Efficacy of Antimicrobial Photodynamic Therapy Compared to Nystatin Therapy in reducing Candida Colony Count in Patients with Candida-Associated Denture Stomatitis: A Systematic Review and Meta-analysis

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Abstract

Purpose: This meta-analysis assessed the efficacy of antimicrobial photodynamic therapy (aPDT) compared to conventional nystatin therapy (NYT) in reducing *Candida* colony count in patients with *Candida*-Associated Denture Stomatitis (CADS) and critically appraised the available literature.

Methods: This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) updated guidelines. A literature search was performed in four electronic databases to identify relevant articles up to 15 August 2021. Randomized controlled trials (RCTs) that assessed the efficacy of aPDT compared to NYT in reducing *Candida* colony count in patients with CADS were investigated. The weighted mean difference (MD) and 95% confidence interval were calculated. The I^2 statistic was used to determine heterogeneity at the level of α= 0.10. The Cochrane risk of bias (RoB 2) tool was used to assess the risk of bias. Certainty of the evidence was determined using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) ranking system.

Results: Only 3 eligible RCTs with 141 participants were included in this systematic review and meta-analysis. Based on the pooled results, NYT compared to aPDT, generally performed better in reducing *Candida* colony count (Log_{10} *CFU/mL*) in patients' palate and patients' denture. The included studies had a moderate risk of bias and the certainty of the evidence was low.

Conclusion: Although still inconclusive**,** based on the current evidence aPDT may be effective in reducing *Candida* colony count, and treating CADS. Nonetheless, it does not appear to be more effective than conventional NYT in this regard. According to the limited number of included studies, more well-designed RCTs with larger sample sizes and standardized methodology should be conducted to validate this conclusion.

1. Introduction

Candida-associated denture stomatitis (CADS) is a fungal infection that presents in up to 70 percent of the edentulous denture wearers that leads to inflammation of the palatal mucosa under the denture [1]. Studies have raised several etiological factors for CADS, including long-term denture use, poor denture hygiene, immune system disorders, and hyposalivation [2]. In addition, it has been suggested that colonization of opportunistic *Candida* species, especially *Candida* albicans, play an important role in the pathogenesis of the disease [3–5].

For the treatment of CADS, denture hygiene should be strengthened, proper fitness of the denture should be evaluated, and the age of denture should be taken into account [6]. Additionally, patients can prevent CADS by using chlorhexidine mouthwashes, soaking denture in water, disinfecting denture with appropriate disinfectants, and removing denture during sleep. Dentists, on the other hand, can prevent CADS by reviewing their patients' dentures and replacing/relining the dentures if required [7].

Nystatin, Miconazole, and the other topical antifungals are the most common agents prescribed for the treatment of CADS and in cases with recurrent and severe CADS, systemic antifungal agents are prescribed which are associated with severe conditions such as hepatic necrosis, allergic reactions, adrenal insufficiency, and drug interactions [4, 8–10]. Other problems are associated with the continuous use of antifungal drugs including the resistance of fungal species and recurrence of CADS after treatment [11–13]. Therefore, it is necessary to seek safe treatments with fewer side effects. Antimicrobial photodynamic therapy (aPDT) is based on the interaction of three components including light, photosensitizer (PS), and oxygen [14]. In aPDT process, light sources can be selected from non-coherent (Light Emitting Diode (LED)), coherent (laser), or even broadband spectrum (lamp) light sources [15]. Methylene blue (MB), toluidine blue ortho (TBO), and indocyanine green (ICG) are the most common PSs used in dentistry [16, 17]. PS absorbs energy from a light source and alters from the ground state to the excited triplet state. More specifically, the PS in the excited triplet state then either loses energy and returns to the ground state or is put in the direction of one of two types of reactions, Type I and Type II [18].

The Type I reaction occurs when energy is transferred to hydrogen or an electron. This energy transfer induces the production of free radicals in nearby molecules, which produces reactive oxygen species (ROS) as they react with oxygen [19]. Type II reactions are those in which PS excited energy is directly transferred to the $^3O_2$ oxygen molecule and resulting in the formation of $^1O_2$ or ROS [18]. Accordingly, microorganisms such as *Candida* species are destroyed through this oxidative stress [20].

Hamblin et al. in 2020[21] proposed an oxygen-independent antimicrobial photoinactivation as a type III photochemical mechanism in aPDT. In this procedure, specific PSs, such as psoralens and tetracyclines, could bind to a specific molecular structure within a target microorganism and then be activated with short-wavelength light (i.e., UVA or blue) without the need for oxygen. Microorganisms are eliminated as a result of the formation of covalent adducts in their DNA or ribosomes [21].

It has been demonstrated that antimicrobial photodynamic therapy (aPDT) can be used to treat periodontal diseases, peri-implant diseases, lichen planus, and a variety of fungal infections [22–25]. An in vitro study showed that aPDT can be an effective method for reducing *Candida* species on resin acrylic dentures [26]. Also, a few randomized controlled trials (RCTs) have recently been published which have suggested aPDT as a promising solution for CADS treatment [20, 27, 28].

The objective of the present systematic review and meta-analysis was to compare the efficacy of aPDT with nystatin therapy (NYT) in reducing *Candida* colony count in patients with CADS and critically appraise the available literature to reveal research gaps in this regard.

2. Materials And Methods

The protocol of this systematic review and meta-analysis was previously registered in PROSPERO (CRD42021243146). The meta-analysis was elaborated in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) updated guideline [29]. In this study, recently published systematic review models were adopted [30, 31].

2.1. Eligibility criteria

Studies were included based on the PICOS components:

Participants (P): Edentulous individuals diagnosed with CADS.

Intervention (I): aPDT with any types of light sources and PS agents.

Comparator (C): Conventional NYT.

Outcome (O): The primary outcome included reduction of *Candida* colony count (Log_{10} *CFU/mL*) in patients' palate and denture.

Study type (S): RCTs

Studies were excluded if they:

1. Had not reported *Candida* colony count values.
2. Had included both NYT and aPDT in the same treatment group.

2.2. Information sources and search strategy

Before 15 August 2021, a comprehensive literature search was conducted by two independent authors (PF, NF) in MEDLINE (PubMed), Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science electronic databases. Also, Google Scholar was searched as an adjunctive tool to find additional eligible studies. The first 100 relevant records were evaluated from this "grey literature" search and considered for inclusion.

Any record relevant to RCTs comparing aPDT and NYT in terms of CADS treatment included for further screening with no restrictions regarding the language. Also, a manual search of the reference lists of relevant articles was conducted. Searches were limited to published and peer-reviewed studies from up to August 2021. A literature search of the aforementioned databases was conducted using MeSH terms and relevant free keywords (**Supplementary file 1**).

Study selection

All records were imported into the EndNote software (version 9.3), and duplicate records were removed. Then titles and abstracts of all retrieved records were prescreened for potentially eligible studies. The full-text version of the previously identified studies was obtained and then evaluated in detail with scrutiny according to predetermined eligibility criteria for inclusion in the review. Two reviewers (PF, NF) performed the screening process and study selection independently. Any Disagreement about eligibility and any controversies between the two reviewers were resolved through a discussion with the third reviewer (RF) until a consensus was reached. *Kappa* test was used to assess the inter-reviewer reliability (0.8 as an acceptable threshold value).

2.3. Data collection and data items

The following data were obtained from included studies: Authors, year of publication, study design, sample size, *Candida* species, light source characteristics, pre-irradiation time for PS agent, type of PS agent, antifungal agent characteristics, and follow-up period. For the meta-analysis, the means and standard deviations regarding the *Candida* colony count values and overall clinical success rate were extracted. Two reviewers (PF, RF) performed the data collection process independently. An Excel predetermined table was used to collect data electronically.

2.4. Risk of bias assessment

Two authors (PF, NF) independently assessed the quality and the risk of bias in this review. Risk of bias was assessed using the *Cochrane Risk of Bias (*RoB 2*) tool* [32] for randomized controlled trials which addresses five main domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result.

2.5. Synthesis methods

All statistical analysis was performed using Review Manager (RevMan, Version 5.4.1, Cochrane Community). The primary outcome included the reduction of *Candida* colony count in patients' palate and denture. Accordingly, all different units of *Candida* colony count values were transformed into $Log_{10}CFU/mL$ then analysis was performed on $Log_{10}CFU/mL$ to compare mycological efficacy of aPDT with NYT in the treatment of CADS. The meta-analysis was performed by measuring the means difference (MD) for continuous variables. Ninety-five percent confidence interval (CI) was used to present all the outcomes, and $P < 0.05$ was considered statistically significant. The I^2 statistic was used to determine heterogeneity at the level of $\alpha = 0.10$. The fixed-effect model was used when $I^2 = 0\%$ and the random effect model was applied in cases with $I^2 > 50\%$. Sensitivity analysis was not performed and funnel plots were not constructed due to a few numbers of included RCTs[33].

2.6. Certainty assessment

The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) ranking system through five analysis criteria (risk of bias, inconsistency, indirect evidence, imprecision, and publication bias). Thus, the quality of evidence was classified as high, moderate, low, or very low certainty of the evidence.

3. Results

3.1. Study selection

In total, the initial search strategies yielded 46 articles. Of the initial searches, 7 studies were retained for further investigation and 3 articles were excluded primarily based on their lack of appropriate endpoints matching our search criteria[34–36]. Finally, 4 randomized controlled trials were initially identified carefully from the proposed electronic databases, of which one study was omitted due to dual intervention (aPDT + NYT) in comparison with NYT [37]. Hence, based on the eligibility criteria, 3 RCTs were considered for qualitative and quantitative analysis [20, 27, 28] (Fig. 1). The interrater agreement in terms of study selection (*kappa*) was 0.95.

3.2. Study characteristics

One hundred forty-one participants with CADS were included in this systematic review and meta-analysis. The mean age of the participants varied from 61.25 to 70. All included studies proposed *Candida* albicans, *Candida* tropicalis, and *Candida* glabrata as the most prevalent *Candida* species responsible for CADS. All studies used the oral suspension form of nystatin (100.000 UI/mL) as an antifungal agent in comparison with aPDT in the treatment of CADS. Moreover, two studies used LED [20, 27] and one study [28] used the diode laser as the light source. Light source wavelength ranged from 455nm to 660nm. Pre-irradiation period and treatment interval varied from 10min to 30min and 4min to 26min, respectively. The main characteristics of the included studies are briefly illustrated in Table 1.

3.3. Results of included studies

Mima et al. compared the efficacies of aPDT to NYT (n = 20 each) for the treatment of CADS. Mycological cultures were taken from the denture and palate at baseline (day 0), at the end of the treatments (day 15), and at the follow-up time intervals (days 30, 60, and 90). It was assessed that at days 15 and 30, *Candida* colony count was significantly reduced in patients' palate and denture for both NYT and aPDT groups, compared to the baseline (day 0) ($P < 0.05$). *Candida* colony count on day 60 of follow-up intervals showed a significant increase compared to obtained values at the end of treatments ($P < 0.05$). Additionally, no statistically significant difference was shown between the *Candida* colony count values obtained from the aPDT and the NYT groups in all time intervals. Therefore, it was concluded that aPDT would be as effective as NYT in reducing *Candida* colony count [20].

In another recent study by Alrabiah et al., *Candida* colony count was measured from denture and palate at baseline (day 0), at the end of the treatments (day 15), and on the follow-up time intervals (days 30, and 60). A substantial decrease was observed in the *Candida* colony count mean values from denture and palate at the end of the treatments (day 15) compared to the baseline (day 0) in both treatment groups. On follow-up time intervals (days 30 and 60) a significant reduction in *Candida* colony count was observed in the NYT group only ($P < 0.05$). The aforementioned reduction was significantly higher on day 15 compared to follow-up days. However, there was no statistically significant difference between aPDT and NYT regarding the *Candida* colony count mean values obtained in all time intervals. Hence, aPDT was concluded as equally effective as NYT in reducing *Candida* colony count [28].

Similar to the previous studies, Alves et al. evaluated the efficacy of aPDT (n = 30) in comparison with NYT (n = 35) for the treatment of CADS. The efficacy of the treatments was verified by *Candida* colony count values from denture and palate at baseline (day 0), at the end of the treatments (day 15), and on the follow-up time intervals (days 30, 45, and 60). A significant decline in *Candida* colony count was shown at the end of the treatments compared to the baseline ($P = 0.018$). The authors showed that aPDT can be a promising treatment for CADS and had a comparable result to NYT in terms of reduction in *Candida* colony count.

3.4. Quality assessment

All included studies had an overall moderate risk of bias. The randomization process was not described appropriately in one study[20]. Additionally, some concerns were observed regarding the deviations from the intended interventions in all included studies[20, 27, 28]. None of the included studies

had missing outcome data. One study had a moderate risk of bias in terms of measurement of the outcome[28]. Regarding the selection of the reported result, all studies had a moderate to high risk of bias[20, 27, 28] (Fig. 2).

3.5. Meta-analysis

Three RCTs were selected for meta-analysis [20, 27, 28]. Mycological comparisons were conducted on the *Candida* colony count ($Log_{10}CFU/mL$) in patients' palate and denture at the end of the treatments (day 15) and on follow-up intervals (days 30, and 60).

3.5.1. Mycological efficacy of aPDT compared to NYT in palate

At the end of the treatments (day 15) NYT was superior to aPDT in reducing *Candida* colony count ($Log_{10}CFU/mL$) in patients' palate (MD = 0.58; 95%CI [0.24, 0.92]; $P = 0.0008$; $I^2 = 0\%$).

Similarly, on day 30, NYT compared to aPDT more reduced *Candida* colony count (MD = 0.60; 95%CI [0.18, 1.02]; $P = 0.005$; $I^2 = 0\%$) in patients' palate.

Nonetheless, on day 60 of follow-up period no statistically significant difference was shown between aPDT and NYT (MD = 0.24; 95%CI [-0.23, 0.70]; $P = 0.31$; $I^2 = 0\%$) (Fig. 3).

3.5.2. Mycological efficacy of aPDT compared to NYT in denture

At the end of the treatments (day 15) NYT was superior to aPDT in reducing *Candida* colony count ($Log_{10}CFU/mL$) in patients' denture (MD = 1.26; 95%CI [0.36, 2.16]; $P = 0.006$; $I^2 = 0\%$). However, on day 30 (MD = 2.59; 95%CI [-0.55, 5.73]; $P = 0.11$; $I^2 = 63\%$) and day 60 (MD = 0.94; 95%CI [-0.11, 1.99]; $P = 0.08$; $I^2 = 0\%$) of follow-up period no statistically significant difference was shown between aPDT and NYT (Fig. 4).

3.6. Certainty of evidence

Based on the GRADE scale, the certainty of evidence in terms of reducing *Candida* colony count with aPDT compared to NYT is low (Table 2). The moderate risk of bias and small sample size of the included studies would introduce a serious concern for the analysis.

4. Discussion

Some RCTs have evaluated the efficacy of aPDT in treating CADS and compared it with NYT [20, 27, 28]. Despite finding only three RCTs meeting our inclusion criteria, we were able to conduct a meta-analysis to compare aPDT with NYT in reducing *Candida* colony count which was not conducted in the previously published qualitative systematic reviews[31, 38]. Moreover, the previous systematic review has not assessed the risk of bias in included studies[38]. Therefore, the current meta-analysis attempted to solve the shortcomings of the previous systematic reviews and provide an evidence-based conclusion based on the available literature.

Even though some in vitro and animal studies [39–42] have been evaluated aPDT on oral candidiasis, since the oral environment of humans is different from animals, and factors such as biofilm and microbiota composition, salivary flux, oral hygiene, and food habits might change the response to aPDT, it is difficult to compare the findings of RCTs with those of in-vitro and animal studies [20].

Qualitative results of all included RCTs showed that aPDT is effective in reducing *Candida* colony count, and thus in improving CADS. Additionally, RCTs did not show a statistically significant difference between aPDT and NYT in reducing *Candida* colony count in all time intervals (days 15, 30, 45, 60, and 90) [20, 27, 28] which was in line with the conclusion of the previously published systematic review[31].

Qualitative results of this systematic review support the results of each included RCT and previously published systematic reviews[31, 38] in terms of the efficacy of aPDT in reducing *Candida* colony count. Nevertheless, the meta-analysis results showed that NYT statistically is superior to aPDT in reducing *Candida* colony count at the end of the treatments (day 15) in both patients' palate and denture. Although the results of each included study showed that there was no statistically significant difference between aPDT and NYT in reducing *Candida* colony count in all time intervals, it seems that the small sample size of these included studies caused the contradiction between their results and the pooled results of the performed meta-analysis.

On day 30, a statistically significant difference was observed between aPDT and NYT groups in reducing *Candida* colony count in patients' palate, however, this difference was not significant in patients' denture. This may be justified by the porous and uneven inner surface of acrylic resin dentures which act as a reservoir for microorganisms that leads for faster recolonization in patients' denture compared to patients' palate after treatments.

Also, the lack of significant difference between aPDT and NYT on day 60 may be justified by the inner surface of acrylic resin dentures which act as a reservoir for *Candida* species [43], and their tendency to recolonize on hard surfaces such as patients' denture and palate immediately after treatments. The aforementioned recolonization may lead to the recurrence of CADS after therapeutic sessions.

Additionally, based on the meta-analysis more success in the NYT group in reducing *Candida* colony count on the aforementioned intervals is probably because NYT can eliminate *Candida* species in other areas of the mouth, such as the buccal mucosa and tongue; however, utilized aPDT technique among studies only affected the palatal mucosa [20, 27, 28]. It seems that if aPDT is not limited to the palate of patients and is used in the whole oral cavity, the same results may be obtained compared to NYT. In addition, the size of fungal cells compared to bacterial cells seems to affect the success of aPDT in reducing *Candida* colony count, because larger cells need more amount of singlet oxygen to be killed [44]. Besides, according to the meta-analysis, the lower success in reducing *Candida* colony count in the aPDT group can be justified by the fact that the number of aPDT sessions was less than that of NYT. On this basis, patients get aPDT only in the office; however, patients in the NYT group used nystatin several times a day [20, 27, 28]. It is possible to achieve the same results compared to NYT by designing a low-cost aPDT devices for home use as is mentioned in a study [45].

It also seems that the parameters related to light sources and types of PSs in the aPDT group are associated with the reduction in *Candida* colony count in aPDT group [27]. Even though the research designs of the included studies were the same, nonetheless, the methodologies used in aPDT varied significantly. One of the most important barriers was a lack of standardization of light source and PS parameters across trials. While conducting the meta-analysis, aPDT was utilized as a catch-all term for any aPDT setting (independent of parameters).

The current systematic review and meta-analysis has shown the promising effect of aPDT in reducing *Candida* colony count (Log_{10} *CFU/mL*) and this effect does not seem to be as effective as NYT. Moreover, the clinical significance of these results must be carefully weighed (Although statistically significant, the clinical significance should be questioned).

This meta-analysis had some limitations that must be considered and due to these limitations, the results should be interpreted with caution. The first limitation was the lack of an appropriate number of RCTs for inclusion. Another limitation was associated with the moderate quality of the included studies. Moreover, the small sample size was the obvious shortcoming of each included study which probably led to inconsistent results between the meta-analysis and the results of each included RCT in terms of comparing aPDT and NYT in reducing *Candida* colony count. Furthermore, Finding the most effective treatment parameters of aPDT has not yet been established in this review.

5. Conclusions

Within the limitations of the current systematic review and meta-analysis, it can be concluded that aPDT may be beneficial in reducing the *Candida* colony count in patients' palate and denture, however, it does not seem to be effective as NYT in this regard. Due to the limited number of included RCTs and the moderate quality of these studies, more well-designed RCTs with larger sample sizes are recommended to compare aPDT with NYT in treatment of CADS.

Declarations

Ethics declarations

The authors declare no conflicts of interest.

Author contributions

PF: Study selection, data extraction, statistical analysis, quality appraisal, wrote manuscript

NF: Study selection, data extraction quality appraisal, edited manuscript

RF: Project design, study selection, final revision

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Tables

Table 1 Main characteristics of the included studies.

	Mima et al. (2012)		Alrabiah et al. (2019)		Alves et al. (2020)	
Design	Parallel RCT		Parallel RCT		Parallel RCT	
aPDT/NYT sample size (No.)	20/20		18/18		30/35	
Patients' age (Years) aPDT/NYT	61.25/62.45		40-65/40-65		70/69	
Candida Species	C. albicans C. tropicalis C. glabrata C. lusitaniae C. parapsilosis C. rugosa C. guillermondii		C. albicans C. tropicalis C. glabrata C. krusei C. lusitaniae C. parapsilosis		C. albicans C. glabrata C. tropicalis	
Treatment Area	Palate	Denture	Palate	Denture	Palate	Denture
Light Source/ Number/light source Wavelength (nm)	LED/10/455	LED/24/455	GaAlAs laser /660	GaAlAs laser /660	LED/10/660	LED/24/660
Photosensitizer Agent (Concentration	Hematoporphyrin derivative (500 mg/L)		Methylene blue (450 µg/mL)		Photodithazine (200 mg/L	
Pre-irradiation Time for Photosensitizer Agent	30	30	10	10	20	20
Energy Density (J/cm2)	122	37.5	28	NR	50	50
Light Power (mW)/intensity (mW/cm2)	260/102	NR/24	100/NR	NR	NR/240	NR/50
Treatment Time/Total sessions/Sessions/Sessions per Week (aPDT Group)	20 min/6/2	26 min/6/2	NR /4/2	NR	4 min/6/3	17 min/6/3
Antifungal Agent (Form)	Nystatin (Oral suspension)		Nystatin (Oral suspension)		Nystatin (Oral suspension)	
Antifungal Dosage	100000 IU/mL		100000 IU/mL		100000 IU/mL	
Treatment Time/Total Days/Usage per Day (NYT Group)	1 min/15/4	NR	1 min/15/4	NR	1 min/15/4	NR
Follow-ups (Days)	30/60/90		30/60		30/45/60	

aPDT: Antimicrobial Photodynamic Therapy; **NYT**: Nystatin Therapy; **LED**: Light Emitting Diode; **NA:** Not Reported

Table 2 Summary of evidence.

Certainty assessment							No of patients		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**aPDT**	**NYS**		
aPDT versus NYT in reducing Candida colony count in patients' palate										
3	randomized trials	serious [a]	not serious	not serious	serious [b]	none	68	73	⨁⨁◯◯ LOW	CRITICAL
aPDT versus NYT in reducing Candida colony count in patients' denture										
3	randomized trials	serious [a]	not serious	not serious	serious [b]	none	68	73	⨁⨁◯◯ LOW	CRITICAL

CI: Confidence interval; **MD:** Mean difference

a. Moderate quality RCTs **b**. Small sample size in both groups

Figures

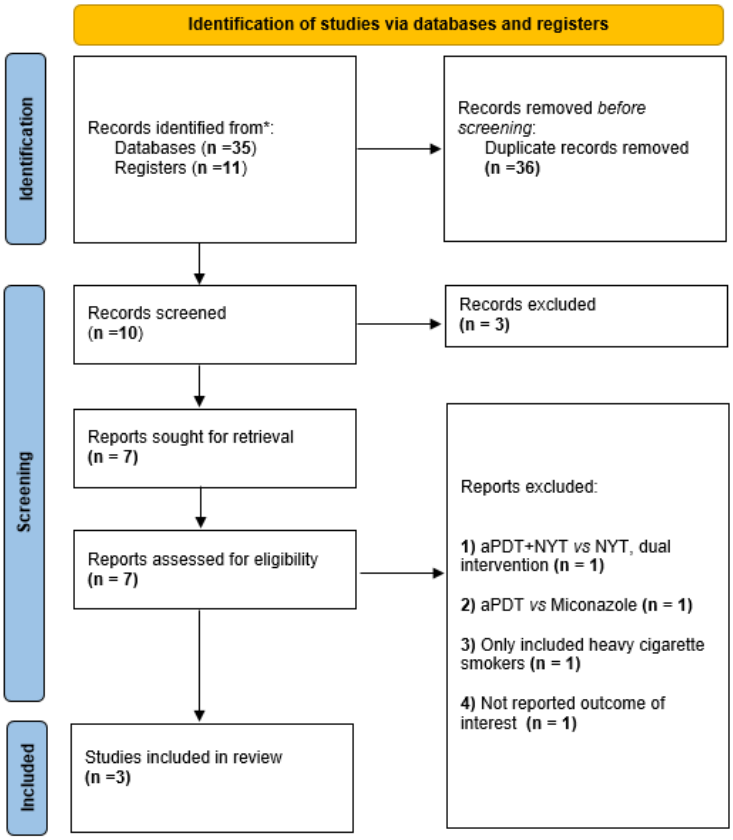

Figure 1

PRISMA flow diagram showing retrieval of papers.

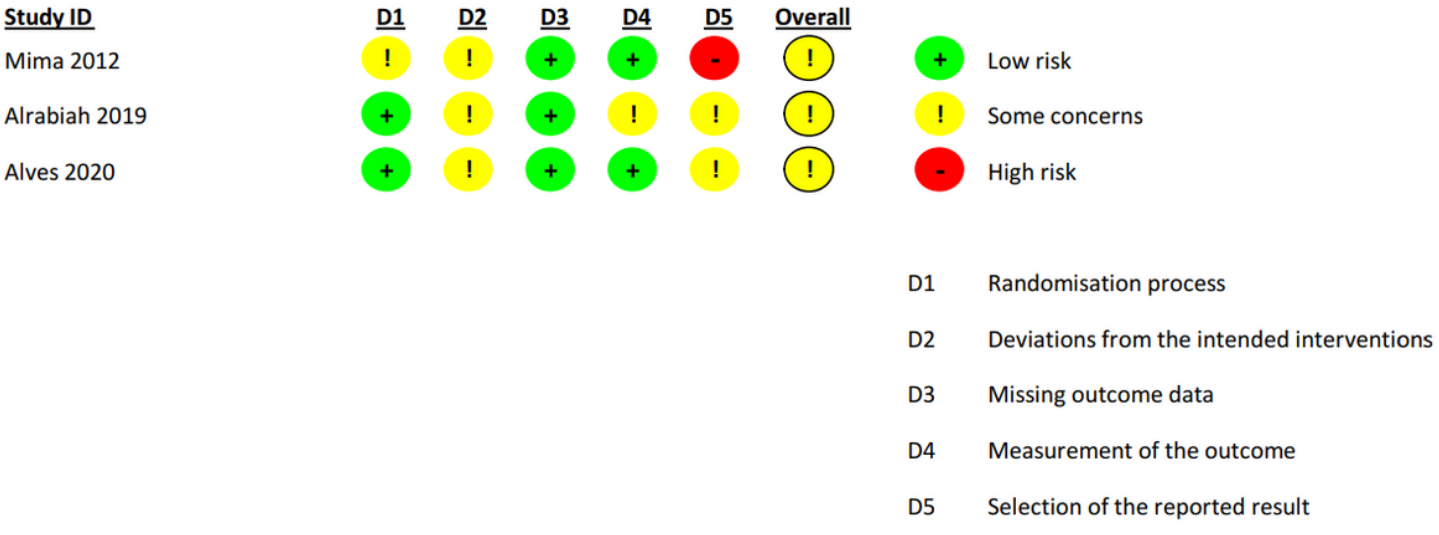

Figure 2

Risk of bias summary.

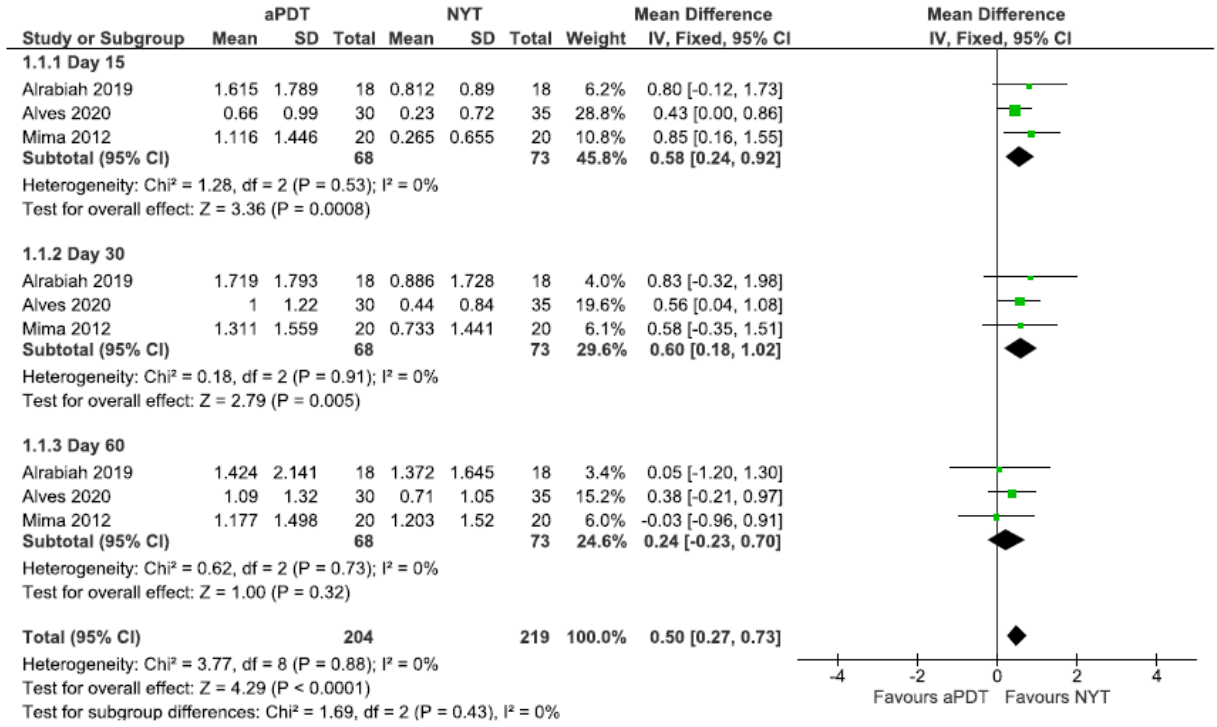

Figure 3

Forest plot of the mycological efficacy of aPDT compared to NYT in reducing Candida colony count (Log10 CFU/mL) in patients' palate.

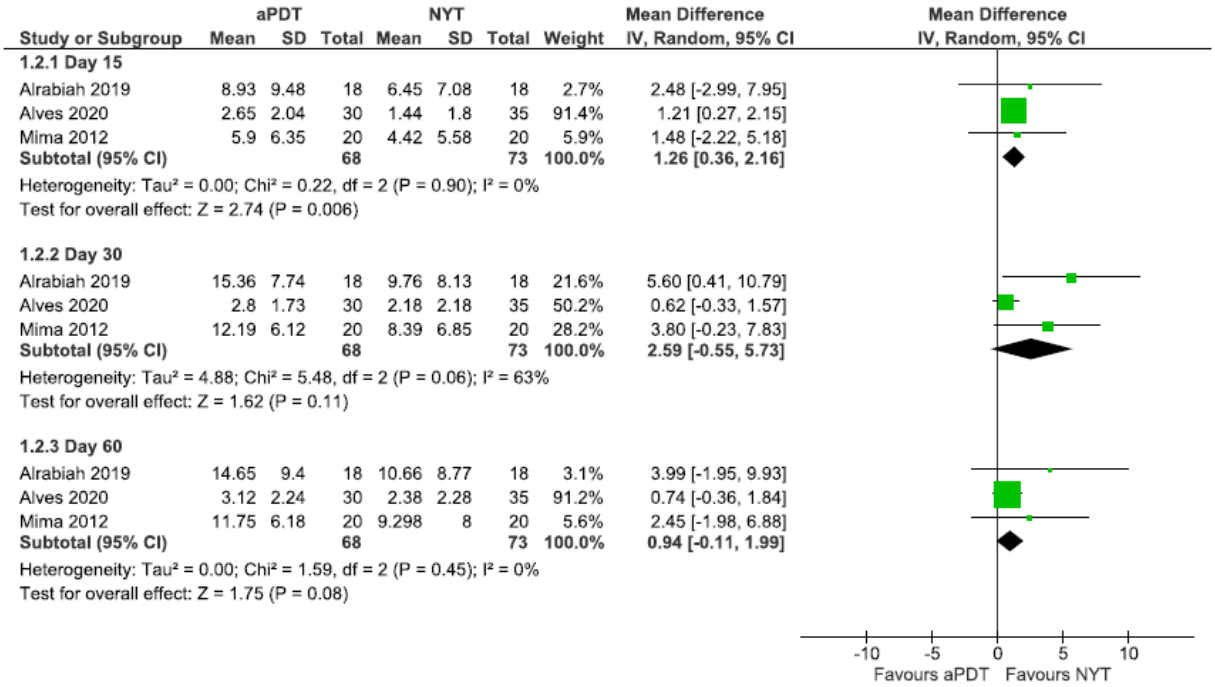

Figure 4

Forest plot of the mycological efficacy of aPDT compared to NYT in reducing Candida colony count (Log10 CFU/mL) in patients' denture.

Supplementary Files

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- Supplementaryfile1.docx