Review Article

The Functional Aspects of Microbiome and Dysbiosis Alterations in Relation to Dental Implant Outcomes: A Meta-analytical Examination

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Abstract

Background: The human oral microbiome plays a crucial role in maintaining oral health, and disruptions in its equilibrium can lead to dysbiosis, contributing to various oral diseases, including peri-implantitis in dental implant patients. This study aims to explore the functionality and dysbiosis dynamics of the oral microbiome in dental implant outcomes to elucidate the microbial factors influencing peri-implant health and disease progression.

Methods: A meta-analytical approach was employed to investigate the functional aspects of microbiome and dysbiosis alterations concerning dental implant outcomes. A comprehensive literature search was conducted to identify relevant studies. Inclusion criteria were applied to select studies focusing on the relationship between the oral microbiome, dysbiosis, and dental implant outcomes. Data extraction was performed to collect relevant information from the selected studies. Statistical analysis, including effect size calculation and heterogeneity assessment, was conducted to synthesize the findings across studies. Sensitivity analysis and assessment of publication bias were performed to ensure the robustness of the results.

Results: Eight studies were analyzed, including 217 subjects in the Experimental group and 201 in the Control group. Using a random effects model with the Mantel-Haenszel method, a significant difference was found between the two groups, with an overall risk ratio of 2.26 and a 95% confidence interval of 1.13 to 4.5.

Conclusion: Significant heterogeneity was observed, indicating that the effects varied widely in magnitude and direction across studies. The I^2 value showed that 95% of the variability among studies was due to heterogeneity rather than random chance.

Keywords: Oral Microbiome, Dental Implants, Peri-Implantitis, Dysbiosis Dynamics

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Introduction

The investigation into the microbial ecology of dental implants has garnered significant attention in recent years. Several studies have delved into the composition and diversity of the microbiome associated with dental implants under various health and disease conditions. Utilizing 16S rRNA gene sequencing, these investigations have scrutinized the microbial communities existing in dental implants, unveiling distinct microbial profiles linked to peri-implantitis characterized by heightened microbial diversity and the presence of specific bacteria like Porphyromonas gingivalis and Filifactor blocks (1). Conversely, healthy dental implants exhibit elevated levels of commensal bacteria and reduced overall microbial diversity (2). The transition from a healthy to a diseased state involves alterations in the microbial community, including an increase in periodontal pathogens and a decrease in commensal bacteria (3), underscoring the significance of comprehending the microbial ecology of dental implants for the development of effective strategies in preventing and treating peri-implant diseases. Peri-implantitis, characterized as a bacterially induced inflammatory ailment, stands as a principal cause of dental implant failure, with the interaction between the host oral microbiome and the development of peri-implantitis serving as a pivotal determinant in implant success or failure (4). Studies have pinpointed peri-implantitis as linked with dysbiosis of the oral microbiota, with specific bacterial species such as Porphiromonas gingivalis, Treponema denticola, and Tannerella forsythia prevailing in peri-implantitis samples (5). The dysbiosis within the peri-implant microbiota incites an inflammatory response and triggers immune cell activation, potentially leading to implant loss (6). Furthermore, microbial genes encoding biofilm thickness, heme transport, and gram-negative cell membrane synthesis are upregulated in diseased implants, indicating a shift towards chronic non-healing wound programming (7). The comprehension of peri-implant microbiome dynamics is vital for optimizing therapeutic approaches and ameliorating dental implant success rates (8). Over the past decade, extensive research has been dedicated to investigating the role of the microbiome in dental implant health. Biofilm, composed of a diverse array of bacteria, emerges as a significant factor in crestal bone loss around dental implants. Probiotics, considered beneficial microorganisms, demonstrate promise in tackling post-implantation challenges and fostering bone tissue homeostasis (9). The composition of the oral microbiota may vary based on oral health conditions, prosthetic materials used, and oral hygiene practices, contributing to bacterial plaque formation (10). Peri-implantitis, a complication arising from dental implantation, is associated with a multitude of bacterial species and an inflammatory response mediated by the host immune system (11). Investigations into probiotics' potential beneficial effects on periodontitis and peri-implantitis are ongoing, though further research is warranted to validate their efficacy (12). Several studies in recent years have focused on microbial dynamics in dental implantology (13). These investigations provide valuable insights into the microbial dynamics associated with dental implant outcomes and underscore the importance of understanding the oral microbiota in the development and treatment of peri- implantitis.

The interaction between the host-oral microbiome and peri-implantitis development has been extensively explored (11). Peri-implantitis is linked with a diverse range of bacterial species, with Porphiromonas gingivalis, Treponema denticola, and Tannerella forsythia being prominent in peri-implantitis samples (10). Peri-implant tissue injury triggers an inflammatory response mediated by innate immune cells, resulting in oral microbiota imbalance and dysbiosis (15). The microbiome composition within dental implants of peri-implantitis subjects significantly differs from healthy controls, with higher levels of Gram-positive bacteria, particularly Enterococci, detected in peri-

implantitis implants (16). Probiotics have been studied for their potential beneficial effects on periodontitis and peri-implantitis, yet conflicting findings persist, necessitating further investigation (17). Dental prostheses, both fixed and removable, are susceptible to microbial colonization, contributing to bacterial plaque formation, underscoring the importance of daily hygiene practices and oral dysbiosis prevention. Microbial diversity is a topic of interest across various disciplines, including the human microbiome, marine environments, and global genetic resources (18). The methods for analyzing microbial diversity have evolved from physiological and morphological traits to genetic makeup. Marker gene-based techniques, such as 16S rRNA gene sequencing, are widely employed for microbial diversity analysis, though limitations such as intragenomic variation and low taxonomic resolution may impact accuracy (19).

Microbial diversity varies across different body sites in the human microbiome and is influenced by external factors like sex, diet, and geography (20). Understanding microbial diversity is crucial for studying disease development, maintaining ecological processes, and conserving global genetic resources (21). The aim of this meta-analysis was to investigate the relationship between microbiome functionality, dysbiosis dynamics, and dental implant outcomes.

Methods

The research question is: "What is the impact of microbiome functionality and dysbiosis on dental implant outcomes?"

Objectives also are included:

1. To systematically review and analyze existing literature on the relationship between microbiome functionality, dysbiosis, and dental implant outcomes.
2. To quantify the effect sizes of microbiome alterations and dysbiosis on the success or failure of dental implants (Table 1).
3. To assess the heterogeneity across studies and explore potential sources of variability in the relationship between microbiome functionality, dysbiosis, and dental implant outcomes.
4. To evaluate the quality of included studies and assess the risk of bias in the available evidence.
5. To provide insights into the clinical implications of microbiome alterations and dysbiosis for dental implant treatment planning and management.

The following steps were undertaken to conduct the study:

1. Literature Search:

A comprehensive search of electronic databases, including PubMed, Scopus, and Google Scholar, was conducted to identify relevant studies published up to [insert end date of search]. The search strategy included keywords related to the oral microbiome, dysbiosis, dental implants, and outcomes.

The inclusion criteria included studies that had investigated microbiome changes and dysbiosis in relation to dental implant outcomes. Studies with relevant data on functional aspects of the microbiome and dysbiosis were considered.

The exclusion criteria involved studies that did not focus on dental implant outcomes or did not provide sufficient data on microbiome alterations. Studies lacking relevance to the meta-analytical examination of the functional aspects of microbiome changes and dysbiosis in relation to dental implant outcomes were excluded.

3. Data Extraction:

Data were extracted from each included study, including study characteristics (e.g., author, publication year, study design), participant demographics (e.g., age, gender, medical history), details of dental implant placement (e.g., implant type, location), methods used for microbiome analysis, and outcome measures.

Two consultants assessed the quality of all the articles retrieved from the specified databases using the given keywords, employing existing checklists for the evaluation. Following a thorough qualitative and quantitative analysis to ensure the studies' validity and reliability, the findings from each study were recorded in a data

entry form as a means of data collection. Subsequently, the data were subjected to meta-analysis (Figure 1).

4. Statistical Analysis:

Statistical analysis was performed to quantitatively synthesize the data across studies. Effect sizes, such as odds ratios or risk ratios, were calculated to measure the association between dysbiosis and dental implant outcomes. Meta-analysis
techniques, including fixed-effects or random-effects models, were used to pool the effect sizes and assess overall associations.

5. Heterogeneity Assessment:

Heterogeneity across studies was assessed using statistical tests such as Cochran's Q test and I-squared statistic. Subgroup analyses were conducted to explore potential sources of heterogeneity, including variations in study populations and methodologies.

6. Sensitivity Analysis:

Sensitivity analysis was performed to assess the robustness of the meta-analysis results. Individual studies were excluded one at a time, and the analysis was re- conducted to evaluate the impact of each study on the overall findings.

7. Publication Bias Assessment:

Potential publication bias was assessed using funnel plots and statistical tests such as Egger's regression test. Visual inspection of funnel plots and examination of asymmetry were performed to identify any evidence of bias.

8. Interpretation of Findings:

The findings of the meta-analysis were interpreted in light of the study objectives, existing literature, and clinical implications. The implications of dysbiosis on dental implant outcomes were discussed, and recommendations for future research were provided.

In this study, SPSS statistical analysis software was employed for data analysis and meta-analysis. Mothur, a bioinformatics tool, was utilized to process and analyze the microbiome sequencing data. Additionally, EndNote bibliographic management software was instrumental in organizing and managing the extensive literature pertinent to our research. These software tools played pivotal roles in facilitating data analysis, interpretation, and literature review throughout our study.

Moreover, adhering to common practices in conducting systematic reviews and meta-analyses, we utilized several other tools:

- Review management software: Rayyan software was utilized to streamline collaborative screening of prospective studies and full-text review.
- Spreadsheet software: Microsoft Excel aided in extracting data and managing information collected from various studies.
- Meta-analysis software: Comprehensive meta-analysis (CMA) software was utilized to calculate effect sizes, assess heterogeneity, and generate forest plots for comprehensive analysis.

In conclusion, this meta-analysis provided valuable insights into the relationship between microbiome functionality, dysbiosis dynamics, and dental implant outcomes, contributing to the understanding of oral health and guiding future research and clinical practice in this area.

Results

From the initial electronic search, 483 references were retrieved, out of which 342 were eliminated following a thorough review of titles. Subsequently, titles and abstracts of the remaining 141 references were scrutinized. After this screening process, 132 references were excluded, demonstrating a substantial agreement rate of 95.66% with a κ coefficient of 0.84.

Upon full-text review, 9 additional references were excluded due to various reasons:

- Some articles failed to meet the predefined inclusion criteria related to the intervention under investigation.
- In certain cases, the control group deviated significantly from the parameters relevant to our research questions.
- Studies with inadequate follow-up durations were also excluded from the analysis.

- Notably, one study exhibited markedly divergent results compared to prior research, particularly concerning control group outcomes in the context of surgical

Peri-implantitis treatment. The characteristics of the nine included studies are shown in Table 2.

All together 8 studies were analyzed with a total of 217 subjects in the Experimental cohort and 201 subjects in the Control cohort. Based on the analysis performed using random effects model with Mantel-Haenszel method to compare the risk ratio, there is a statistical difference between the two cohorts, the overall risk ratio is 2.26 with a 95% confidence interval of 1.13 - 4.5.

The test for overall effect shows a significance at $p<0.05$

A significant heterogeneity was detected (0), suggesting inconsistent effects in magnitude and/or direction. The I^2 value indicates that 95% of the variability among studies arises from heterogeneity rather than random chance.

Discussion

The composition of the microbiome significantly influences dental implant outcomes. Smoking has been identified as a factor affecting the peri-implant microbiome, resulting in a sub-healthy state that exhibits poor responsiveness to peri-implant therapies (29). Peri-implantitis, a frequently encountered complication of dental implants, correlates with alterations in bacterial diversity, notably an upsurge in Gram-positive bacteria, particularly Enterococci (30). Notable variations in microbiological profiles have been detected among healthy, periodontally affected, and peri-implantitis sites, suggesting the potential utility of microbial analyses in identifying biomarkers for periodontal health and disease (31). The presence of peri-implantitis modifies both the quantitative and qualitative composition of the oral microbiota, with specific microorganisms such as Tannerella forsythia, Prevotella intermedia, and Treponema denticola being more predominant in peri-implantitis patients (32). Although probiotics have been explored for their potential benefits in managing periodontitis and peri-implantitis, further research is warranted to validate their efficacy in dental implant management (9). The incorporation of microbiome research into dental implantology has garnered increasing attention in recent years. Investigations have highlighted the pivotal role of the oral microbiota in the development of peri-implantitis, a prevalent complication associated with dental implants (11). Peri-implantitis is linked to an imbalance in the oral microbiota, with specific bacterial species such as Porphiromonas gingivalis, Treponema denticola, and Tannerella forsythia showing higher prevalence in peri-implantitis samples (33). Understanding the composition and dynamics of the oral microbiota in peri- implantitis holds promise for developing preventive and therapeutic strategies for this condition. Moreover, research has delved into the influence of implant surfaces on microbial colonization and biofilm formation, aiming to engineer antimicrobial surfaces to mitigate the risk of peri-implantitis. By integrating microbiome research into dental implantology, there exists the potential to enhance the success and longevity of dental implants through targeted interventions addressing the oral microbiota and averting peri-implant complications. The intricate interplay between the oral microbiome and dysbiosis in dental implant health constitutes a significant area of investigation. Several studies contribute insights into this domain. D'Ambrosio et al. explore the colonization patterns of bacteria, fungi, and viruses on both removable and fixed dental prostheses, underscoring the importance of optimal oral hygiene practices to prevent dysbiosis and uphold periodontal health (34). Lo Muzio and Ten Have underscore the role of oral pathogens in precipitating periodontitis and the nexus between periodontitis and systemic ailments such as obesity, diabetes, and cardiovascular diseases. They also discuss the potential anti- inflammatory and antioxidant properties of natural compounds in managing oral dysbiosis (9). Raza et al. delve into the significance of biofilms in peri-implant health and

stress the importance of early interventions to preserve peri-implant bone, offering insights into the microbiome across various stages of peri-implant infection (7). Amato et al. review the potential therapeutic benefits of probiotics in ameliorating periodontitis and peri-implantitis, emphasizing the necessity for further investigations to validate their efficacy (35). Kahharova et al. explore the associations between the oral microbiome and caries risk factors in children, highlighting the presence of dysbiosis dominated by proteolytic taxa before clinical caries detection (36). Looking ahead, the translation of microbiome revelations into therapeutic interventions for dental implant recipients represents a pivotal realm of inquiry. Several studies delve into the microbiome concerning periodontal ailments and peri- implant well-being. Siddiqui et al. shed light on the potential utility of dental probiotics and oral microbiome transplants as therapeutic avenues for rectifying bacterial imbalances in periodontal disorders (37). Raza et al. underscore the impact of biofilms on crestal bone resorption around dental implants and stress the imperative of early intervention to safeguard peri- implant bone integrity (14). Gazil et al. scrutinize the composition of peri-implant microbiota and its distinctions from periodontal microbiota under healthy and pathological circumstances, offering insights to refine therapeutic approaches (38). Robertson introduces the notion of personalized dental medicine, encompassing implantogenomics, as a strategy to augment the durability and clinical outcomes of dental implant therapy. Hernandez et al. deliberate on the significance of pinpointing pathobionts and patho-modulators within the periodontal biofilm to forge innovative prophylactic, diagnostic, and therapeutic interventions directed at periodontitis. The utilization of dental implants represents a prevalent remedy for tooth loss; nevertheless, attaining enduring health and stability for implants poses ongoing challenges. Probiotics have emerged as a potential avenue for managing dental implant well-being by restraining pathogens, fostering bone tissue equilibrium, and modulating immune-inflammatory levels (39). Implant-associated infections linked to biofilms stand out as a principal contributor to implant malfunction, with recent advancements shedding light on the microbiota's role in these infections. Microbiome compositions across diverse bodily sites, encompassing the skin, nasopharyngeal region, neighboring tissue, and the gut, can impact biofilm formation and infection dynamic (5). Extensive exploration has gone into devising antimicrobial coatings for dental implant materials to counteract microbial adhesion. Various methodologies, such as nano-texturing, surface chemistry modifications, and controlled release mechanisms, have been investigated to thwart initial biofilm development (6). Disturbances in the oral microbiota can precipitate oral ailments, and the utilization of probiotics and prebiotics exhibits potential in reinstating microbial equilibrium and impeding disease advancement (9). Navigating the intricacies of the microbiome in dental implant outcomes calls for a deeper comprehension of the influence of implant surfaces on microbial colonization and biofilm establishment (30). The detrimental impact of smoking on the peri- implant microbiome has been evidenced, even among individuals deemed clinically healthy, resulting in heightened resistance of the microbiome and diminished responsiveness to peri-implant interventions (11). Further exploration into host- microbiome interplays in peri-implantitis is imperative to refine treatment efficacy (7). Transcriptional events occurring at the mucosal-microbial interface within the peri- implant crevice offer valuable insights into the dysbiosis and chronic programming characterizing non-healing wounds in peri-implantitis (39). Next-generation sequencing methodologies present opportunities to comprehend the intricate interactions among oral microorganisms, host responses, and implant surface coatings. In essence, a thorough comprehension of the microbiome and its

interplay with implant surfaces and host factors stands pivotal for enhancing dental implant outcomes. In recent years, substantial research has delved into microbiome dynamics and their implications for dental implant health. Numerous investigations have explored the role of biofilm in peri-implant infections and the ensuing alterations in the oral microbiota. Notably, certain microorganisms such as Tannerella forsythia, Prevotella intermedia, Treponema denticola, Porphyromonas gingivalis, Fusobacterium nucleatum, and Campylobacter rectus have demonstrated heightened prevalence in peri-implantitis patients (1). Conversely, probiotics have garnered attention as a potential adjunctive therapy for periodontitis and peri-implantitis. Nonetheless, conflicting outcomes have emerged, necessitating further exploration to ascertain the efficacy of probiotics in managing these conditions (40). Additionally, notable disparities in microbial diversity have been observed within dental implants, particularly between healthy implants and those afflicted by peri- implantitis, with diseased implants exhibiting a higher abundance of Gram-positive bacteria, notably Enterococci (41). Collectively, these investigations furnish valuable insights into microbiome dynamics and their implications for dental implant health. Microbiome dysbiosis within dental implantology carries significant clinical implications. The composition of the peri-implant microbiota contrasts with that of the periodontal microbiota in both healthy and pathological states (1). Even in clinically healthy individuals, smoking has been shown to affect the peri-implant microbiome, leading to a compromised state that exhibits poor responsiveness to peri-implant treatments (42). Peri-implantitis manifests a shift in bacterial diversity, marked by elevated levels of Gram-positive bacteria, notably Enterococci, in comparison to healthy implants (14). The onset of peri-implantitis involves a spectrum of bacterial species, including Porphiromonas gingivalis, Treponema denticola, and Tannerella forsythia, alongside an inflammatory response mediated by innate immune cell activation (43). Dysbiosis in periodontal and peri-implant regions correlates with changes in bacterial interactions, community structures, and microbial stability, potentially impacting implant viability. These discoveries underscore the imperative of comprehending microbiome dysbiosis in dental implantology and devising tailored therapeutic approaches. Closing the chasm between microbiome research and its clinical application in dental implant care is paramount for enhancing patient outcomes. Various studies have scrutinized microbiome compositions within dental implants and peri-implantitis cases. Kensara et al. observed a substantial rise in microbial diversity in peri-implantitis vis-à-vis healthy implants, characterized by heightened Gram-positive bacteria levels, particularly Enterococci (39). In a systematic review, Yu et al. delineated distinct microbial profiles in peri- implantitis compared to healthy implants and periodontitis-afflicted teeth, with Actinomyces, Campylobacter, Fusobacterium, Mogibacterium, Moraxella, Prevotella, Treponema, and Porphyromonas as the predominant genera (10). Vernon et al. underscored the necessity for optimal implant surfaces to mitigate peri- implantitis burden, accentuating the significance of surface modifications like anti- adhesion strategies and antimicrobial release in combating biofilm formation (11). Meanwhile, Song et al. explored the microbiome within the internal screw space of implants, revealing notable discrepancies in bacterial composition compared to the implant's supra-structure, underscoring the importance of sustained monitoring and management of the implant screw (44). These studies furnish invaluable insights into the microbiome associated with dental implants and peri-implantitis, hinting at potential clinical applications in dental implant care.

Conclusion

Significant heterogeneity was observed, indicating that the effects varied widely in

magnitude and direction across studies. The I^2 value showed that 95% of the variability among studies was due to heterogeneity rather than random chance.

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All authors contributed toward data analysis, Drafting and revising the paper and agreed to be Responsible for all the aspects of this work

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Tables & Figures

Table 1- The effect size is based on the size of the statistics

Effect size levels	The value of r	The value of d
Min.	Less than 0.3	Less than 0.5
Medium	Between 0.5 - 0.3	Between 0.5 and 0.8
Max.	0.5 and more	0.8 and more

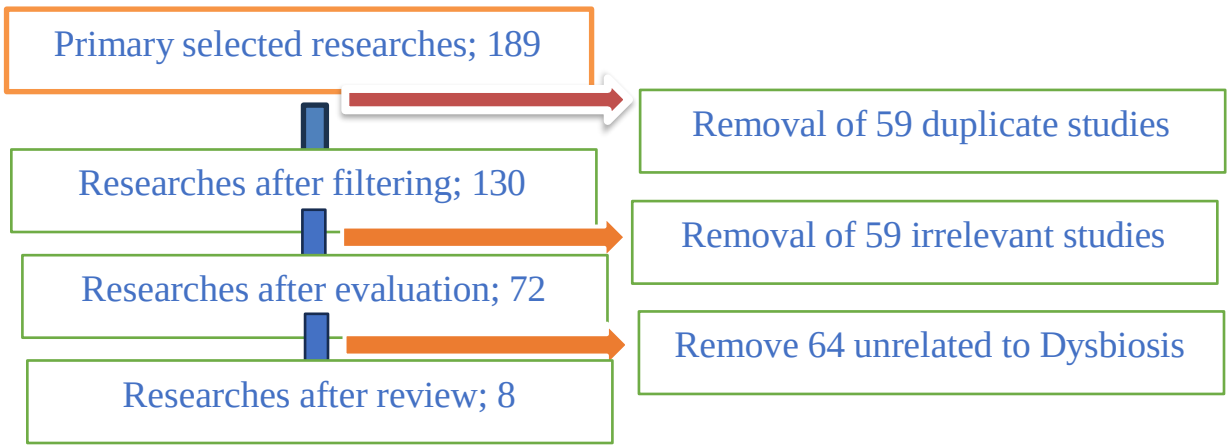

Figure 1- Stages of research selection

Table 3- Forest plot

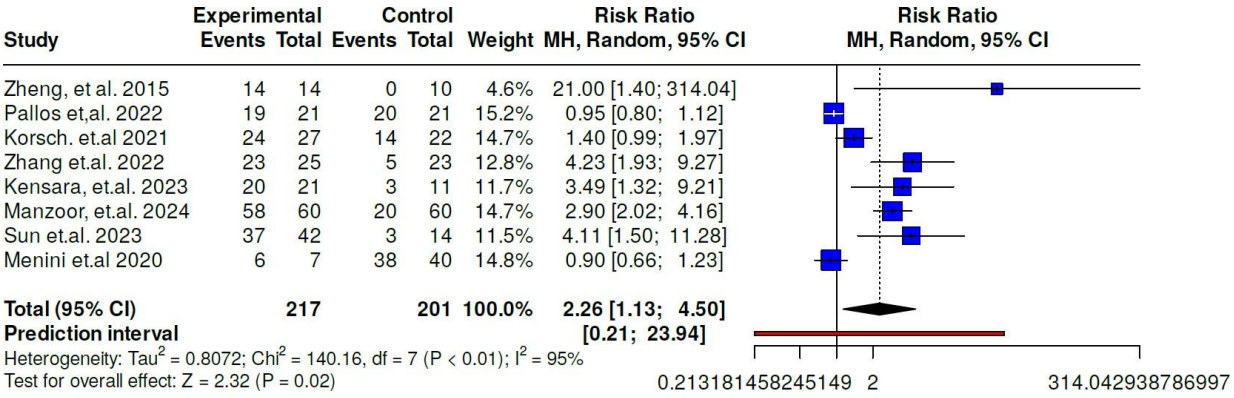

Table 4- Funnel plot

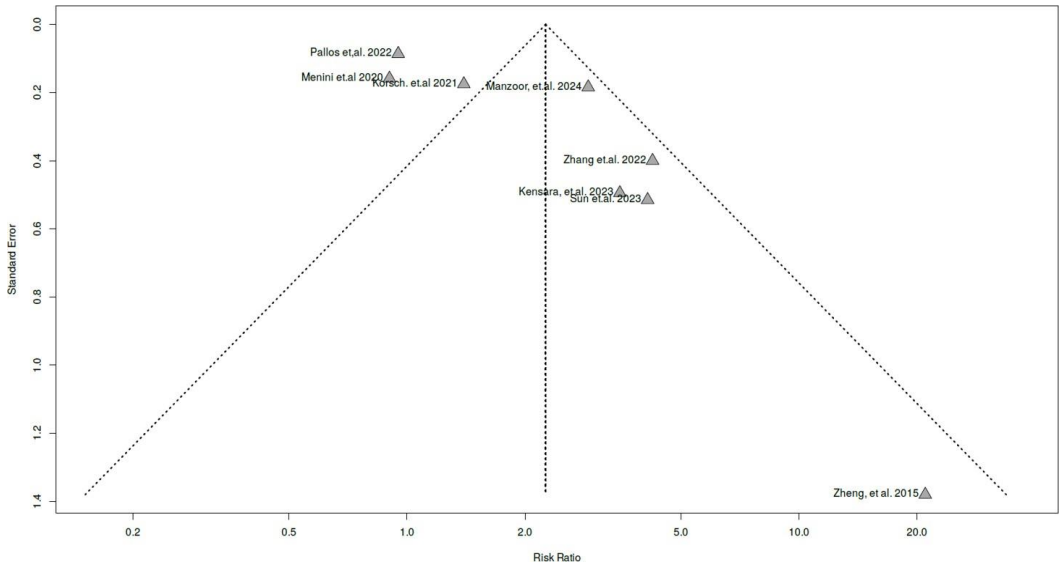

Table 5- Summary tables

	Study	Experimental	Control	RR	95% CI	Weight	t	p-value
1	Zheng, et al. 2015	14 / 14	0 / 10	21.00	1.404 - 314.043	4.55		
2	Pallos et,al. 2022	19 / 21	20 / 21	0.95	0.803 - 1.124	15.16		
3	Korsch. et.al 2021	24 / 27	14 / 22	1.40	0.991 - 1.968	14.74		
4	Zhang et.al. 2022	23 / 25	5 / 23	4.23	1.932 - 9.269	12.77		
5	Kensara, et.al. 2023	20 / 21	3 / 11	3.49	1.324 - 9.21	11.74		
6	Manzoor, et.al. 2024	58 / 60	20 / 60	2.90	2.021 - 4.16	14.68		
7	Sun et.al. 2023	37 / 42	3 / 14	4.11	1.499 - 11.278	11.52		
8	Menini et.al 2020	6 / 7	38 / 40	0.90	0.661 - 1.231	14.84		
9	Random effects model	201 / 217	103 / 201	2.26	1.135 - 4.499	100.00	2.32	0.02039

Table 6- Quantifying heterogeneity

	Parameter	Value	95% CI
1	tau^2	0.81	NA - NA
2	tau	0.90	NA - NA
3	I2	0.95	0.922 - 0.968
4	H	4.48	3.578 - 5.596

Table 7- Test of heterogeneity

	Q	d.f.	p-value
1	140.16	7.00	0.00