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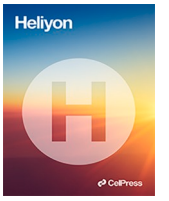

Research article

Comprehensive analysis of clinical research profiles and study characteristics of oral potentially malignant disorders: an observational study

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A R T I C L E I N F O

Keywords:
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ClinicalTrials.gov
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Registration

A B S T R A C T

Objective: The study aims to present an observational study of clinical trials on Oral Potentially Malignant Disorders (OPMDs) and corresponding publications.

Study design and setting: We searched the OPMDs-related clinical studies registered in the ClinicalTrials.gov database before March 1, 2024. Subsequently, we investigated the publication status of primary completed studies using PubMed and Google Scholar.

Results: A total of 185 studies were identified for analysis, including 141 interventional studies and 44 observational studies. The most commonly studied disease type was oral lichen planus (OLP), accounting for 113 studies (61.1 %). Interventional studies on OPMDs were predominantly early-phased, blind, randomized, parallel and single-center. The primary purpose of these studies was treatment (106, 75.2 %). Among the treatments, herbal medicine (21, 19.8 %), photodynamic therapy (17, 16.0 %), and glucocorticoids (14, 13.2 %) were of greatest interest. In addition, 58 (63.0 %) of the primarily completed interventional studies were published, with a median time to publication of 33.6 months. Published interventional studies including OLP patients and factorial designs had shorter time to publication. However, these studies were less frequently published in high-impact journals and most primary results were positive.

Conclusions: Clinical trials on OPMDs predominantly focused on OLP and herbal medicine. The quality of studies is unsatisfactory and publication rate is suboptimal. Improvements are needed in ClinicalTrials.gov registration standards, high-quality study design and more stringent publishing requirements.

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1. Introduction

Oral Potentially Malignant Disorders (OPMDs) are a series of chronic lesions and conditions associated with a statistically increased risk of malignant transformation to oral squamous cell carcinoma (OSCC) [1]. According to the 2020 workshop coordinated by the World Health Organization (WHO) Collaborating Centre for Oral Cancer in the UK [1,2], OPMDs include Oral Leukoplakia (OLK), Oral Lichen Planus (OLP), Oral Submucous Fibrosis (OSF), Discoid Lupus Erythematosus (DLE), Oral Erythroplakia (OE), Actinic Cheilitis (AC), Oral Epidermolysis Bullosa (OEB), Dyskeratosis Congenita (DC), Proliferative Verrucous Leukoplakia (PVL), Oral Lichenoid Lesion (OLL), and Palatal Lesions in Reverse Smokers.

Over the past few decades, the prevalence of OPMDs has exponentially increased worldwide, especially in Asian and South American populations with the rates of 10.54 % and 3.93 %, respectively [3–5]. Given the increasing prevalence of OPMDs and high malignant transformation rate (MTR) to OSCC (7.9 %, 99 % CI = 4.9%–11.5 %) [6], early diagnosis and effective treatment are crucial to improving the overall well-being and reducing the MTR. Various studies have reported multidisciplinary care approaches, including surgical excision with or without carbon dioxide laser, chemoprevention with naturally or synthetically fabricated compounds, photodynamic therapy [7–10]. However, no approach has yet gained universal approval as a standard method of prevention and treatment due to the lack of clinical trials and the low overall quality of the evidence [11–14]. Therefore, a thorough understanding of the current landscape and characteristics of clinical trials on OPMDs is essential for identifying neglected areas of research, improving trial design, and providing references for clinicians to further explore the effective treatment methods.

Well-designed randomized controlled clinical trials (RCTs), with appropriate sample sizes and transparency, remain the gold standard to generate the highest level of evidence in determining therapy guidelines and form the solid foundation of evidence-based medicine [15]. In clinical practice, RCTs also inform clinicians about the comparative efficacy and safety of medical interventions and contribute to key clinical practice decision-making [16–18]. The ClinicalTrials.gov database, currently including detailed registries on more than 370,000 international clinical studies, serves as the oldest and largest platform of its kind, continually updating the most comprehensive information about the clinical research worldwide. This database offers an opportunity to explore, inspect and supervise the clinical research landscape [19–21].

Despite constant proliferation of OPMDs clinical studies, there is no systematic, up-to-date evaluation of the clinical trial landscape. Consequently, we still lack a thorough understanding of latest clinical studies regarding OPMDs. This study is the first to investigate OPMDs clinical trials registered on the ClinicalTrials.gov, aiming to: 1) outline the current composition and comprehensive landscape of OPMDs studies; 2) thoroughly evaluate the characteristics and publication status of these studies; 3) suggest future research focuses and identify neglected research areas.

2. Methods

2.1. Searching the ClinicalTrials.gov database and Identifying Eligible studies

This observational study focused on research studies. We searched the ClinicalTrials.gov database on March 01, 2024, using the search terms “Oral Leukoplakia (OLK)”, “Oral Lichen Planus (OLP)”, “Oral Submucous Fibrosis (OSF)”, “Discoid Lupus Erythematosus (DLE)”, “Oral Erythroplakia (OE)”, “Actinic Cheilitis (AC)”, “Epidermolysis Bullosa (EB)”, “Dyskeratosis Congenita (DC)”, “Proliferative Verrucous Leukoplakia (PVL)”, “Oral Lichenoid Lesion (OLL)”, “Palatal Lesions in Reverse Smokers”, “Oral Potentially Malignant Disorders (OPMDs)”. All available results were downloaded as CSV files and imported into a database for systematic and coherent data inclusion, elimination, extraction, classification and management. Duplicate and non-oral relevant studies were excluded.

2.2. Study variables

Based on the information from the ClinicalTrials.gov database, the following variables were categorized by two independent investigators: status (ongoing/completed/terminated/withdrawn/unknown status), primary complete (yes/no), register(before study start/after study start), year of study register (1999–2005/2006-2010/2011–2015/2016-2020/2021–2024), sample size (≤50/51–100/>100), results (unavailable/available), age (with children/without children), disease type (AC/DC/DLE/EB/OLK/OLP/OSF/OPMDs), study design (single arm/parallel/factorial/cross-over/cross-sectional/case-control/cohort), countries where the study was carried out (American/European/African/Asian/Multiple), center (single-center/multi-center), funder (NIH/industry/others), purpose of the interventional studies (basic science/diagnostic/prevention/screening/supportive care/treatment/others), primary outcome (negative/positive), phase (early stage/late stage/missing), blind (open label/single-blind/double-blind/triple-blind/quadruple-blind), randomization (yes/no). Whether a study was multi-center was judged by the brief summary, locations, sponsors and collaborators. Trials with an industry listed as the main investor were classified as industry-funded. With similar principles, the others can be divided into the corresponding categories [22]. Primary completion duration was defined as the time interval between study initiation point and the accomplishment of the primary endpoint. The study duration was defined as the time interval between study initiation point and the completion of the entire study.

The therapies of the interventional studies aimed at treatment were categorized as glucocorticoid (GC), biologics (BO), NSAID, antimicrobial (AM), herbal medicine (HM), immunotherapy (IM), photodynamic therapy (PDT), stem cell transplant (SCT), dietary supplement (DS), surgery and other therapies. Biologics included enzymes, monoclonal antibodies, glucosamine sulfate, etc. Antimicrobial therapy consisted of antifungal, antibacterial and antiviral drugs. Herbal medicine included curcuminoids, chamomile, chamaemelum nobile, quercetin, etc. Immunotherapy was composed of immunosuppressants and immunomodulators. Photodynamic

therapy involved treatment with various photosensitive compounds and lasers, such as aminolevulinic acid hydrochloride, YAG or YSGG laser.

2.3. Searching for the publication status

Under a standardized strategy, two investigators independently searched for peer-reviewed publications of studies under primary completion on the platform of "publication" field in ClinicalTrials.gov database, PubMed and Google Scholar, using NCT number, headline, sponsor and collaborator. Publications were carefully identified by matching study details, including study description, design, arms and interventions, outcome measures, and eligibility criteria in the ClinicalTrials.gov database with the literature. If multiple publications were retrieved, the original literature demonstrating the primary outcome results was selected. Interim analyses, commentaries, study protocols, reviews and other non-relevant publications were excluded. A third investigator reaffirmed and further searched for the publications not discovered. Disputes were resolved through discussion and verification. For each published article, study design, sample size, primary results (negative or positive), published date, magazine and impact factor (IF $<$ 5/5–9.99/$\geq$10) were collected. Publication status retrieval was updated and finalized by March 12, 2024. The time to publication was defined as the interval time from the study's primary completion date to the publication date or the last search date.

2.4. Statistical analysis

Categorical variables were described as frequencies and percentages and compared between groups using Chi-square tests or Fisher's exact tests. Continuous variables were described as medians and interquartile ranges (IQR) and compared between groups using Mann-Whitney U tests. Missing data were excluded from specific variable analyses. The time to publication was estimated using the Kaplan-Meier method, and the median time to publication was calculated for overall and subgroups. Cox regression analysis was performed to identify factors influencing the time to publication. Hazard ratios (HRs) and 95 % confidence intervals (CIs) were calculated for these factors. Variables with $p < 0.05$ in univariate analysis were included in the multivariate model. All statistical tests were performed using Stata/MP version 14.0 (Stata Corporation LP, College Station, TX, USA), with a two-sided $p < 0.05$ considered statistically significant.

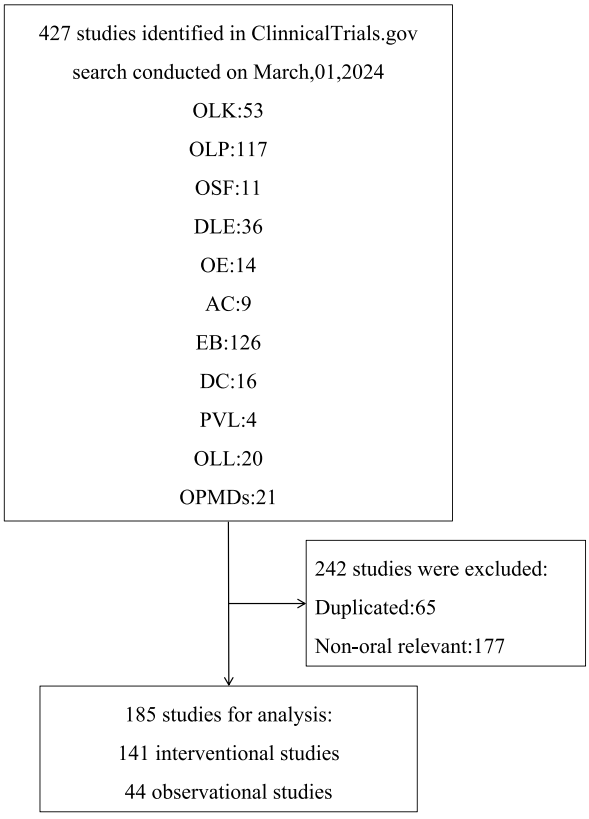

Fig. 1. Study selection flow chart.
Abbreviations: OLK, oral leukoplakia; OLP, oral lichen planus; OSF, oral submucous fibrosis; DLE, discoid lupus erythematosus; OE, Oral Erythroplakia; AC, actinic cheilitis; EB, epidermolysis bullosa; DC, dyskeratosis congenita; PVL, proliferative verrucous leukoplakia; OLL, oral lichenoid lesion; OPMDs, oral potentially malignant disorders.

3. Results

3.1. Distribution of OPMDs-Relevant studies on ClinicalTrials.gov

As shown in Fig. 1, a total of 427 studies registered in ClinicalTrials.gov Database were identified. After excluding 242 duplicate and non-oral relevant studies, 185 studies were retained for analysis: 141 (76.2 %) interventional and 44 (23.8 %) observational studies. The search term "Discoid Lupus Erythematosus (DLE)" yielded results irrelevant to oral health. Additionally, studies with the terms "Oral Erythroplakia (OE)", "Proliferative Verrucous Leukoplakia (PVL)", "Oral Lichenoid Lesion (OLL)" and "Palatal Lesions in Reverse Smokers" were either duplicated with other terms or presented no results, leading to the deletion of these five terms.

The distribution of the interventional and observational studies according to the registered year is summarized in Fig. 2. In general, the number of registered studies has gradually increased over the past twenty years, with some fluctuations. Notably, the number of observational studies began to rise after 2017, but it remained significantly lower than the number of interventional studies.

3.2. General characteristic of interventional and observational studies

The characteristics of included interventional and observational studies are summarized in Table 1. Overall, most studies focused on OLP patients (113, 61.1 %), were registered after study start(127, 68.6 %), had small-sample size (105, 56.8 %), and were single-center (161, 87.0 %).

For study design, interventional studies were mostly parallel design (97, 68.8 %), early-phase (70, 68.6 %), randomized (100, 70.9 %), blind (92, 65.2 %), single-center (123, 87.2 %) and aimed for treatment (106, 75.2 %) (Table 1). Among observational studies, 19 (43.2 %) were case-control studies, 17 (38.6 %) were cohort studies and 8 (18.2 %) were cross-sectional studies (Table 1).

Fifteen studies were terminated or withdrawn (Table 1), with the most common reason being slow accrual of enrollment (8, 53.3 %). Four terminated studies were also published.

3.3. Distribution and Comparison of disease types

In terms of disease type distribution by registered year (Supplementary Figure 1), studies focusing on OLP have received considerable attention since 2005. Between 2004 and 2007, researchers showed interest in OLK. However, over time, a noticeable rise in the prevalence of OSF was observed from 2015 to 2018. Since 2009, the studies on AC have emerged, but their number remained low. Mixed studies emerged in 2012 and subsequently experienced a general upward trend, despite occasional fluctuations.

Study characteristics were compared between the different disease types among 141 interventional studies (Table 2). Nearly all study characteristics showed significant differences between different disease types ($p < 0.05$). Studies on DC or EB patients included children, while studies on other diseases mostly did not. Most studies on OLP were parallel design, while most studies on OLK or DC were single-arm design. The proportion of randomized studies was highest in OLP studies (84.7 %), while most OLK and DC studies did not use randomization. The majority of OLP studies employed blinding (80 %), while over half of studies on other diseases were open-label. OLP studies had a higher proportion from Africa and Europe, while OLK, AC, DC, or EB studies had a higher proportion from America, and studies on OSF were all from Asia. Although the number of centers and funding sources varied among studies on different diseases, most studies were still single-center (66.7%–100 %) and non-NIH/industry funded (66.7%–100 %).

Although the purposes of studies on different disease types varied, the majority of studies still aimed for treatment (50%–100 %), except for mixed-type disease studies (20 %). Subsequently, we extracted data from 106 interventional studies with the purpose of treatment for deeper analysis. In terms of treatment, the public showed higher interest in herbal medicine (21, 19.81 %), photodynamic therapy (17, 16.04 %), glucocorticoid (14, 13.21 %), immunotherapy (12, 11.32 %), dietary supplement (10, 9.43 %). Herbal medicine was primarily used in the treatment of OLP and OSF. Notably, OLP studies employed the most diverse types of treatment,

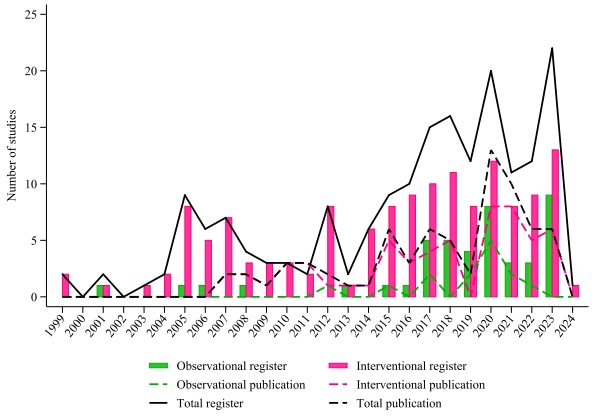

Fig. 2. Study distributions of register and publication for observational and interventional studies according to the registered or published year.

Table 1
Study characteristics between interventional and observational studies.

	Overall (n = 185)	Observational studies (n = 44)	Interventional studies (n = 141)
Study status			
Ongoing	38 (20.5)	13 (29.5)	25 (17.7)
Completed	99 (53.5)	22 (50.0)	77 (54.6)
Terminated	10 (5.4)	1 (2.3)	9 (6.4)
Withdrawn	5 (2.7)	0	5 (3.5)
Unknown status	33 (17.8)	8 (18.2)	25 (17.7)
Duration of study completed (mo.)	17.0 (10.0, 35.5)	12.0 (5.8, 35.4)	19.5 (11.7, 37.9)
Primary completed			
No	68 (36.8)	19 (43.2)	49 (34.8)
Yes	117 (63.2)	25 (56.8)	92 (65.2)
Duration of primary completed (mo.)	17.0 (10.0, 35.5)	12.0 (5.8, 35.4)	19.5 (11.7, 37.9)
Register			
Before study start	58 (31.4)	15 (34.1)	43 (30.5)
After study start	127 (68.6)	29 (65.9)	98 (69.5)
Year of study registered			
1999–2005	16 (8.6)	2 (4.5)	14 (9.9)
2006–2010	23 (12.4)	2 (4.5)	21 (14.9)
2011–2015	27 (14.6)	2 (4.5)	25 (17.7)
2016–2020	73 (39.5)	23 (52.3)	50 (35.5)
2021–2024	46 (24.9)	15 (34.1)	31 (22.0)
Age			
Without child	146 (78.9)	33 (75.0)	113 (80.1)
With child	39 (21.1)	11 (25.0)	28 (19.9)
Sex			
Only female	1 (0.5)	1 (2.3)	0
All	184 (99.5)	43 (97.7)	141 (100.0)
Sample size			
≤50	105 (56.8)	10 (22.7)	95 (67.4)
51-100	51 (27.6)	19 (43.2)	32 (22.7)
>100	27 (14.6)	15 (34.1)	12 (8.5)
missing	*2*		*2*
Disease types			
OLP	113 (61.1)	28 (63.6)	85 (60.3)
OLK	31 (16.8)	4 (9.1)	27 (19.1)
AC	9 (4.9)	0	9 (6.4)
OSF	8 (4.3)	3 (6.8)	5 (3.5)
DC	4 (2.2)	1 (2.3)	3 (2.1)
EB	2 (1.1)	0	2 (1.4)
Mixed	18 (9.7)	8 (18.2)	10 (7.1)
Study design			
Single arm	35 (18.9)	–	35 (24.8)
Parallel	97 (52.4)	–	97 (68.8)
Factorial	3 (1.6)	–	3 (2.1)
Cross-over	6 (3.2)	–	6 (4.3)
Cross-Sectional	8 (4.3)	8 (18.2)	–
Case-Control	19 (10.3)	19 (43.2)	–
Cohort	17 (9.2)	17 (38.6)	–
Region			
American	54 (29.2)	7 (15.9)	47 (33.3)
European	44 (23.8)	11 (25.0)	33 (23.4)
African	46 (24.9)	16 (36.4)	30 (21.3)
Asian	37 (20.0)	10 (22.7)	27 (19.1)
Multiple	4 (2.2)	0	4 (2.8)
Center			
Single-center	161 (87.0)	38 (86.4)	123 (87.2)
Multi-center	24 (13.0)	6 (13.6)	18 (12.8)
Funder			
NIH	13 (7.0)	3 (6.8)	10 (7.1)
Industry	8 (4.3)	3 (6.8)	5 (3.5)
Others	164 (88.6)	38 (86.4)	126 (89.4)

Except where indicated otherwise, values are the number (%).
Abbreviations: mo., months; OLP, oral lichen planus; OLK, oral leukoplakia; AC, actinic cheilitis; OSF, oral submucous fibrosis; DC, dyskeratosis congenita; EB, epidermolysis bullosa.

Table 2
Study characteristics for interventional studies overall and by disease types.

	Overall (n = 141)	OLP (n = 85)	OLK (n = 27)	AC (n = 9)	OSF (n = 5)	DC (n = 3)	EB (n = 2)	Mixed (n = 10)	*p*-value
Year of study registered									0.012
1999–2005	14 (9.9)	6 (7.1)	8 (29.6)	0	0	0	0	0	
2006–2010	21 (14.9)	10 (11.8)	8 (29.6)	2 (22.2)	0	1 (33.3)	0	0	
2011–2015	25 (17.7)	17 (20.0)	2 (7.4)	2 (22.2)	0	2 (66.7)	1 (50.0)	1 (10.0)	
2016–2020	50 (35.5)	31 (36.5)	5 (18.5)	4 (44.4)	4 (80.0)	0	0	6 (60.0)	
2021–2024	31 (22.0)	21 (24.7)	4 (14.8)	1 (11.1)	1 (20.0)	0	1 (50.0)	3 (30.0)	
Age									<0.001
Without child	113 (80.1)	69 (81.2)	24 (88.9)	9 (100.0)	3 (60.0)	0	0	8 (80.0)	
With child	28 (19.9)	16 (18.8)	3 (11.1)	0	2 (40.0)	3 (100.0)	2 (100.0)	2 (20.0)	
Sample size									0.088
≤50	95 (68.4)	61 (71.8)	16 (64.0)	8 (88.9)	4 (80.0)	3 (100.0)	1 (50.0)	2 (20.0)	
51–100	32 (23.0)	16 (18.8)	8 (32.0)	1 (11.1)	1 (20.0)	0	1 (50.0)	5 (50.0)	
>100	12 (8.6)	8 (9.4)	1 (4.0)	0	0	0	0	3 (30.0)	
missing	*2*		*2*						
Study design									<0.001
Single arm	35 (24.8)	10 (11.8)	13 (48.2)	4 (44.4)	2 (40.0)	2 (66.7)	1 (50.0)	3 (30.0)	
Parallel	97 (68.8)	72 (84.7)	11 (40.7)	4 (44.4)	3 (60.0)	1 (33.3)	0	6 (60.0)	
Factorial	3 (2.1)	0	1 (3.7)	1 (11.1)	0	0	0	1 (10.0)	
Cross-over	6 (4.3)	3 (3.5)	2 (7.4)	0	0	0	1 (50.0)	0	
Phase									0.024
Early stage	70 (68.6)	38 (65.5)	21 (91.3)	4 (50.0)	1 (25.0)	1 (50.0)	2 (100.0)	3 (60.0)	
Late stage	32 (31.4)	20 (34.5)	2 (8.7)	4 (50.0)	3 (75.0)	1 (50.0)	0	2 (40.0)	
missing	*39*	*27*	*4*	*1*	*1*	*1*		*5*	
Randomization									<0.001
No	41 (29.1)	13 (15.3)	15 (55.6)	4 (44.4)	2 (40.0)	3 (100.0)	1 (50.0)	3 (30.0)	
Yes	100 (70.9)	72 (84.7)	12 (44.4)	5 (55.6)	3 (60.0)	0	1 (50.0)	7 (70.0)	
Blind									0.022
Open label	49 (34.8)	17 (20.0)	16 (59.3)	5 (55.6)	3 (60.0)	3 (100.0)	1 (50.0)	4 (40.0)	
Single	34 (24.1)	23 (27.1)	2 (7.4)	1 (11.1)	2 (40.0)	0	1 (50.0)	5 (50.0)	
Double	32 (22.7)	24 (28.2)	7 (25.9)	1 (11.1)	0	0	0	0	
Triple	13 (9.2)	11 (12.9)	1 (3.7)	0	0	0	0	1 (10.0)	
Quadruple	13 (9.2)	10 (11.8)	1 (3.7)	2 (22.2)	0	0	0	0	
Purpose									<0.001
Treatment	106 (75.2)	72 (84.7)	15 (55.6)	8 (88.9)	5 (100.0)	3 (100.0)	1 (50.0)	2 (20.0)	
Prevention	19 (13.5)	3 (3.5)	11 (40.7)	0	0	0	0	5 (50.0)	
Diagnostic	5 (3.6)	3 (3.5)	0	0	0	0	0	2 (20.0)	
Supportive care	5 (3.6)	3 (3.5)	0	1 (11.1)	0	0	1 (50.0)	0	
Basic science	3 (2.1)	2 (2.4)	0	0	0	0	0	1 (10.0)	
Screening	1 (0.7)	1 (1.2)	0	0	0	0	0	0	
Other	2 (1.4)	1 (1.2)	1 (3.7)	0	0	0	0	0	
Treatment									<0.001
HM	21 (19.8)	17 (23.6)	0	0	2 (40.0)	0	0	2 (100.0)	
PDT	17 (16.0)	6 (8.3)	6 (40.0)	5 (62.5)	0	0	0	0	
GC	14 (13.2)	13 (18.1)	0	0	1 (20.0)	0	0	0	
IM	12 (11.3)	11 (15.3)	0	1 (12.5)	0	0	0	0	
DS	10 (9.4)	8 (11.1)	1 (6.7)	0	1 (20.0)	0	0	0	
NSAID	7 (6.6)	3 (4.2)	4 (26.7)	0	0	0	0	0	
BO	5 (4.7)	3 (4.2)	1 (6.7)	0	0	0	1 (100.0)	0	
AM	5 (4.7)	4 (5.6)	1 (6.7)	0	0	0	0	0	
SCT	3 (2.8)	0	0	0	0	3 (100.0)	0	0	
Surgery	2 (1.9)	1 (1.4)	0	0	1 (20.0)	0	0	0	
Others	10 (9.4)	6 (8.3)	2 (13.3)	2 (25.0)	0	0	0	0	
Region									<0.001
American	47 (33.3)	15 (17.7)	20 (74.1)	7 (77.8)	0	2 (66.7)	2 (100.0)	1 (10.0)	
European	33 (23.4)	25 (29.4)	3 (11.1)	1 (11.1)	0	0	0	4 (40.0)	
African	30 (21.3)	27 (31.8)	0	0	0	0	0	3 (30.0)	
Asian	27 (19.2)	17 (20.0)	2 (7.4)	1 (11.1)	5 (100.0)	0	0	2 (20.0)	
Multiple	4 (2.8)	1 (1.2)	2 (7.4)	0	0	1 (33.3)	0	0	
Center									0.017
Single-center	123 (87.2)	78 (91.8)	18 (66.7)	8 (88.9)	5 (100.0)	2 (66.7)	2 (100.0)	10 (100.0)	
Multi-center	18 (12.8)	7 (8.2)	9 (33.3)	1 (11.1)	0	1 (33.3)	0	0	
Funder									0.033
NIH	10 (7.1)	3 (3.5)	7 (25.9)	0	0	0	0	0	
Industry	5 (3.6)	2 (2.4)	2 (7.4)	0	0	0	0	1 (10.0)	
Others	126 (89.4)	80 (94.1)	18 (66.7)	9 (100.0)	5 (100.0)	3 (100.0)	2 (100.0)	9 (90.0)	

Except where indicated otherwise, values are the number (%).
Abbreviations: OLP, oral lichen planus; OLK, oral leukoplakia; AC, actinic cheilitis; OSF, oral submucous fibrosis; DC, dyskeratosis congenita; EB,

epidermolysis bullosa; HM, herbal medicine; PDT, photodynamic therapy; GC, glucocorticoid; IM, immunotherapy; DS, dietary supplement; BO, biologics; AM, antimicrobial; SCT, stem cell transplantation.

including photodynamic therapy, glucocorticoids, immunotherapy, dietary supplements, NSAID, biologics, antimicrobials, surgery and other treatments.

3.4. Publication status of primary completed studies

Among 92 primary completed interventional studies, 58 (63.0 %) were published, containing 50 (86.2 %) positive primary outcomes and 16 (27.6 %) with impact factors (IFs) over 5. Additionally, 56.0 % (14/25) of completed observational studies were published, containing 12 (85.7 %) with positive primary outcomes, but only 2 (14.3 %) with IFs over 5 (Table 3). According to Fig. 2, the number of publications, to our delight, has been increasing in the past decade, providing the public with greater access to contemporary clinical trials on OPMDs.

The median times to publication of interventional and observational studies were 33.6 months (95 % CI = 24.4–46.9) and 19.7 months (95 % CI = 10.9-NA), respectively. The 1, 2, and 3-year cumulative publication rates were 17.8 %, 36.7 % and 54.8 % for interventional studies, 35.4 %, 54.9 % and 66.2 % for observational studies (Fig. 3).

Comparing to unpublished interventional studies, published interventional studies were more often registered between 2016 and 2020 and conducted in European and Asian, were less often funded by NIH, included more OLP patients, had less PDT (Table 3). Univariable and multivariable Cox regressions analyses for publication among primary completed interventional studies are shown in Table 4. Studies registered after 2016, involving OLP patients, using factorial design, conducted outside of America or funded by others had less time to publication (less than 30 months). However, in multivariate Cox analysis, only study design and disease type were found to be significant factors.

4. Discussion

To our knowledge, this study represents the most systematic evaluation and overview of clinical studies on OPMDs, providing high-level evidence based on the data extracted from the ClinicalTrials.gov database. We identified 185 relevant studies for a detailed analysis, comparing observational studies and interventional studies, and examining factors that might influence publication. During our review, five search terms—"Discoid Lupus Erythematosus (DLE)", "Oral Erythroplakia (OE)", "Proliferative Verrucous Leukoplakia (PVL)", "Oral Lichenoid Lesion (OLL)", and "Palatal Lesions in Reverse Smokers"—were excluded. Initially, 36 studies on DLE were identified; however, none were oral-relevant upon closer examination. DLE is predominantly considered as a skin disease, with diagnostic criteria and treatment guidelines defined by dermatology experts [23]. Mucosal discoid lupus erythematosus occurs in 3 %–25 % of DLE patients [24], usually involved in systemic dermatologic treatment, with few treatments specifically targeting oral lesions. Therefore, future studies focusing on oral lesions in DLE are recommended. For OE, all relevant studies overlapped with studies in OLP, OLK, OPMDs and AC, likely because OE is traditionally described as the red counterpart of oral leukoplakia [25].

Numerous studies have analyzed the landscape of clinical trials for various diseases using medical trial registration databases. Existing studies, including those involving OPMDs patients, primarily emphasize clinical outcomes based on databases like ClinicalTrials.gov, [26,27]. These studies have assessed the results to ascertain whether specific treatment methods or diagnostic approaches provide significant guidance for clinical practice. In contrast, we are the first to specifically focus on clinical studies related to OPMDs, examining the overall research landscape, its characteristics, and the publication of results.

Most OSF studies were conducted in Asian countries, except for one, due to the high prevalence of OSF among Asians who chew betel quid products [28]. AC is associated with solar radiation, resulting in a higher incidence in tropical countries and among outdoor workers [29]. However, the number of registered studies on AC remains low, possibly because histopathological confirmation is rather laborious, making biopsy not usually recommended for AC diagnosis [3]. While the prevalence of AC is highest in Asia (10.54 %) [3], most clinical trials were carried out in US/Canada and Brazil, likely due to the stringent registration and transparency requirements of the ClinicalTrials.gov database, managed by US federal organizations such as the FDA and NIH. This focus may introduce a location bias in our study. Solely based on ClinicalTrials.gov database, our study may have a location bias.

Our research revealed that many clinical trials are in early phases and single-center with small sample sizes (Table 1), highlighting limitations and orientation needing improvement. Early-phase clinical trials (phase I and II), are typically small and single-center, economizing resources but providing limited evidence compared to well-designed, randomized, multi-center, phase III trials. Proper sample size planning is crucial to avoiding resources waste or compromising results [30,31]. Additionally, although there has been an upward trend in registrations in recent years, many trials are registered post-study start, which contradicts the 2004 advocacy by the International Committee of Medical Journal Editors (ICMJE) [32,33]. We also found information inconsistencies between ClinicalTrials.gov database and published literature, underscoring the need for improved transparency and supervision of clinical trials.

There is a notable divergence in therapy distribution across diseases. PDT was the predominant therapy for AC, consistent with its favorable therapeutic profile despite higher recurrence rates [34,35]. The significant use of herbal medicine in OLP studies might be correlated with the high prevalence of OLP in Africa and the region's long history of herbs application [36].

Anti-inflammatory therapies have been proved to reduce carcinogenesis for its characteristic of reducing angiogenesis, proliferation, metastasis and increasing the response to the immune system [37–39]. Given its key role in precancerous lesion's development and progression, anti-inflammatory therapy has been put into wide application on OPMDs patients over the past decades and showed

Table 3
Study characteristic comparisons by publication status among primary completed intervational studies.

	Overall (n = 92)	No publication (n = 34)	Publication (n = 58)	*p*-value
PrimaryDuration	19.5 (11.7, 37.9)	19.0 (12.0, 45.8)	19.5 (11.4, 32.0)	0.596
Register				0.603
Before study start	20 (21.7)	6 (17.7)	14 (24.1)	
After study start	72 (78.3)	28 (82.3)	44 (75.9)	
Year of study registered				0.004
1999–2005	13 (14.1)	9 (26.5)	4 (6.9)	
2006–2010	16 (17.4)	6 (17.7)	10 (17.2)	
2011–2015	19 (20.7)	6 (17.7)	13 (22.4)	
2016–2020	31 (33.7)	5 (14.7)	26 (44.8)	
2021–2024	13 (14.1)	8 (23.5)	5 (8.6)	
Age				0.605
Without child	73 (79.3)	26 (76.5)	47 (81.0)	
With child	19 (20.7)	8 (23.5)	11 (19.0)	
Sample size				0.435
≤50	63 (70.0)	20 (62.5)	43 (74.1)	
51–100	22 (24.4)	10 (31.3)	12 (20.7)	
>100	5 (5.6)	2 (6.2)	3 (5.2)	
missing	*2*	*2*		
Disease types				0.001
OLP	61 (66.3)	16 (47.1)	45 (77.6)	
OLK	17 (18.5)	12 (35.3)	5 (8.6)	
AC	4 (4.3)	3 (8.8)	1 (1.7)	
OSF	4 (4.3)	0	4 (6.9)	
DC	1 (1.1)	0	1 (1.7)	
EB	1 (1.1)	0	1 (1.7)	
Mixed	4 (4.3)	3 (8.8)	1 (1.7)	
Study design				0.214
Single arm	17 (18.5)	9 (26.5)	8 (13.8)	
Parallel	70 (76.1)	23 (67.6)	47 (81.0)	
Factorial	2 (2.2)	0	2 (3.5)	
Cross-over	3 (3.3)	2 (5.9)	1 (1.7)	
Phase				1.000
Early stage	45 (67.2)	16 (69.6)	29 (65.9)	
Late stage	22 (32.8)	7 (30.4)	15 (34.1)	
missing	*25*	*11*	*14*	
Purpose				0.264
Treatment	76 (82.6)	26 (76.5)	50 (86.2)	
Others	16 (17.4)	8 (23.5)	8 (13.8)	
Treatment				0.007
HM	16 (21.1)	3 (11.5)	13 (26.0)	
PDT	15 (19.7)	8 (30.8)	7 (14.0)	
IM	9 (11.8)	1 (3.8)	8 (16.0)	
GC	8 (10.5)	2 (7.7)	6 (12.0)	
DS	7 (9.2)	5 (19.2)	2 (4.0)	
NSAID	6 (7.9)	4 (15.4)	2 (4.0)	
BO	4 (5.3)	1 (3.8)	3 (6.0)	
AM	3 (3.9)	2 (7.7)	1 (2.0)	
SCT/surgery/others	8 (10.5)	0	8 (16.0)	
Randomization				0.801
No	22 (23.9)	9 (26.5)	13 (22.4)	
Yes	70 (76.1)	25 (73.5)	45 (77.6)	
Blind				0.486
Open Label	28 (30.4)	12 (35.3)	16 (27.6)	
Blind	64 (69.6)	22 (64.7)	42 (72.4)	
Region				0.048
American	28 (30.4)	16 (47.1)	12 (20.7)	
European	23 (25.0)	6 (17.7)	17 (29.3)	
African	22 (23.9)	8 (23.5)	14 (24.1)	
Asian	17 (18.5)	3 (8.8)	14 (24.1)	
Multiple	2 (2.2)	1 (2.9)	1 (1.7)	
Center (n,%)				1.000
Single-center	83 (90.2)	31 (91.2)	52 (89.7)	
Multi-center	9 (9.8)	3 (8.8)	6 (10.3)	
Funder (n,%)				0.019
NIH	8 (8.7)	6 (17.6)	2 (3.5)	
Industry	3 (3.3)	2 (5.9)	1 (1.7)	
Others	81 (88.0)	26 (76.5)	55 (94.8)	
Primary outcome				

(*continued on next page*)

Table 3 (*continued*)

	Overall (n = 92)	No publication (n = 34)	Publication (n = 58)	*p*-value
Negative			8 (13.8)	
Positive			50 (86.2)	
IFgroup				
<5			22 (37.9)	
5–9.99			11 (19.0)	
≥10			5 (8.6)	
missing			*20*	

Abbreviations: OLP, oral lichen planus; OLK, oral leukoplakia; AC, actinic cheilitis; OSF, oral submucous fibrosis; DC, dyskeratosis congenita; EB, epidermolysis bullosa; HM, herbal medicine; PDT, photodynamic therapy; GC, glucocorticoid; IM, immunotherapy; DS, dietary supplement; BO, biologics; AM, antimicrobial; SCT, stem cell transplantation.

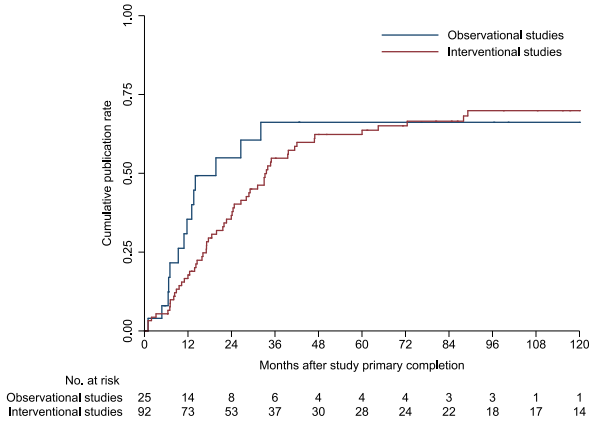

Fig. 3. Cumulative publication rate curve of primary completed studies.

excellent therapeutic potential [40,41]. In our comprehensive analysis, more than 30 % of the interventional studies concentrated on anti-inflammatory therapy including glucocorticoid, immunotherapy and NSAID for OPMDs, especially for OLP. Notably, studies combining corticosteroids with supplements like zinc (NCT04278599), vitamin E (NCT04126720), and glutamine (NCT04442633) showed promising outcomes in OLP patients, suggesting a potential for improved treatments [42–46]. However, not all combinations are effective, as seen with the use of miconazole with corticosteroid [47], indicating a need for further research. As far as we have known, the common mechanism of the three supplements is their anti-oxidant and anti-inflammatory properties. In recent years, the increase of oxidative stress is related to the pathogenesis of erosive oral lichen planus. If it can be proven to be effective with more clinical trials and higher-level evidence in the future, antioxidants can be used as a safer alternative of long-term use of NSAIDs or other medicine for therapy with adverse reactions [46,48].

Another efficacious substitution of glucocorticoids is herbal medicine. Though herbal medicine is not considered to be a first-line treatment method for clinical application [49], it has attracted growing attention, with a significant increase in research quantity. In consideration of their anti-inflammatory, anti-oxidant, and anti-carcinogenesis properties, it's rational to consider that herbal medicine is effective in other autoimmune conditions where glucocorticosteroids are applied [50]. Compared with the side-effects of glucocorticosteroids – candidiasis, diabetes mellitus, adrenal insufficiency, herbal medicine is safer and also possesses the merit of availability and low cost [51,52]. These results indicate another promising alternative and more clinical trials evaluating herbal medicine in other autoimmune diseases are supposed to be considered in the future [50].

Timely dissemination of clinical trial results is crucial for public benefit [53], yet many findings remain unpublished years after study completion [54–57]. Our study found that only 63.0 % of primary completed interventional studies were eventually published, with an increasing trend over the past few decades. Resources limitation, time restrictions, changed interests, inadequate advocation for negative findings dissemination were potential reasons of the postponement or non-publication [53]. Positive primary outcomes were more likely to be published, while negative results often faced delays or suppression [58]. Hence, it is essential to mandate the release of all study results, regardless of outcome, to accelerate knowledge dissemination [59].

Inevitably, our study has certain limitations. In spite of the ClinicalTrials.gov database serving as the oldest and largest platform that allows clinical trials from all over the world to register and meets the ICMJE registration requirements, there are some other registry platforms as well [60]. Therefore, our research included the potential selection bias. In addition, the information on ClinicalTrials.gov database is absent in some columns, not invariably up-to-date and inconsistent with the detailed descriptions in published literature, all of which may weaken our evidence. Moreover, we are unable to completely eliminate the probability of errors due to certain data not being obtained or misclassified during the whole procedure. Despite these limitations, our comprehensive analysis provides valuable insights into research quality and publication trends in OPMDs, emphasizing the need for improved trial

Table 4
Univariable and multivariable Cox regressions for publication among primary completed interventional studies (n = 92).

	Median TTP[a] (mo.)	Univariable		Multivariable	
		HR (95 % CI)	*p*-value	HR (95 % CI)	*p*-value
Duration of primary completed (mo.)	33.6	0.99 (0.98, 1.00)	0.211		
Register					
After study start	35.0	1.00	0.118		
Before study start	21.6	1.62 (0.89, 2.97)			
Year of study registered					
1999–2005	*NA*	1.00		1.00	
2006–2010	34.0	2.82 (0.88, 9.02)	0.080	1.79 (0.47, 6.72)	0.394
2011–2015	42.1	2.98 (0.97, 9.18)	0.057	1.35 (0.36, 5.08)	0.660
2016–2020	17.1	6.29 (2.16, 18.33)	0.001	3.38 (0.96, 11.91)	0.058
2021–2024	24.0	4.74 (1.23, 18.27)	0.024	2.44 (0.52, 11.42)	0.257
Sample size					
≤50	28.1	1.00			
51-100	88.0	0.61 (0.32, 1.16)	0.135		
>100	47.0	0.69 (0.22, 2.24)	0.542		
Age					
Without child	33.6	1.00			
With child	33.2	0.90 (0.47, 1.74)	0.759		
Disease type					
Others	*NA*	1.00		1.00	
OLP	28.1	2.46 (1.32, 4.60)	0.005	2.45 (1.16, 5.17)	0.019
Study Design					
Single arm	*NA*	1.00		1.00	
Parallel	31.2	2.41 (1.01, 4.53)	0.048	0.84 (0.33, 2.10)	0.703
Factorial	1.0	17.49 (3.45, 88.77)	0.001	20.46 (3.28, 127.69)	0.001
Cross-over	*NA*	0.82 (0.10, 6.55)	0.851	0.30 (0.03, 2.70)	0.286
Phase					
Early stage	33.6	1.00			
Late stage	33.0	1.16 (0.62, 2.16)	0.644		
Purpose					
Others	47.0	1.00			
Treatment	31.2	1.83 (0.86, 3.86)	0.114		
Treatment					
HM	33.6	1.00			
PDT	*NA*	0.56 (0.22, 1.42)	0.224		
IM	24.2	1.61 (0.61, 4.27)	0.339		
GC	15.9	1.21 (0.50, 2.93)	0.674		
DS	33.2	0.64 (0.14, 2.85)	0.560		
NSAID	*NA*	0.32 (0.07, 1.42)	0.134		
BO	13.8	1.39 (0.39, 4.89)	0.610		
AM	*NA*	0.22 (0.03, 1.71)	0.148		
SCT/surgery/others	12.0	1.66 (0.69, 4.01)	0.261		
Randomization					
No	46.9	1.00			
Yes	31.2	1.39 (0.75, 2.59)	0.294		
Blind					
Open Label	46.9	1.00			
Blind	31.2	1.31 (0.74, 2.34)	0.359		
Region					
American	*NA*	1.00			
European	28.1	2.25 (1.07, 4.74)	0.032	1.16 (0.48, 2.79)	0.746
African	21.6	2.25 (1.17, 5.57)	0.019	0.96 (0.37, 2.51)	0.931
Asian	29.1	2.65 (1.22, 5.77)	0.014	1.07 (0.43, 2.67)	0.879
Multiple	28.8	1.23 (0.16, 9.48)	0.845	1.01 (0.09, 11.66)	0.995
Center					
Single-center	33.0	1.00			
Multi-center	46.9	0.94 (0.40, 2.19)	0.882		
Funder					
NIH	*NA*	1.00			
Industry	*NA*	1.50 (0.14, 16.53)	0.741	1.14 (0.07, 18.79)	0.927
Others	29.1	5.36 (1.30, 22.07)	0.020	2.62 (0.49, 14.03)	0.260

Abbreviations: TTP, time to publication; mo., months; NA, not available, OLP, oral lichen planus; HM, herbal medicine; PDT, photodynamic therapy; GC, glucocorticoid; IM, immunotherapy; DS, dietary supplement; BO, biologics; AM, antimicrobial; SCT, stem cell transplantation.

[a] The median times to publication were estimated by Kaplan-Meier method.

design, registration, and result dissemination.

5. Conclusion

Overall, OLP-related studies account for the largest proportion of disease types, with herbal medicine being the most frequently studied treatment, followed by photodynamic therapy and glucocorticoids. There is a need for more high-quality, randomized, late-phase clinical trials and timely publication of results. Improvements in ClinicalTrials.gov registration standards, study design quality and publishing requirements are essential for the future advancements.

CRediT authorship contribution statement

Lijian Zhao: Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Yuqing Qu:** Writing – original draft, Methodology, Conceptualization. **Yanshu Zhang:** Writing – original draft, Conceptualization. **Zhaolei Zou:** Formal analysis. **Jingyi Lu:** Data curation. **Zhi Wang:** Writing – review & editing, Supervision. **Bin Li:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation. **Juan Fang:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Ethics committee approval

Not required.

Data availability statement

All raw data were sourced from the ClinicalTrials.gov database, with the corresponding NCT numbers provided in the supplementary materials. Also, the data supporting the findings of this study are available from the corresponding author upon request.

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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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e39408.

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