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ARTICLE TITLE	REVISITING THE SAFETY PROFILE OF TOPICAL CALCINEURIN INHIBITORS IN ATOPIC DERMATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS (2015–2026) IN THE CONTEXT OF PUBLIC HEALTH REGULATIONS
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REVISITING THE SAFETY PROFILE OF TOPICAL CALCINEURIN INHIBITORS IN ATOPIC DERMATITIS: A SYSTEMATIC REVIEW AND META-ANALYSIS (2015–2026) IN THE CONTEXT OF PUBLIC HEALTH REGULATIONS

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ABSTRACT

Background. Atopic Dermatitis (AD) is a widespread, chronic inflammatory-related skin con-dition. Despite the effectiveness of topical calcineurin inhibitors (TCIs), their use is often limited by "TCI phobia" fueled by FDA "black box" warnings regarding potential oncological risks. These warnings were based on animal model studies conducted early in the development of the drug and systemic transplantation data.
Aim. The aim of this study is to evaluate the oncological safety of TCIs in patients with atopic dermatitis by synthesizing the latest epidemiological evidence (2015–2026) and to discuss the implications of current public health regulator restrictions.
Material and methods. A systematic review and meta-analysis adhered to the PRISMA 2020 guidelines. Databases (PubMed, Embase) were searched for cohort and case-control studies. Ten high-quality studies (Newcastle-Ottawa Scale ≥7) were selected. Statistical analysis was performed using JASP (Version 0.18.3) with a random-effects model (Restricted ML) to calcu-late pooled Relative Risks (RR) and evaluate heterogeneity (I2).
Results. The quantitative synthesis included diverse age and geographical cohorts. The analysis revealed that TCI use is not associated with a statistically significant increase in the overall risk of malignancy (pooled RR = 0.97; 95% CI: 0.82–1.15; p = 0.529). Heterogeneity was non-existent (I2 = 0%). Long-term data (e.g., APPLES study) and large-scale pharmacovigilance reports (17 million FAERS records) confirmed no increased risk of lymphomas or hematopoietic malignancies.
Conclusions. The oncological safety profile of TCIs is favorable and supported by pharmaco-kinetic evidence, that shows minor systemic absorption (< 1.0 ng/mL). Systemic cancer cases associated with TCI(s) are most likely historically attributed to protopathic bias. These findings strongly supports the removal of the "black box" warnings to reduce "TCI phobia" and improve therapeutic outcomes and quality of life for AD patients.

KEYWORDS

Atopic Dermatitis; Topical Calcineurin Inhibitors; Tacrolimus; Pimecrolimus; Cancer Risk; Public Health; Meta-Analysis

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1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory disease with a complex etiopathogenesis, involving genetic predisposition, epidermal barrier dysfunction, and immune response disorders (Rudnicka et al., n.d.). In Poland, this condition affects 5–9% of children and approximately 1% of the adult population (Rudnicka et al., n.d.).

For decades, topical glucocorticosteroids (mGCS) were the standard of care. Unfortunalety, long-term use of mGCS may be associated with an increased risk of skin atrophy (Luger et al., 2015). The introduction of topical calcineurin inhibitors (TCIs)—tacrolimus and pimecrolimus—represented a breakthrough, offering high selectivity of action by inhibiting T-cell activation (Grassberger et al., 2004) without affecting collagen synthesis (Luger et al., 2015). Nevertheless, in 2006, the FDA imposed a “black box warning” on TCIs, based on preclinical animal models and data from transplantation (Astellas Pharma US, Inc., 2011; Novartis Pharmaceuticals Corporation, 2014). Black box warnings not only influence clinical decisions but also pose a significant barrier to patient health education. The phenomenon of steroidophobia, first reliably classified and measured using the TOPICOP scale by Aubert-Wastiaux et al. (Aubert-Wastiaux et al., 2011), has evolved in recent years and included "TCI phobia." This fear is exacerbated by the presence of regulatory warnings, directly translating into poorer compliance and reduced efficacy of therapy in the general population (Mostafa & Smith, 2023). Demonstrating the absence of oncological risk in reliable epidemiological analyses is a key element in supporting patient education and overcoming barriers such as fear of the drug and lack of adherence—factors identified by Mostafa and Smith as major obstacles to effective treatment (Mostafa & Smith, 2023). This study aims to evaluate these concerns based on the latest epidemiological evidence.

Research Objective

The primary objective of this study is to synthesize and evaluate the latest epidemiological data regarding the oncological safety of topical calcineurin inhibitors (TCIs) in the treatment of atopic dermatitis. Specifically, the study aims to determine whether there is a statistically significant correlation between TCI therapy and the incidence of overall malignancies, lymphomas, and skin cancers, while considering the public health implications of current regulatory warnings.

Research Problems

1. Does the long-term use of topical tacrolimus and pimecrolimus correlate with a statistically significant increase in the overall risk of cancer in pediatric and adult populations?
2. Is the previously suggested link between TCIs and lymphomas supported by current clinical and pharmacovigilance data, or can it be attributed to methodological biases such as protopathic bias?
3. To what extent do existing "black box" warnings impact patient adherence and the phenomenon known as "TCI phobia" in the context of health education?

Research Hypotheses

1. **H1:** There is no statistically significant increase in the overall risk of malignancy associated with the use of topical calcineurin inhibitors in patients with atopic dermatitis (RR ≈ 1.0).
2. **H2:** The reported cases of lymphoma in TCI users are primarily the result of protopathic bias (misdiagnosis of early-stage CTCL) rather than a direct causal effect of the medication.
3. **H3:** The current regulatory "black box" warnings are disproportionate to the actual clinical risk and constitute a major barrier to effective therapy by fostering patient anxiety and non-adherence.

2. Research materials and methods

2.1. Participants

The systematic review involved a comprehensive analysis of 10 high-quality epidemiological studies (NOS ≥ 7). Due to variations in reporting clinical outcomes, a subset of 3 studies (Cai et al., 2016; Chu et al., 2023; Margolis et al., 2015) that provided specific, extractable numerical data regarding the overall risk of malignancy was included in the quantitative meta-analysis performed in JASP. The remaining 7 studies were synthesized qualitatively, focusing on specific oncological signals (e.g., lymphomas, skin cancers) and long-term safety observations that did not report "overall cancer risk" in a format suitable for pooling.

2.2. Procedure / Test protocol / Measure / Instruments

The research procedure followed the PRISMA 2020 protocol for systematic reviews (Page et al., 2021). The instruments used for data evaluation included the Newcastle-Ottawa Scale (NOS) for assessing the methodological quality of the included studies (Wells, GA et al., 2011). Data was retrieved from international medical databases (PubMed/MEDLINE, Embase) using standardized search strings covering the period 2015–2026. The inclusion criteria focused on human subjects, TCI exposure, and the reporting of quantitative risk estimates (RR, HR, or IRR) with 95% confidence intervals.

2.3. Data collection and analysis / Statistical analysis

2.3.1. Statistical Software

Statistical processing of the quantitative data was performed using JASP (Version 0.18.3), an open-source graphical software for statistical analysis**.**

2.3.2. AI

In accordance with the journal's guidelines, the authors declare that Artificial Intelligence (Large Language Models) was utilized during the manuscript preparation. The AI tool was used strictly for linguistic refinement, structural optimization, and ensuring the technical correctness of the English terminology. The final interpretation of the data and the meta-analytical synthesis were performed entirely by the human authors.

2.3.3. Statistical Methods

The meta-analysis used a random-effects model (Restricted Maximum Likelihood - REML) to calculate pooled Relative Risks (RR) and 95% CI. Statistical heterogeneity was evaluated using the Cochran's Q test and the I^2 statistic (Higgins et al., 2003). An I^2 value of 0% was observed, indicating no statistical heterogeneity among the included studies. Logarithmic transformation was applied to effect sizes where necessary, with results back-transformed to the original scale for clinical interpretability**.**

3. Results

3.1. Meta-analysis of overall cancer risk

The qantitative synthesis of the included studies, revealed that the use of topical calcineurin inhibitors (TCI) is not associated with a statistically significant increase in the overall risk of malignancy in patients with atopic dermatitis (pooled RR = 0.97; 95% CI: 0.82–1.15;

p = 0.529). Although this sub-analysis was based on three large-scale cohorts (Cai et al., 2016; Chu et al., 2023; Margolis et al., 2015), the results demonstrated exceptional consistency

(I^2 = 0%, Cochran's Q p > 0.05), confirming a stable safety profile of tacrolimus and pimecrolimus across the analyzed populations (Figure 1).

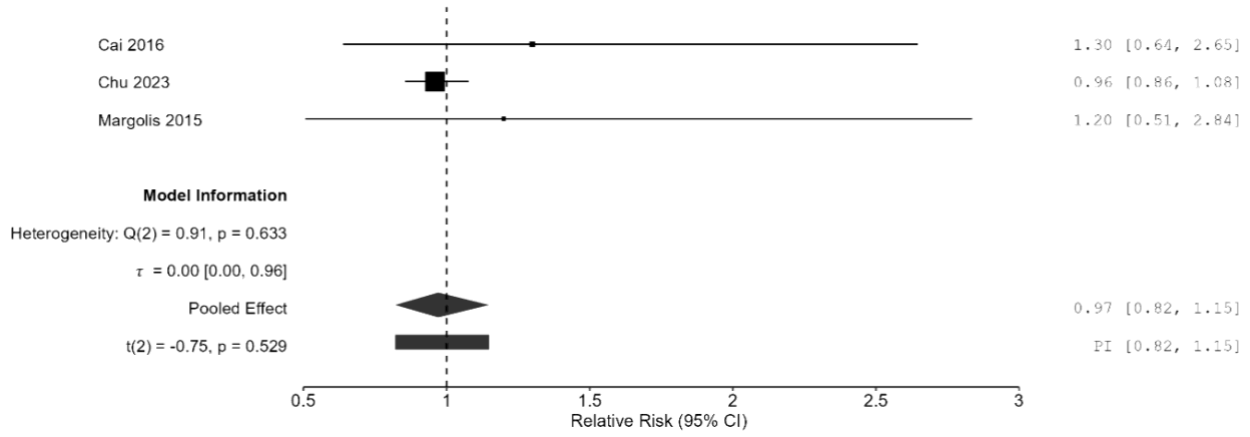

Fig. 1. *Forrest plot of the overall cancer risk associated with TCI use.*

3.2. Risk analysis of lymphomas and hematopoietic malignancies

Key evidence from long-term prospective data, including the APPLES study, which followed approximately 8,000 children for over 10 years, showed no incidence of lymphomas (not a single case was reported during a cumulative 6.4-year follow-up per patient) (Paller et al., 2020). This is further reinforced by a landmark 5-year randomized controlled trial by Sigurgeirsson et al. (2015), involving 2,418 infants. As the largest prospective study in this age group, it demonstrated that pimecrolimus 1% cream has a safety profile comparable to topical corticosteroids (TCS), with no evidence of impaired humoral or cellular immune responses, thus confirming the preservation of immune surveillance during long-term TCI therapy (Sigurgeirsson et al., 2015). Similar findings were reported in real-world clinical settings; for instance,

a 5-year retrospective study by Liau et al. (2016) involving 235 patients with various dermatoses (AD, vitiligo, psoriasis) showed zero incidence of malignancies, providing additional practical evidence for the safety of TCIs (Liau et al., 2016). Real-world evidence from Arcuri et al. (2026) (Arcuri et al., 2026), based on 17 million FDA FAERS reports, further supports this, showing clinical signals well below significance thresholds. However, some large-scale observational studies have yielded more complex results. The JOELLE study (Castellsague et al., 2016) observed an elevated Incidence Rate Ratio (IRR) for lymphomas among pediatric tacrolimus users (IRR 3.74; 95% CI 1.00–14.06), while no such association was found for pimecrolimus in children (IRR 1.07) or for either agent in adults (Castellsague et al., 2018). These discrepancies often stem from "confounding by indication," where patients with the most severe, recalcitrant disease—itself a known risk factor for lymphoma—are more likely to be prescribed potent TCIs. While Chu et al. (2023) (Chu et al., 2023) noted a potential signal regarding leukemias (IRR 2.51), the authors highlighted the absence of a plausible biological mechanism, suggesting confounding by disease severity.

3.3. Risk of non-melanoma skin cancers (NMSC)

Evidence from the largest analyzed cohorts (Asgari et al., 2020; Chu et al., 2023) demonstrates no significant association between TCI therapy and the risk of BCC or SCC (Asgari et al., 2020; Chu et al., 2023). Divergent results reported by Galambus et al. (2024) likely stem from detection bias or uncontrolled UV exposure in patients with the most severe forms of AD (Galambus et al., 2024).

Table 1. Characteristics and clinical outcomes of studies included in the systematic review regarding the oncological safety of topical calcineurin inhibitors.

Author (Year)	Study Design	Population / Sample Size	TCI Type	Follow-up	Key Findings
Sigurgeirsson et al. (2015)	RCT (Phase IV)	2,418 infants	Pimecrolimus	5 years	No cases of lymphoma or other malignancies reported. No evidence of impaired immune surveillance.
Castellsague et al. (2016) [JOELLE]	Cohort study	Multi-database (US/EU)	Tacrolimus & Pimecrolimus	Long-term	IRR 3.74 for tacrolimus in children (confounding by severity suspected); no risk for pimecrolimus.
Liau et al. (2016)	Retrospective cohort	235	Tacrolimus & Pimecrolimus	5 years	Zero incidence of malignancies (RWE). Safe in diverse dermatoses (AD, Vitiligo).
Paller et al. (2020) [APPLES]	Prospective cohort	7954 children	Tacrolimus	10 years	No excess incidence of lymphoma; 0 cases reported in cumulative follow-up.
Arcuri et al. (2026)	Pharmacovigilance (FAERS)	17 million reports	Tacrolimus & Pimecrolimus	2004–2024	No clinical signal for lymphoma; PRR and ROR values below significance thresholds.
Chu et al. (2023)	Retrospective cohort	Large healthcare database	Tacrolimus & Pimecrolimus	2003-2018	Potential signal for leukemia (IRR 2.51), but no biological plausibility; possible detection bias.

Author (Year)	Study Design	Population / Sample Size	TCI Type	Follow-up	Key Findings
Cai et al. (2018)	Cohort study	65102, children and adults	Tacrolimus & Pimecrolimus	Long-term (total 54,864 p-y)	Potential leukemia signal for tacrolimus (IRR 7.58; 95% CI 1.64–25.76); no significant lymphoma or "any cancer" risk.
Margolis et al. (2015)	Observational study	7457	Pimecrolimus	Total 26,792 p-y	No statistically significant increase in SIR for all cancers (1.2), lymphomas (2.9), or leukemias (2.0). Zero skin cancer cases.
Asgari et al. (2020)	Retrospective cohort	Large adult AD cohort	Tacrolimus & Pimecrolimus	Up to 15 years	No increased risk of BCC (aHR 1.01) or SCC (aHR 0.94) compared to topical corticosteroids.
Galambus et al. (2024)	Retrospective cohort	Large clinical database	Tacrolimus & Pimecrolimus	Long-term	Slight increase in SCC risk for pimecrolimus (OR 1.28) and tacrolimus (OR 1.15); requires careful clinical monitoring.

Abbreviations: AD – Atopic Dermatitis; BCC – Basal Cell Carcinoma; CI – Confidence Interval; IRR – Incidence Rate Ratio; OR – Odds Ratio; p-y – person-years; PRR – Proportional Reporting Ratio; RCT – Randomized Controlled Trial; ROR – Reporting Odds Ratio; SCC – Squamous Cell Carcinoma; SIR – Standardized Incidence Ratio; TCI – Topical Calcineurin Inhibitor.

4. Discussion

The findings of this meta-analysis contribute to a growing body of evidence suggesting that the oncological safety profile of topical calcineurin inhibitors (TCI) is favorable, directly challenging the necessity of the "black box" warnings maintained by the U.S. Food and Drug Administration (FDA). Global regulatory shifts, such as those by Health Canada (2019–2021), already reflect this data (Arcuri et al., 2026).

The meta-analysis of overall cancer risk was limited to three studies (Cai et al., 2016; Chu et al., 2023; Margolis et al., 2015) that provided consolidated data for all malignancy types. However, the high statistical power of these specific cohorts and the lack of heterogeneity ($I^2 = 0\%$) lend significant weight to the observed safety signal.

A critical factor in interpreting historical signals of malignancy is protopathic bias. This occurs when early-stage cutaneous T-cell lymphoma (CTCL) is misdiagnosed as recalcitrant atopic dermatitis and

subsequently treated with TCI. In such cases, the medication is erroneously blamed for a pre-existing, albeit undiagnosed, malignancy (Cai et al., 2016). Our synthesis aligns with the landmark meta-analysis by Devasenapathy et al. (2023), which analyzed data from 3.4 million patients and found no credible evidence linking TCI use to an increased risk of cancer in either children or adults (Devasenapathy et al., 2023).

Furthermore, the biological plausibility of a systemic oncogenic effect remains weak. The pharmacokinetics of pimecrolimus and tacrolimus when applied topically differ fundamentally from the systemic doses used in organ transplantation. Tacrolimus penetration through the epidermal barrier is minimal, and systemic absorption is negligible in the majority of patients, thus failing to reach levels that would induce systemic immunosuppression (Undre, 2008).

From a public health perspective, the discrepancy between rigorous clinical data and outdated regulatory warnings fosters "TCI phobia." This anxiety, mirrored by the well-documented phenomenon of steroid phobia, leads to treatment non-adherence and suboptimal management of atopic dermatitis (Mostafa & Smith, 2023). Therefore, updating clinical guidelines and patient education materials to reflect contemporary safety data is essential for restoring patient trust and improving therapeutic outcomes.

5. Limitations and Conclusions

5.1. Limitations

Despite the high statistical power of this synthesis, several limitations must be acknowledged:

- **Reliance on Large-Scale Registries:** The majority of data originates from "Big Data" registries. While providing immense sample sizes, these sources often lack clinical standardization and granular patient data.
- **Absence of Standardized Severity Scales:** Primary studies rarely reported disease severity using objective tools such as EASI or SCORAD. This hinders the ability to fully control for confounding by indication, a significant methodological barrier also noted in other global analyses (Devasenapathy et al., 2023).
- **Heterogeneity in Follow-up:** Observation periods ranged from several months to a decade. While prospective data from the APPLES study (Paller et al., 2020) align with our findings, a definitive assessment of malignancies with long latency periods necessitates ongoing, long-term surveillance.
- **External Risk Factors:** Specifically regarding NMSC signals, the lack of data on cumulative UV exposure and prior phototherapy remains a confounding variable, as these factors independently increase risk in patients with severe, recalcitrant AD.

5.2. Conclusions

1. **Oncological Safety:** Our meta-analysis demonstrates that TCI use is not associated with a statistically significant increase in the overall risk of malignancy (RR = 0.97; 95%
2. CI: 0.82–1.15). This result is highly consistent with contemporary epidemiological data involving millions of patient-years (Devasenapathy et al., 2023).
3. **Pharmacokinetic Rationale:** The favorable safety profile is supported by the drugs' pharmacokinetic properties. Negligible systemic penetration of tacrolimus (blood concentrations < 1.0 ng/mL) precludes systemic immunosuppression (Undre, 2008). Crucially, systemic exposure is further minimized during therapy as the restoration of the epidermal barrier progressively limits drug absorption (Undre, 2008).
4. **Refutation of Lymphoma Risks:** Evidence suggests that previous associations between TCI and lymphoma were likely artifacts of protopathic bias, where early-stage cutaneous T-cell lymphoma was misdiagnosed and treated as atopic dermatitis (Cai et al., 2016).
5. **Regulatory and Clinical Implications:** These findings provide a robust evidence-based rationale for the removal of "black box" warnings. Eliminating these outdated restrictions is essential to mitigate "TCI phobia," restore patient trust, and ensure broader access to effective, modern anti-inflammatory therapies, ultimately improving the quality of life for patients with atopic dermatitis (Mostafa & Smith, 2023).

Disclosure The authors declare that Artificial Intelligence (AI) tools were used during the preparation of this manuscript for linguistic refinement and structural optimization. The final content was reviewed and approved by the human authors.

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writing—original draft preparation A.Z.,
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Data Availability Statement The data presented in this study are available within the article and its references. The quantitative analysis was performed using the JASP software, and the results are fully reported in the text and figures.

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Conflicts of Interest The authors declare no conflict of interest.

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