history of autoimmune thyroid disease were identified as being at higher risk and warranted closer endocrinological monitoring.

Table 1: Characteristics of the Included Papers

Author (Year)	Country	Design	N (ALZ)	Mean Age	% Female	MS Type	Follow-up Duration	Thyroid Events (%)	Time to Onset	NOS
Castro *et al.* [25]	Spain	Retrospective single-center cohort	23	38.3±8.3 yrs	74%	RRMS	≥18 months	26.1%	≥18 months post-ALZ	5
Eichau *et al.* [31]	Spain	Retrospective, single-center	123	40.3±9.1 yrs	78%	RRMS/SPMS	~2.5 yrs	23 cases	NR	6
Willis *et al.* [26]	UK	Multicenter, retrospective cohort	100	28.4±8.9 yrs	67%	RRMS	6.1 yrs	35%	Mean 2.7 yrs	6
Sovetkina *et al.* [28]	UK	Single-center retrospective cohort	126	40.5±1.2 yrs	64%	RRMS	≥12 months	26%	24±1.8 months	9
Bose et al. [27]	Canada	Retrospective cohort	46	36 yrs (median)	83%	RRMS	3.3 yrs (median)	48%	NR	8
Yap *et al.* [29]	Ireland	Retrospective observational	52	NR (~40 yrs)	75%	RRMS	4.6 yrs (mean)	16 cases	2.2 yrs (mean)	8
Manso [17]	Italy	Single-center longitudinal	57	33±9yrs	74%	RRMS	32 months (mean)	39%	17±11 months	9
Fox *et al.* [32]	USA	Single-arm, open-label	45	37.1±8.7 yrs	76%	RRMS	24.5 months (median)	5 (GD)	NR	-
Dayan [18]	Multination al	CARE-MS I/II post-hoc analysis	811	34±8.3 yrs	65%	RRMS	6 yrs	35.3%	26.4 months (median)	-
Daniels *et al.* [16]	Europe/US A	Phase 2 RCT (CAMMS223)	216	30.7-33.4 yrs	75%	RRMS	57 months (median)	34%	6–61 months (peak Yr 3)	-
Coles *et al.* [30]	UK	Prospective open-label trial (Campath-1H)	27	36 yrs (mean)	no sex distribution given	RRMS	Up to 4 yrs	33% (GD)	1–3 yrs	-

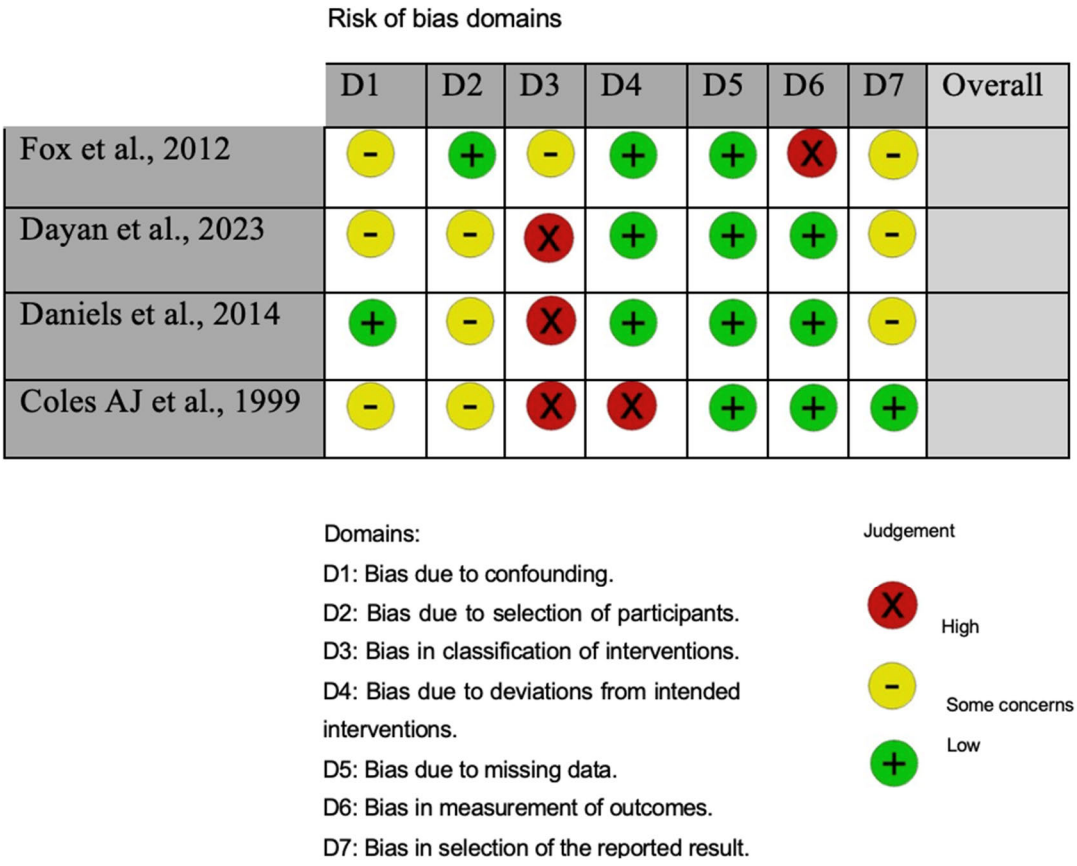

Figure 2: Illustrates the Risk of Bias Assessment across the Included Studies

Management approaches generally followed standard clinical protocols. Antithyroid drugs such as carbimazole and beta-blockers were commonly used for hyperthyroidism [20,21], thyroxine replacement therapy was administered for hypothyroidism [22,23] and definitive interventions such as radioiodine ablation or thyroidectomy were reserved for relapsing or refractory Graves' disease [24]. Outcome data were variably reported but indicated that most cases were successfully managed with standard medical therapy. A small proportion of patients, approximately 10-12%, achieved apparent spontaneous remission, although differentiating true remission from transient immune oscillations was challenging due to limited longitudinal antibody measurements [16].

DISCUSSION

Across the eleven included studies encompassing approximately 1,626 patients with RRMS treated with alemtuzumab, Autoimmune Thyroid Events (ATEs) were consistently identified as the most frequent secondary autoimmune complication of therapy. Reported prevalence of ATEs varied across studies, ranging from approximately 23% to 41%, confirming that thyroid autoimmunity represents a common post-treatment outcome [16-18,25-30]. The time to onset varied considerably, from a few weeks to seven years after infusion, but most cases occurred between 18 and 30 months following the first course, coinciding with the recognized period of immune reconstitution and B-cell hyperproliferation [16,17,30]. None of the included studies demonstrated a significant relationship between the number of alemtuzumab cycles, dosing interval, or cumulative dose and the likelihood of developing thyroid autoimmunity [26,27].

Most observational studies achieved satisfactory methodological quality (≥6 on the Newcastle–Ottawa Scale), with overall low to moderate risk of bias. The main limitations were cohort comparability and incomplete follow-up, particularly for thyroid outcomes beyond two years [17,25-29,31]. Randomized and open-label extension studies showed low to moderate bias based on the Cochrane Risk of Bias and ROBINS-I tools, mainly due to open-label designs, lack of randomization and confounding from baseline antibody status or prior treatments [16,18,30,32]. Despite methodological variability, outcome assessment and thyroid monitoring were consistent across studies.

Graves' Disease (GD) emerged as the dominant phenotype of alemtuzumab-related autoimmune thyroid events, consistently reported across cohorts and affecting approximately one-fifth of treated individuals [16,17,28-30]. Most cases presented as overt hyperthyroidism requiring active treatment, while subclinical disease was uncommon [16,17,26,28,32]. Several cohorts described fluctuating courses of thyroid function, with some patients experiencing spontaneous transitions between hyperthyroid and hypothyroid states [16,17,26]. This fluctuating clinical course is thought to reflect dynamic shifts between stimulating and blocking TSH-receptor antibodies during immune reconstitution [33].

Other autoimmune thyroid phenotypes occurred less frequently and largely followed this same immunological spectrum [16,26,32,35,36]. Hashimoto's thyroiditis represented the main hypothyroid manifestation, accounting for approximately 10–15% of autoimmune thyroid events and a smaller proportion of the overall treated population, with similar distributions reported across studies [17,25,26,34, 35]. Graves' orbitopathy was infrequently reported, identified only in a single cohort and affecting a minority of patients with GD; however, its true prevalence may be underestimated due to limited systematic ophthalmologic assessment in most observational studies [31]. Rare entities such as painless thyroiditis and TSH-receptor-antibody-positive hypothyroidism were also described, further supporting the concept of a shared, evolving autoimmune process rather than distinct static disease subtypes [16,26,32,35,36].

Pre-treatment antibody screening was inconsistently reported across studies and only a few cohorts assessed baseline TPOAb or TRAb status [16-18]. Nevertheless, evidence from immunologic sub-studies suggested that TRAb seropositivity may precede the clinical onset of thyroid dysfunction in a subset of patients, supporting the integration of autoantibody testing before alemtuzumab initiation as a potential risk-stratification tool [37,38].

The management and outcome of GD developing after alemtuzumab treatment remain variable, reflecting differences in follow-up protocols, definitions of remission and diagnostic ascertainment across studies. In the adjudicated CARE-MS analysis [18], approximately 40% of thyroid adverse events were classified as GD, with 54.8% of thyroid cases overall achieving recovery within a six-year window. However, as this figure includes all forms of thyroid dysfunction rather than isolated GD, it likely overestimates the true remission rate of GD itself. A fluctuating course, characterized by alternating hyper- and hypothyroid phases, was described in up to 7% of adjudicated cases and in 57% of patients in a real-world cohort [17]. This "switching" phenotype may reflect the dynamic balance between stimulating and blocking TSH-receptor antibodies (TRAb), although the lack of functional TRAb assays in most studies limits the ability to confirm this mechanistically [39].

In the context of thyroid dysfunction following alemtuzumab, management is predominantly conservative and relies on standard therapeutic principles applied to autoimmune thyroid disease. Most patients achieve biochemical control with antithyroid drugs, typically carbimazole, methimazole, or thiamazole, as shown across multiple cohorts [17,18,28,30]. In patients exhibiting a fluctuating course of Graves' disease, alternating between hyper- and hypothyroidism, a block-and-replace regimen combining methimazole with levothyroxine proved effective in restoring temporary stability, though recurrences were common [17,29]. The need for definitive therapy was limited to a minority radioiodine in approximately 67% and thyroidectomy in 1-10% and was generally reserved for refractory or relapsing cases [16,18,27]. Despite these fluctuations, the majority of events were mild or moderate, allowing continuation of alemtuzumab without interruption [30,32]. Notably, the timing of onset clustered within the first five years post-treatment [26], underscoring the importance of sustained endocrine surveillance.

CONCLUSION

This systematic review indicates that autoimmune thyroid dysfunction is a common complication following alemtuzumab therapy in patients with MS, affecting nearly one-third of treated individuals. Graves' disease emerged as the predominant subtype, often developing within two to three years after treatment and occasionally displaying a fluctuating course between hyper- and hypothyroidism. Hypothyroid forms, including Hashimoto's thyroiditis and TRAb-positive hypothyroidism, were less frequent but clinically relevant.

Most cases were successfully managed with standard medical therapy, whereas definitive interventions were

rarely required. The unpredictable evolution of some cases underscores the importance of long-term endocrine surveillance and patient education regarding late-onset thyroid autoimmunity. Routine monitoring every three months for at least four years after the last infusion remains essential. Future prospective multicenter studies with standardized endocrine and immunologic follow-up are needed to clarify risk factors, characterize antibody dynamics and optimize management strategies for alemtuzumab-associated thyroid disease.

Limitations

Some limitations of the present systematic review should be acknowledged. First, the review was not prospectively registered in PROSPERO, which limits transparency regarding predefined methodological decisions. Second, most included studies were retrospective or observational in design, thereby restricting the ability to establish causal relationships between alemtuzumab exposure and autoimmune thyroid disease development. Third, baseline clinical and immunological characterization was incomplete in several cohorts; pre-treatment antibody screening (TPOAb or TRAb), smoking status and family history were inconsistently reported, preventing firm conclusions regarding potential predisposing factors. Fourth, heterogeneity across studies was moderate to high, mainly reflecting differences in follow-up duration, diagnostic criteria for thyroid dysfunction and variability in local clinical practices for thyroid monitoring and management. Fifth, most studies lacked standardized definitions for remission, relapse and fluctuating phenotypes, limiting comparability of outcomes and interpretation of apparent spontaneous recoveries. Finally, restriction to English-language publications may have introduced language bias and contributed to the omission of relevant studies. Therefore, caution is warranted when extrapolating these findings to broader clinical contexts and future prospective multicenter studies with standardized protocols are needed to confirm and refine these observations.

Author Contributions

Conceptualization was performed by TRA and ZA. Methodology was developed by EA, TMA and NH. Formal analysis was carried out by AH, while data curation was undertaken by NA and NH. The original draft was written by TRA and ZA and all authors contributed to the review and editing of the manuscript. Supervision was provided by MA. All authors have read and approved the final version of the manuscript for publication.

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Data Availability Statement

All data extracted and analyzed during this study are included in this published article and its supplementary materials.

Conflicts of Interest

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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