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The Efficacy of Utilizing Platelet-Rich Fibrin for Managing Periodontal Intrabony Defects in Conjunction with Graft Material: A Systematic Review and Meta-Analysis

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Abstract: Platelet-rich fibrin has become increasingly popular in recent years due to its remarkable capacity to accelerate the post-surgery wound healing process, reduce inflammation, and promote tissue repair. This study aimed to perform a meta-analysis to evaluate the effect of platelet-rich fibrin in mixture form with bone substitute, as a membrane, or in combination. A comprehensive search using a combination of controlled vocabulary (MeSH) and free-text terms was undertaken by two reviewers to identify published randomized clinical trials. Three major electronic databases (Medline via PubMed, Cochrane database, and Embase) and the clinical trials registry (clinicaltrials.gov) were searched up to 9 July 2023. The results of the meta-analysis showed that the pooled standardized mean difference of probing depth for platelet-rich fibrin was 0.61 (95% CI, 0.33 to 0.88). The results of the meta-analysis showed that the mean difference in clinical attachment level for platelet-rich fibrin was 0.68 (95% CI, 0.35 to 1.01). The results of the meta-analysis showed that the mean difference in bone fill for platelet-rich fibrin was 0.50 (95% CI, 0.23 to 0.78). In conclusion, the study found that platelet-rich fibrin was effective as adjunct to periodontal regeneration.

Keywords: bone regeneration; bone transplantation; periodontal disease; platelet-rich fibrin

Citation: Park, W.-J.; Han, S.-H.; Kim, N.J.; Park, J.-B. The Efficacy of Utilizing Platelet-Rich Fibrin for Managing Periodontal Intrabony Defects in Conjunction with Graft Material: A Systematic Review and Meta-Analysis. *Appl. Sci.* **2024**, *14*, 3371. https://doi.org/10.3390/app14083371

Academic Editor: Rossella Bedini

Received: 6 March 2024
Revised: 6 April 2024
Accepted: 14 April 2024
Published: 17 April 2024

1. Introduction

Platelet-rich fibrin and similar biological products are obtained from the plasma portion of one's own blood, exhibiting a platelet concentration higher than that found in the initial blood sample [1]. Platelet-rich fibrin is distinguished from other platelet concentrates, such as platelet-rich plasma and platelet-rich growth factors, by its distinct preparation process and clinical applicability [2]. Platelet-rich fibrin does not require the addition of anticoagulants or thrombin during its preparation when compared with platelet-rich plasma and platelet-rich growth factors [3]. Platelet-rich fibrin has become increasingly popular in recent years due to its remarkable capacity to accelerate the post-surgery wound healing process, reduce inflammation, and promote tissue repair [4,5]. Platelet-rich fibrin finds extensive applications in dentistry, with dental implantology, oral and maxillofacial surgery, endodontics, and cosmetic dentistry witnessing a surge in its popularity [6]. The use of platelet-rich fibrin, with or without biomaterials, demonstrated superior efficacy

compared to open flap debridement [7]. There was a notable enhancement in clinical indications when platelet-rich fibrin was combined with demineralized bone matrix, as opposed to using platelet-rich fibrin alone [7,8]. Additionally, the group receiving both platelet-rich fibrin and demineralized bone matrix displayed a greater degree of bone fill on radiographs [9]. Platelet-rich fibrin offers the benefit of maintaining a continuous release of growth factors and facilitating cell migration by stimulating the expression of type I collagen and transforming growth factor mRNA [10]. The secretomes of platelet-rich fibrin represent an innovative growth factor-based approach for promoting bone and periodontal regeneration, and differentially expressed proteins have been identified from the platelet-rich fibrin, including key growth factors, cytokines, and components of the extracellular matrix that play crucial roles in the process of wound healing [11]. The proliferation of human gingival fibroblast cells exhibited a direct correlation with the concentration of platelet-rich fibrin, demonstrating a dose-dependent effect [12].

Hence, the impact of platelet-rich fibrin on periodontal regeneration has remained a topic of continuous discussion. The rationale behind the functioning of platelet-rich fibrin can be elucidated as follows: The reasoning behind the use of platelet-rich fibrin lies in its role as a biomaterial, facilitating the delivery of essential growth factors and cytokines sourced from platelet granules to the specific area of focus, and this process, in turn, fosters tissue regeneration across a range of tissues, including bone regeneration [13]. In addition to utilizing platelet-rich fibrin and graft materials in managing periodontal intrabony defects, a range of other treatment methods, such as targeted delivery of antibiotics, the application of laser therapy, and the use of various medications, can be employed for the treatment of periodontal disease [14,15]. As a result of its additional benefits, platelet-rich fibrin appears to be a naturally appropriate complement in bone regenerative surgery, leading to positive results with minimal associated risks [16]. Therefore, this study aims to perform a meta-analysis to evaluate the effect of platelet-rich fibrin in mixture form with bone substitute, as a membrane, or in combination. The null hypothesis posited that there would be no noteworthy distinction in the effect of platelet-rich fibrin on periodontal regeneration. The primary goal of this research is to assess the extent of periodontal regeneration that can be attained with platelet-rich fibrin by examining improvements in reductions in periodontal probing, clinical attachment levels, and the attainment of bone fill. Additionally, the secondary objective is to carry out a subgroup analysis that categorizes the findings based on the type of graft material used.

2. Materials and Methods

2.1. Protocol and Registration

This present systematic review adheres to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement [17], as outlined in reference.

2.2. Eligibility Criteria

Question: Does the application of platelet-rich fibrin enhance periodontal regeneration when compared to a group where it is not applied?

Participants: Patients with intrabony defects.

Interventions: Surgical procedures involving a flap, with the addition of platelet-rich fibrin.

Comparisons: Periodontal regeneration without the application of platelet-rich fibrin.

Outcomes: Pre-operative and 6-month post-operative periodontal probing depth, clinical attachment level, and bone fill.

Study design: Randomized controlled trials.

The following criteria were required for studies to be included in this study: (1) studies with randomized controlled trials; (2) studies involving the use of platelet-rich fibrin in the management of periodontal intrabony defects; and (3) studies making a comparison between interventions and control groups. We excluded the following from our study:

in vitro and animal studies, studies with a sample size of less than six, studies that involved additional procedures such as LASER application to enhance healing, literature reviews, case reports, case-control study designs, retrospective study designs, and studies published in languages other than English.

2.3. Sources of Information and Search Methodology

A single reviewer (NJK, library-affiliated searching personnel) conducted an extensive search using a combination of controlled vocabulary (MeSH) and free-text terms to locate published systematic reviews. The reviewer (SHH) conducted searches on three major electronic databases (Medline via PubMed, Cochrane database, and Embase), and another reviewer (WJP) conducted a search on the clinical trials registry known as clinicaltrials.gov up to 9 July 2023. The search results were meticulously transferred to the EndNote reference management software (Version 21, Clarivate, Philadelphia, PA, USA) for a thorough deduplication process. This step was essential to ensure that no duplicate entries or redundant references would compromise the integrity of the research findings. To maximize the accuracy and relevance of our search, the search strategy employed was thoughtfully customized to align with the distinct criteria and nuances of each database under consideration. This strategic adaptation allowed us to effectively harness the full potential of each database, optimizing the retrieval of pertinent and valuable information for our research objectives. Details of the search strategy are shown in Supplementary Tables S1–S3.

2.4. Assessment of the Risk of Bias

The reviewers employed the Cochrane Risk-Of-Bias (ROB 2.0) tool for randomized studies, which comprises a checklist with questions pertaining to various aspects of bias. This checklist covers aspects such as the randomization process (selection bias), deviations from the intended interventions (performance bias), missing outcome data (attrition bias), measurement of the outcome (detection bias), selection of the reported result (reporting bias), and an overall assessment of bias. The risk of bias for the included studies was assessed and categorized as low risk, some concerns, or high risk. The evaluation of study quality was conducted by two reviewers, namely WJP and SHH.

2.5. Missing Data Imputation

Both the mean change in variables and the standard deviation of this change need to be imputed if they are missing. The missing mean change in variables was filled by calculating the difference between the mean follow-up and mean baseline data. We used the formula from the Cochrane Handbook to estimate missing standard deviations [18]. The data from the selected papers, where the mean and standard deviation for baseline, follow-up, and change were all provided, were used to calculate the mean correlation for the control group. The obtained correlation values were 0.65 for probing depth, 0.8 for clinical attachment level, and 0.85 for bone gain, and these values were used to estimate missing standard deviations.

2.6. Synthesis and Analysis of Data

We conducted a meta-analysis utilizing R (Version 3.5.0; R Project for Statistical Computing). Summary statistics were represented by the mean difference and a 95% confidence interval. A random-effects model was employed for the meta-analysis, and the significance level was set at 0.05. To assess heterogeneity across studies, we calculated I^2 and performed a chi-square test.

3. Results

3.1. Study Selection

The initial search yielded 1003 articles, and after removing 661 duplicates, 684 studies were taken into consideration. The abstracts were reviewed by two independent reviewers (WJP and SHH), finding that 661 articles did not meet the inclusion criteria. Subsequently,

the inclusion and exclusion criteria were applied to the 23 full-text articles, leading to the exclusion of 5 that did not meet the inclusion criteria. Ultimately, 18 studies were assessed for eligibility. A visualization of this literature-screening process is shown in Figure 1.

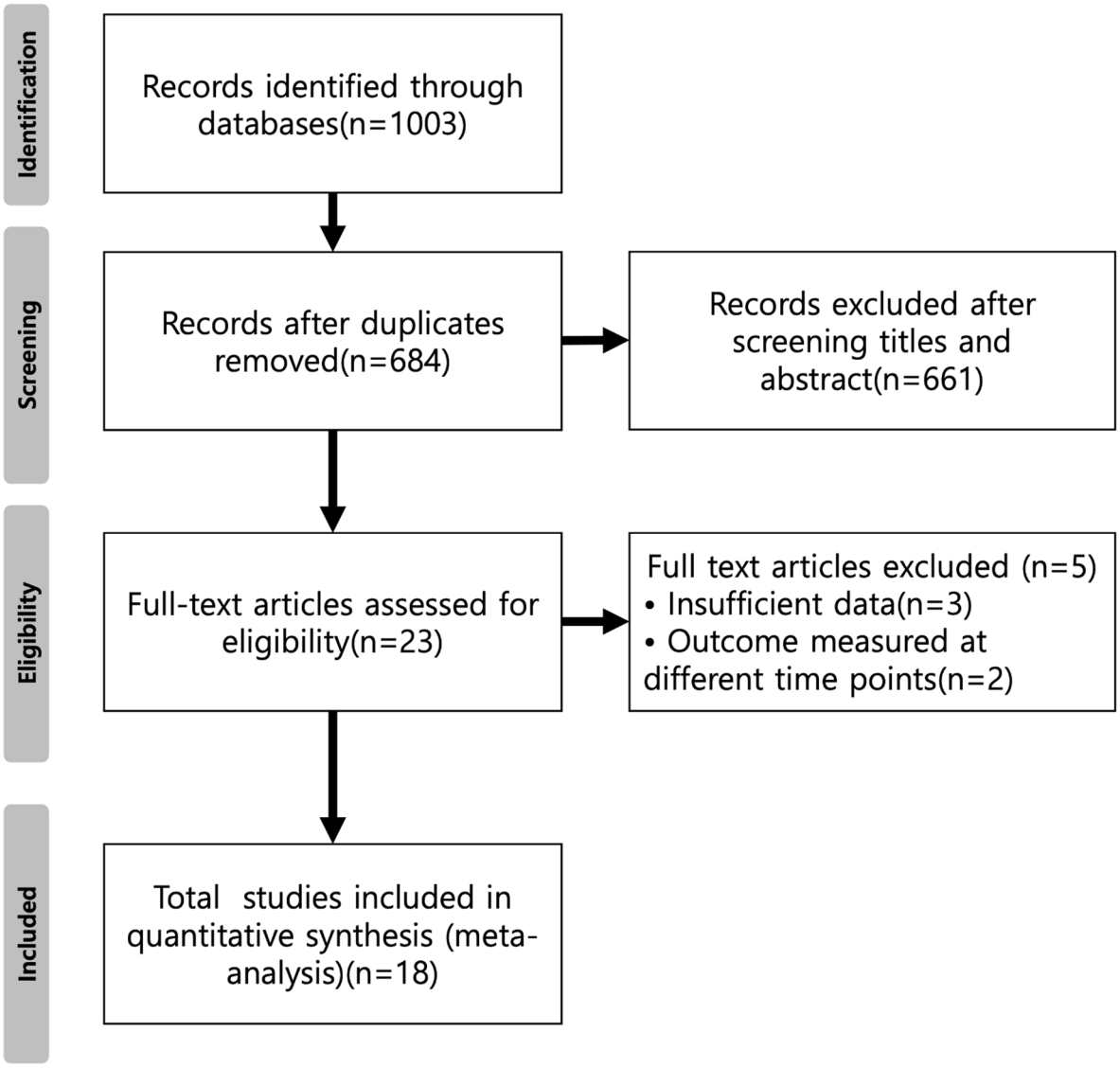
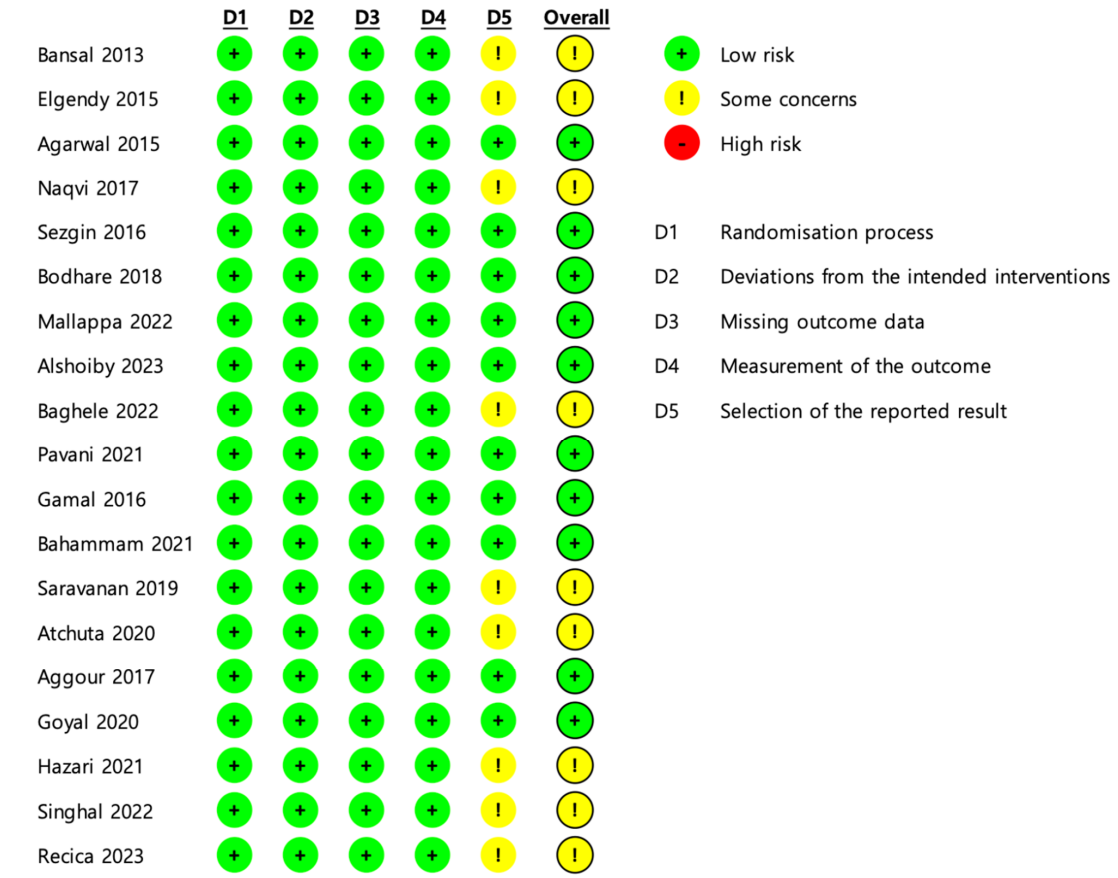


Figure 1. Flow chart illustrating the process regarding the articles that have been encompassed within the systematic reviews.

3.2. Risk of Bias

The overview of bias risk and the overall bias score for each domain within the included articles are displayed in Figure 2A,B. Out of the total, nine trials were categorized as having a low risk of bias, while nine raised some concerns regarding bias. Most of the trials employed an appropriate randomization process. Nevertheless, in nine studies, the reported results were influenced by an inadequate selection of reported results. Figure 2B illustrates the collective bias risk score across all fields.



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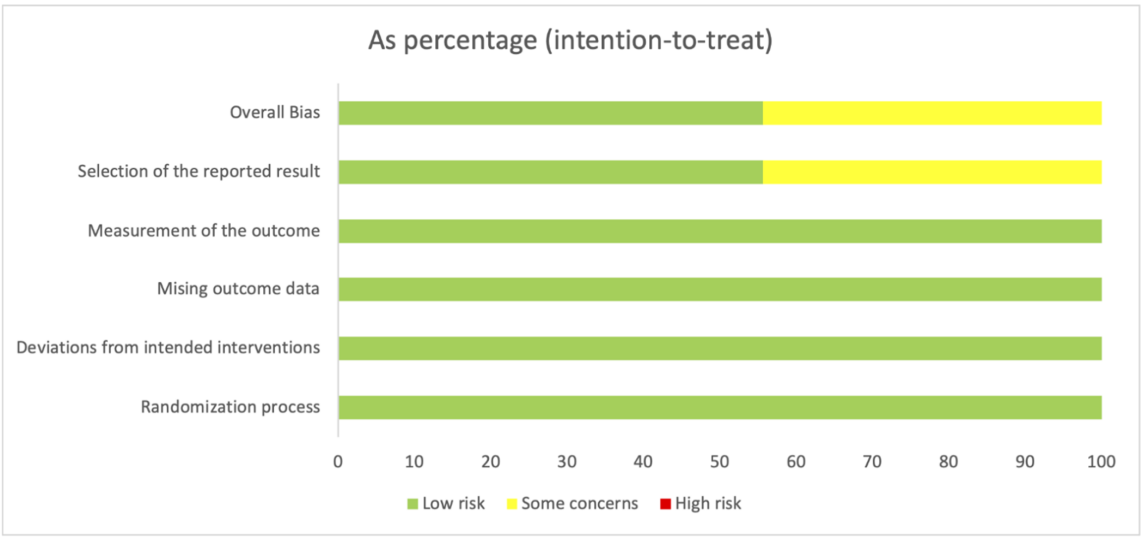


(**B**)

Figure 2. Risk of bias. (**A**) Summary of the risk of bias in the included studies. (**B**) Overall risk of bias score for each field.

3.3. Meta-Analysis

Table 1 shows the main characteristics of the included studies. Periodontal regeneration without the use of platelet-rich fibrin was considered the control group. Supplementary Table S4 lists the outcome parameters of the included studies, including periodontal probing depth, clinical attachment level, and bone filling.

Table 1. Main characteristics of the included studies.

Author	Study Design	Sample Size (Control:Intervention)	Type of Graft Material	Platelet-Rich Fibrin Preparation Method (Centrifuge System)	Application Method	Follow-Up Period
Bansal 2013 [19]	RCT (split-mouth)	10:10	Allograft (DFDBA)	3000 rpm for 10 min (NR)	Mixture of PRF with graft material	6 months
Elgendy 2015 [20]	RCT (split-mouth)	20:20	Synthetic material	3000 rpm for 10 min (NR)	Membrane	6 months
Gamal 2016 [21]	RCT (parallel)	9:10	Xenograft	2500 rpm for 10 min (NR)	Mixture of PRF with graft material & membrane	6, 9 months
Naqvi 2017 [22]	RCT (split-mouth)	10:10	Synthetic material	400× *g* for 10 min (NR)	Membrane	3, 6, 9 months
Sezgin 2017 [23]	RCT(split-mouth)	15:15	Xenograft	2700 rpm (approximately 400× *g*) for 12 min (PC-02 table centrifuge, Process for PRF, Nice, France))	Mixture of PRF with graft material & membrane	6 months
Aggour 2017 [24]	RCT (split-mouth)	16:16	Autograft + xenograft	400× *g* for 10 min (tabletop centrifuge, Shanghai Medical Instruments, Shanghai, China)	Membrane	6 months
Bodhare 2019 [25]	RCT (split-mouth)	20:20	Synthetic material	3000 rpm for 10 min (REMI® Laboratories, Mumbai, Maharashtra, India)	Membrane & graft material mixed with few drops of top layer of straw-colored acellular plasma	3, 6 months
Saravanan 2019 [26]	RCT (split-mouth)	15:15	Synthetic material	3000 rpm for 10 min (NR)	Mixture of PRF with graft material	6 months
Atchuta 2020 [27]	RCT (parallel)	13:13	Allograft (DFDBA)	3000 rpm for 10 min (NR)	Mixture of PRF with graft material	3, 6 months
Goyal 2020 [28]	RCT (split-mouth)	12:12	Xenograft + synthetic material	2700 rpm for 10 min (REMI® Laboratories, Mumbai, Maharashtra, India)	Mixture of PRF with graft material	3, 6 months
Pavani 2021 [29]	RCT (parallel)	10:10	Synthetic material	3000 rpm for 10 min (NR)	Mixture of PRF with graft material	6 months

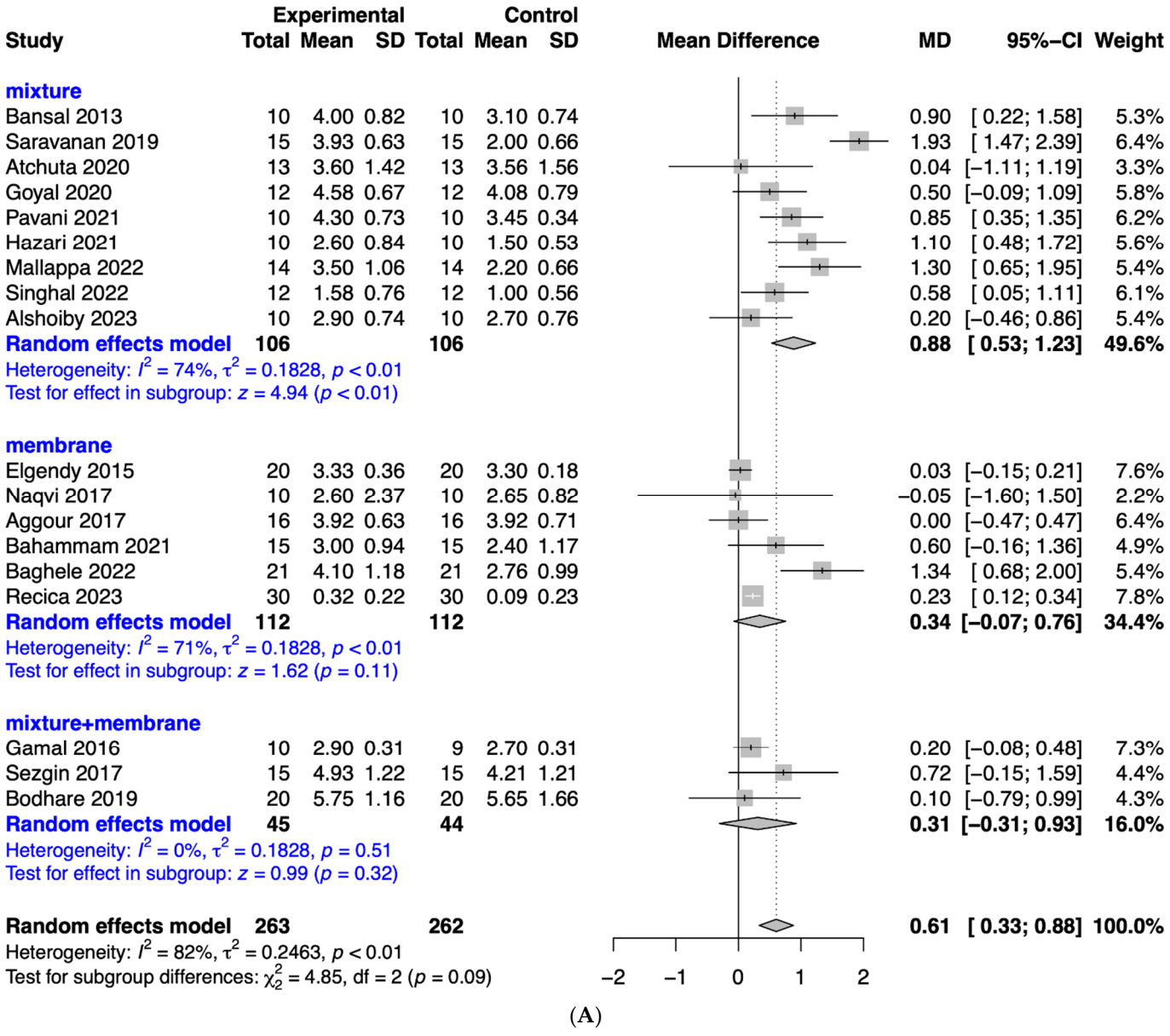
Table 1. *Cont.*

Author	Study Design	Sample Size (Control:Intervention)	Type of Graft Material	Platelet-Rich Fibrin Preparation Method (Centrifuge System)	Application Method	Follow-Up Period
Bahammam 2021 [30]	RCT (parallel)	15:15	Synthetic material	3000 rpm for 10 min (NR)	Membrane	6 months
Hazari 2021 [31]	RCT (parallel)	10:10	Synthetic material	3000 rpm for 10 min (NR)	Mixture of PRF with graft material	3, 6 months
Mallappa 2022 [32]	RCT (parallel)	14:14	Synthetic material	1500 rpm for 14 min (A-PRF) 700 rpm for 3 min (i-PRF) (Process for PRF, Nice, France)	Mixture of A-PRF, i-PRF and graft material	6 months
Baghele 2022 [33]	RCT (parallel)	21:21	Synthetic material	3000 rpm for 10 min (NR)	Membrane	6 months
Singhal 2022 [34]	RCT (parallel)	12:12	Xenograft	3000 rpm for 12 min (NR)	Mixture of PRF with graft material	3, 6 months
Alshoiby 2023 [35]	RCT (parallel)	10:10	Allograft (DFDBA)	60× *g* (700 rpm) for 3 min (i-PRF) (VE-4000, Velab, Pharr, TX, USA)	mixture of PRF with graft material	6, 9 months
Recica 2023 [36]	RCT (split-mouth)	30:30	Synthetic material	(NR)	Membrane	6, 12, 18 months

PRF: platelet-rich fibrin; RCT: randomized controlled trial; DFDBA: demineralized freeze-dried bone allograft; NR: not reported.

3.4. Evaluation of the Effects of Platelet-Rich Fibrin on Periodontal Probing Depth

Figure 3A provides a forest plot illustrating the comparison between platelet-rich fibrin and control for reduction in periodontal probing depth. This forest plot serves as a valuable tool for comprehending the nuances of the research findings. The results of the meta-analysis showed that the mean difference in probing depth for platelet-rich fibrin was 0.61 (95% confidence interval, 0.33 to 0.88). Subgroup analysis categorized by application method showed that platelet-rich fibrin, which is diced and mixed with the graft material, resulted in a mean difference of probing depth of 0.88 (95% confidence interval, 0.53 to 1.23; $p < 0.01$). The mean difference in probing depth for platelet-rich fibrin applied as a membrane was 0.34 (95% confidence interval, −0.07 to 0.76; $p = 0.11$). Platelet-rich fibrin applied as a mixture with the graft material and additional application as a membrane showed the mean difference in probing depth for platelet-rich fibrin was 0.31 (95% confidence interval, −0.31 to 0.93; $p = 0.32$). Subgroup analysis categorized by application method did not reach statistical significance.



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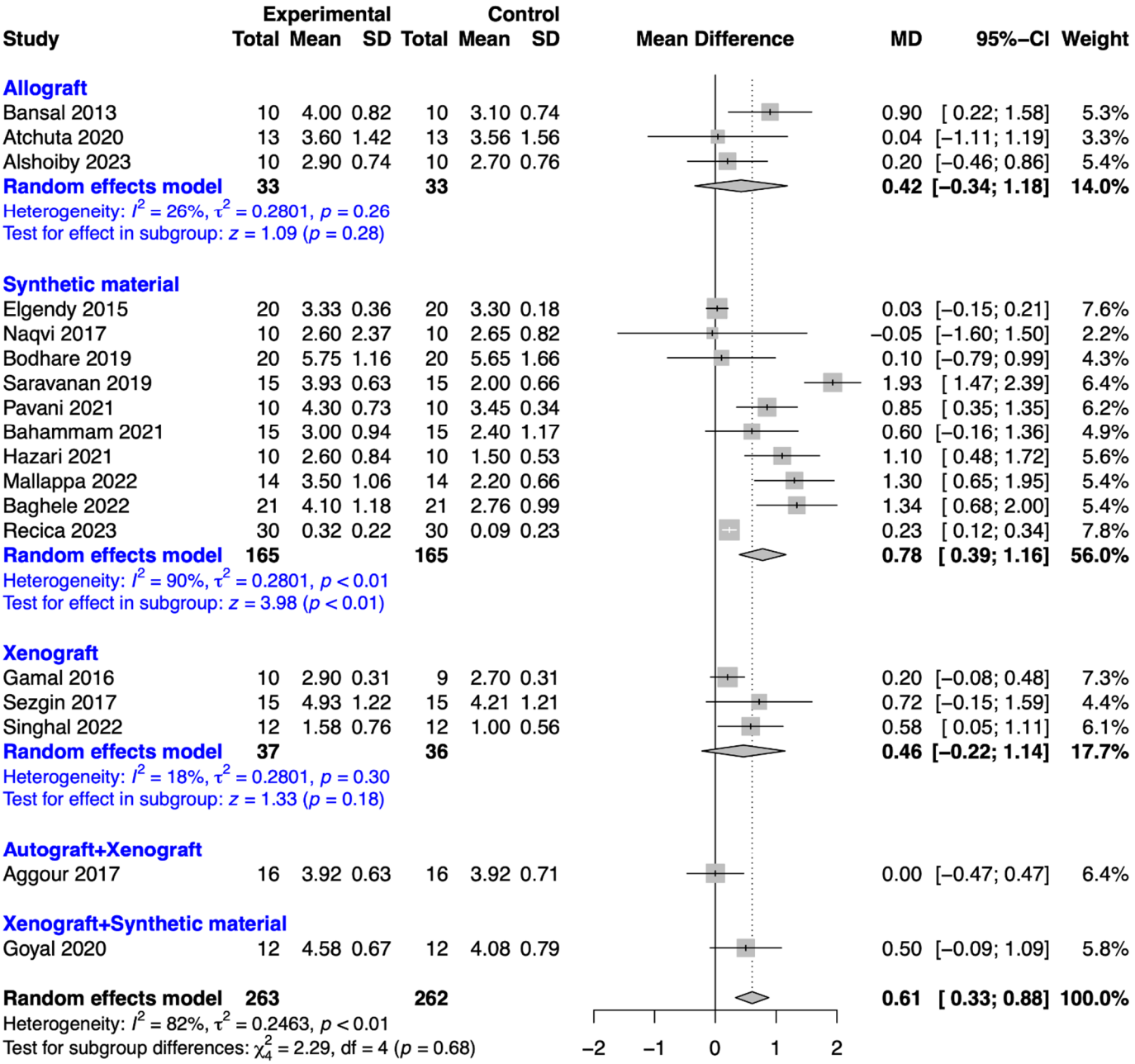
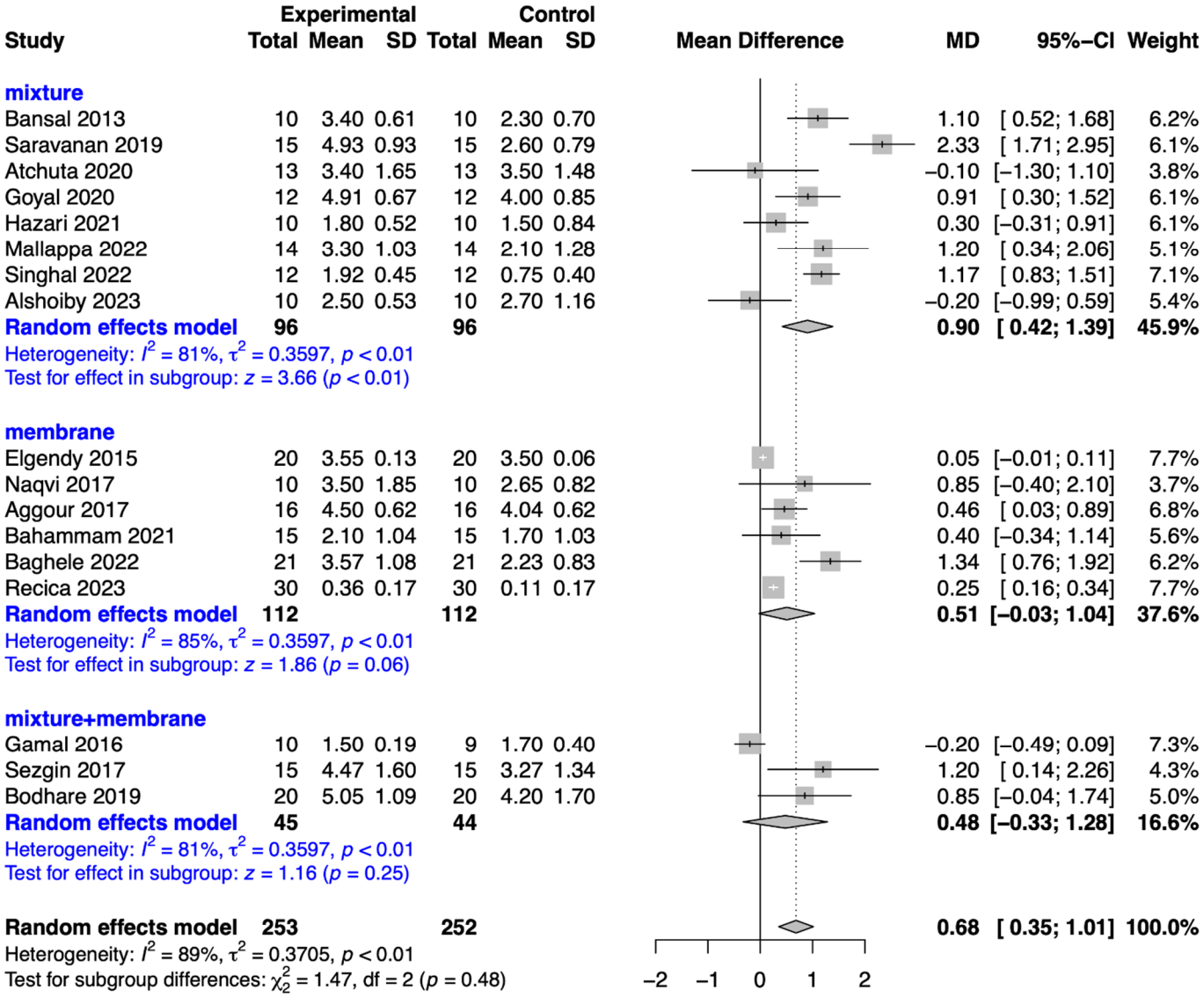


Figure 3. Forest plot illustrating the comparison between platelet-rich fibrin and control for reduction in periodontal probing depth [19–36]. (**A**) Subgroup analysis categorized by application method. (**B**) Subgroup analysis categorized by types of graft material.

Figure 3B shows a subgroup analysis categorized by types of graft material. The results of the meta-analysis showed that the mean difference in probing depth for platelet-rich fibrin applied with allograft was 0.42 (95% confidence interval, −0.34 to 1.18; $p = 0.28$). Subgroup analysis categorized by graft material of synthetic material resulted in the mean difference of probing depth for platelet-rich fibrin being 0.78 (95% confidence interval, 0.39 to 1.16; $p < 0.01$). Platelet-rich fibrin applied with xenograft showed the mean difference in probing depth for platelet-rich fibrin was 0.46 (95% confidence interval, −0.22 to 1.14; $p = 0.18$). Subgroup analysis categorized by types of graft material did not reach a significant difference ($p = 0.68$).

3.5. Analysis of the Effects of Platelet-Rich Fibrin on Clinical Attachment Level

Figure 4A shows a forest plot meticulously crafted to provide a visual representation of the comparison between platelet-rich fibrin and the control group concerning their impact on enhancing clinical attachment level. The analysis has yielded a mean difference of 0.68, with a 95% confidence interval ranging from 0.35 to 1.01. This statistically robust finding underscores the potential clinical benefits associated with the utilization of platelet-rich fibrin in improving clinical attachment levels. Subgroup analysis categorized by application method showed that platelet-rich fibrin, which is diced and mixed with the graft material, resulted in a mean difference in clinical attachment level for platelet-rich fibrin of 0.90 (95% confidence interval, 0.42 to 1.39; $p < 0.01$). The mean difference in clinical attachment level for platelet-rich fibrin applied as a membrane was 0.51 (95% confidence interval, −0.03 to 1.04; $p = 0.06$). Platelet-rich fibrin applied as a mixture with the graft material and additional application as a membrane showed the mean difference in clinical attachment level for platelet-rich fibrin was 0.48 (95% confidence interval, −0.33 to 1.28; $p = 0.25$).



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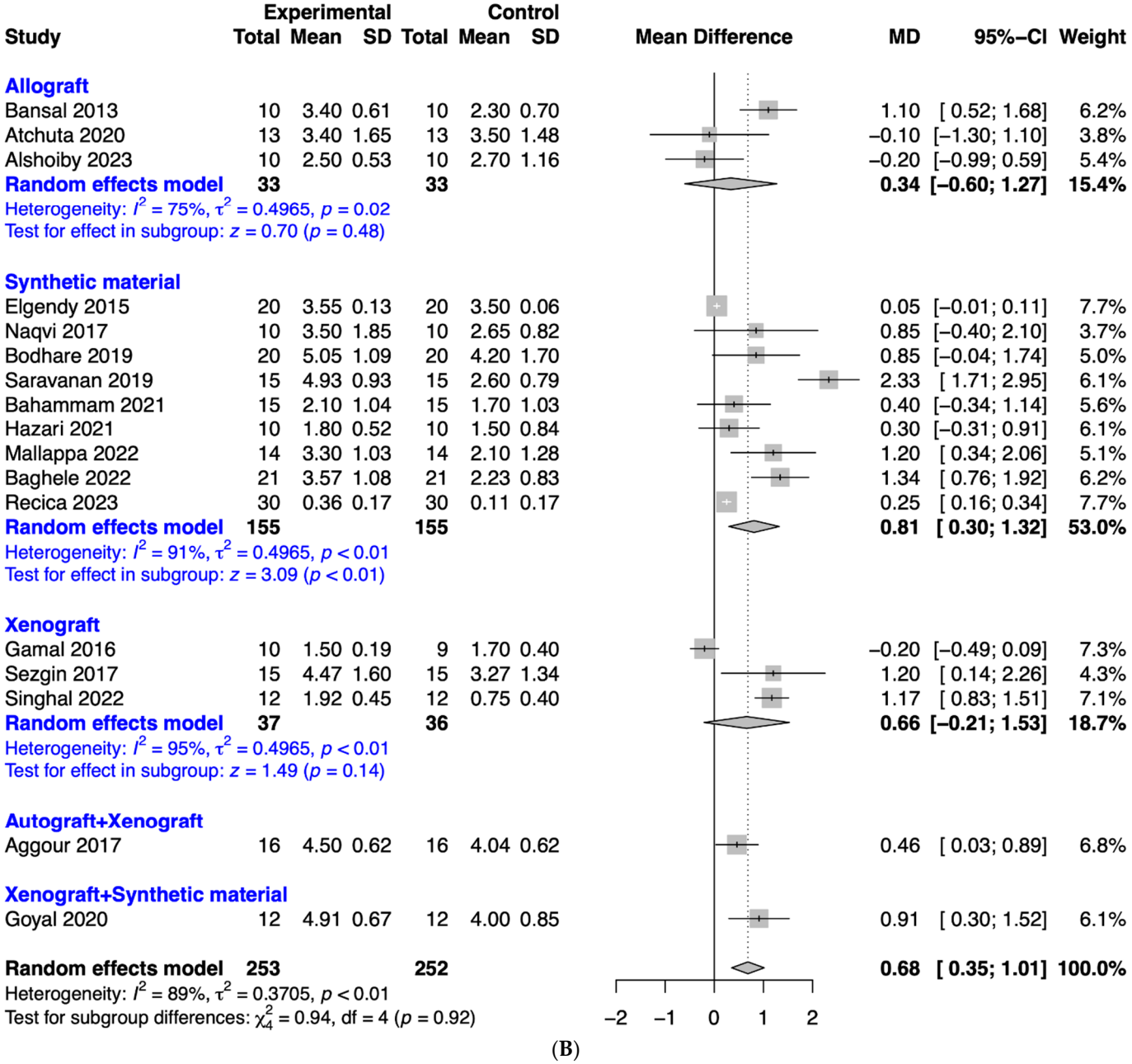


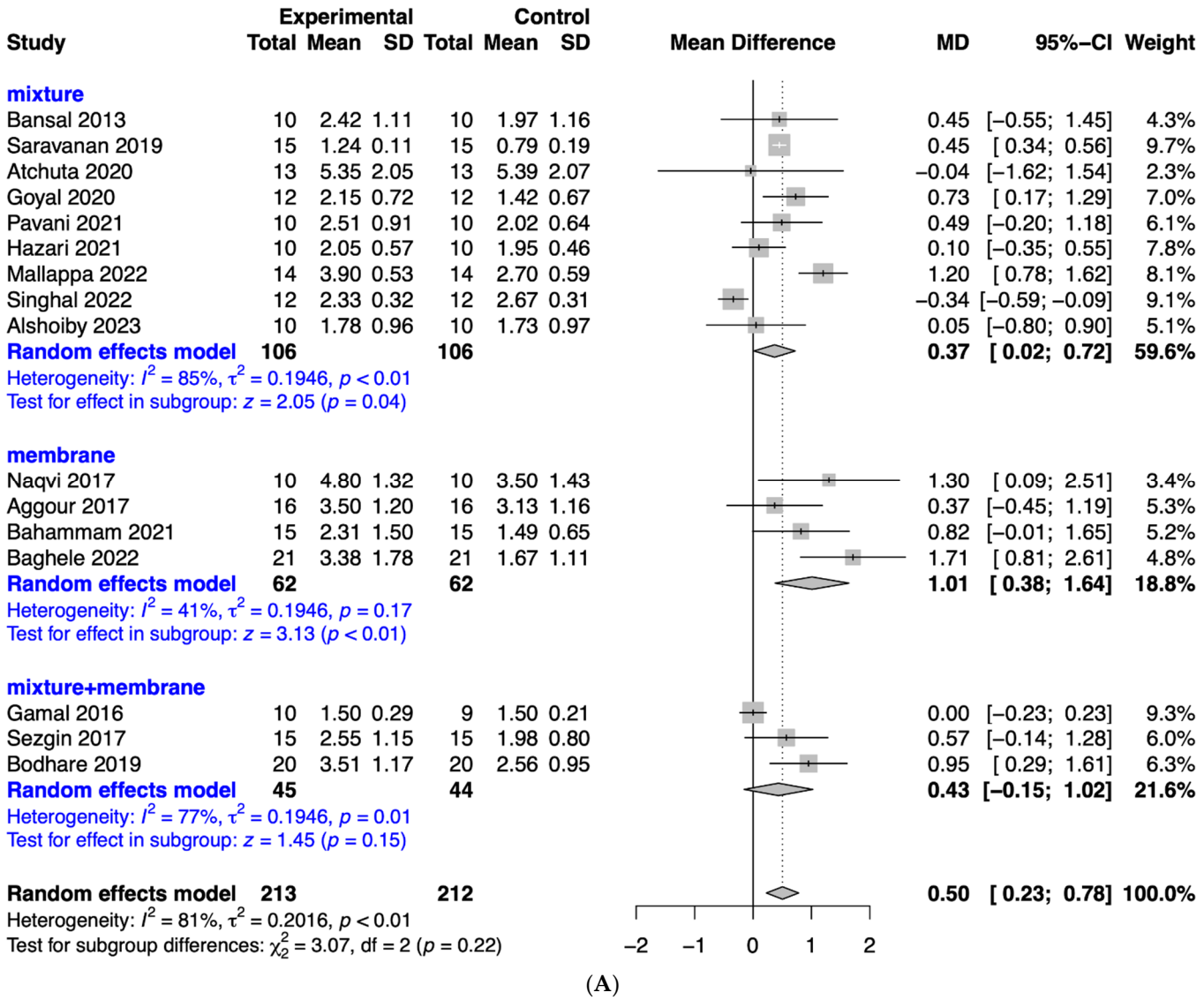
Figure 4. Forest plot illustrating the comparison between platelet-rich fibrin and control for improving clinical attachment level [19–28,30–36]. (**A**) Subgroup analysis categorized by application method. (**B**) Subgroup analysis categorized by types of graft material.

Figure 4B shows a subgroup analysis categorized by types of graft material. The results of the meta-analysis showed that the mean difference in clinical attachment level for platelet-rich fibrin for allografts was 0.34 (95% confidence interval, −0.60 to 1.27; $p = 0.48$). Subgroup analysis categorized by graft material of synthetic material resulted in the mean difference of clinical attachment level for platelet-rich fibrin being 0.81 (95% confidence interval, 0.30 to 1.32; $p < 0.01$). The mean difference in clinical attachment level for platelet-rich fibrin applied as a membrane was 0.66 (95% confidence interval, −0.21 to 1.53; $p = 0.14$).

3.6. Evaluation of the Effects of Platelet-Rich Fibrin on Bone Fill

In Figure 5A, a forest plot that visually represents the comparison between platelet-rich fibrin and the control group in terms of achieving bone fill is presented. The mean

difference, a robust marker of the efficacy of platelet-rich fibrin, stands resolute at an impressive 0.50. This value, encased within the reassuring confines of a 95% confidence interval that stretches from 0.23 to 0.78, signifies a noteworthy effect size. The magnitude of this finding cannot be overstated, for it points to a clear and statistically significant advantage in favor of platelet-rich fibrin in the realm of achieving bone fill. Subgroup analysis categorized by application method showed that platelet-rich fibrin, which is diced and mixed with the graft material, resulted in a mean difference of 0.37 (95% confidence interval, 0.02 to 0.72; $p = 0.04$). The mean difference in bone fill for platelet-rich fibrin applied as a membrane was 1.01 (95% confidence interval, 0.38 to 1.64; $p < 0.01$). Platelet-rich fibrin applied as a mixture with the graft material and additional application as a membrane showed the mean difference in bone fill for platelet-rich fibrin was 0.43 (95% confidence interval, −0.15 to 1.02; $p = 0.15$). Subgroup analysis categorized by application method did not reach statistical significance ($p = 0.22$).



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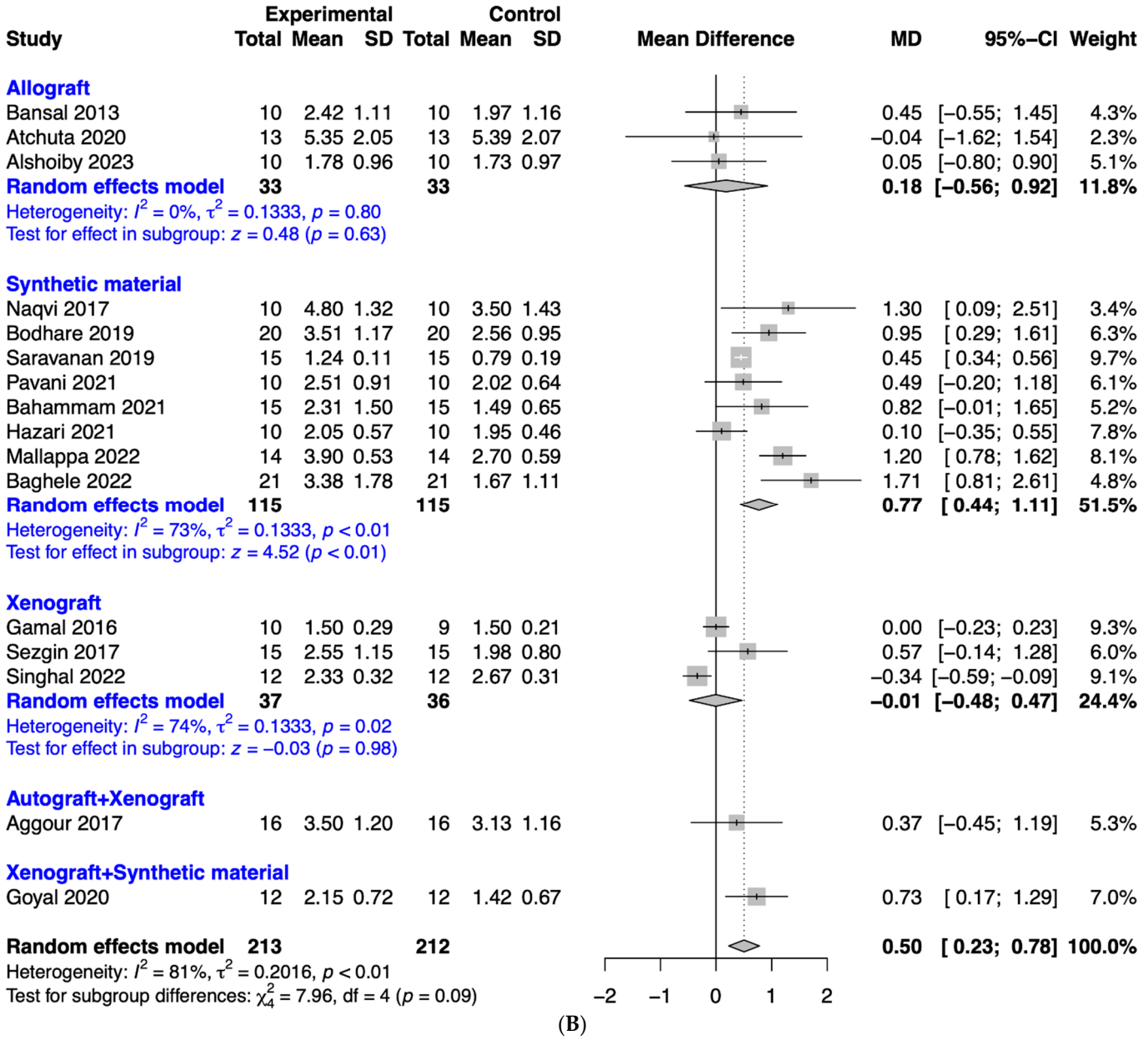

Figure 5. Forest plot illustrating the comparison between platelet-rich fibrin and control for obtaining bone fill [19–28,30–36]. (**A**) Subgroup analysis categorized by application method. (**B**) Subgroup analysis categorized by types of graft material.

Figure 5B shows a subgroup analysis categorized by types of graft material. The results of the meta-analysis showed that the mean difference in bone fill for platelet-rich fibrin applied with allograft was 0.18 (95% confidence interval, −0.56 to 0.92; p = 0.63). Subgroup analysis categorized by graft material of synthetic material resulted in the mean difference of bone fill for platelet-rich fibrin being 0.77 (95% confidence interval, 0.44 to 1.11; p < 0.01). Platelet-rich fibrin applied with xenograft showed the mean difference in bone fill for platelet-rich fibrin was −0.01 (95% confidence interval, −0.48 to 0.47; p = 0.98). However, subgroup analysis categorized by types of graft material did not reach significant difference (p = 0.09).

4. Discussion

In this study, a meta-analysis was conducted to analyze the effect of platelet-rich fibrin in mixture form with bone substitute, as a membrane, or in combination. The study

demonstrated the effectiveness of platelet-rich fibrin as a valuable addition to periodontal regeneration procedures.

In general, this meta-analysis demonstrated that platelet-rich fibrin offered substantial advantages in periodontal regeneration, as evidenced by a reduction in probing depth, an improvement in clinical attachment level, and an enhancement of bone fill. The application of a mixture, membrane, or a combination of both produced varying outcomes, which need to be considered clinically. The importance of customizing platelet-rich fibrin applications for particular clinical situations becomes evident due to the variability observed and the need to achieve optimal healing and regeneration. The utilization of platelet-rich fibrin in a mixture could potentially provide significant advantages due to its increased adaptability and interaction with the treatment site. This allows for a more direct and concentrated release of growth factors and cytokines, which are crucial for tissue regeneration. The use of platelet-rich fibrin as a membrane may be limited by its physical form, which could impede its ability to integrate and interact with the host tissue, potentially reducing its effectiveness. The application of the combined approach did not produce enhanced effects. Similarly, previous research indicated that the pairing of bone grafting material and enamel matrix derivative did not offer any additional advantages compared to using enamel matrix derivative alone [37,38].

Different outcomes emerged from using various bone graft materials, such as synthetic materials, allografts, and xenografts. The employment of synthetic materials as the graft choice yielded the most favorable outcomes when applied with platelet-rich fibrin. A previous report demonstrated the significance of choosing appropriate graft materials for successful treatment [39]. Synthetic materials are inorganic, biocompatible substitutes designed to mimic the properties of natural bone, effectively filling and repairing bone defects [40]. Indeed, beyond biocompatibility, the versatility of synthetic materials lies in their ability to be tailored in terms of pore diameter, porosity, and interconnectivity [41]. These modifications can significantly influence the material's integration with surrounding tissues, promoting better bone ingrowth and vascularization, which are essential for effective bone regeneration and healing. Through this study, we propose that the type of bone graft should also be considered when applying platelet-rich fibrin.

A biological substance called platelet-rich fibrin, which is created from a patient's own blood, has been employed in a number of surgical and dental procedures, including the repair of periodontal defects [42]. In an earlier study, platelet-rich fibrin was utilized to address endo-perio lesions, and the findings demonstrated an improvement in periodontal attachment along with a reduction in the depth of periodontal pockets [43]. A systematic review and meta-analysis assessing the impact of platelet-rich fibrin on periapical healing and the alleviation of clinical symptoms in patients undergoing periapical surgery revealed significant advantages, suggesting it could be regarded as a valuable complement to periapical surgical procedures [44]. Platelet-rich fibrin finds application in regenerative endodontic therapy due to its capacity to stimulate cellular proliferation and differentiation [45,46]. The utilization of platelet-rich fibrin has been linked to notable enhancements in various wound healing parameters, resulting in a more favorable outcome in terms of scar formation and overall scar appearance [47]. The combination of platelet-rich fibrin with nanosilver particles exhibited superior antimicrobial effectiveness compared to platelet-rich plasma with nanosilver [48]. Furthermore, when tested against anaerobic bacteria *E. faecalis* and yeast-like fungi Candida albicans, both platelet-rich fibrin and simple platelet-rich plasma demonstrated equivalent performance [48]. The utilization of platelet-rich fibrin in various dental fields is experiencing a significant increase. Platelet-rich fibrin has been observed to demonstrate noteworthy effectiveness when incorporated into dental implant procedures. The impact of platelet-rich fibrin on the stability of dental implants was evaluated, and it was shown that platelet-rich fibrin enhanced secondary implant stability, offering potential implications for clinical application [49]. The platelet-rich fibrin matrix was combined with peripheral blood mesenchymal stem cells to enhance implant stability, which was evaluated by measuring bone-to-implant contact using resonance frequency

analysis [50,51]. This approach showed promise as a regenerative material for improving and reinforcing bone-to-implant contact, ultimately enhancing implant stability. Utilizing platelet-rich fibrin in the alveolus following tooth extraction effectively diminished the discomfort associated with alveolar osteitis [52].

The variations in the impacts of platelet-rich fibrin may arise from differences in factors such as relative centrifugal force or revolutions per minute, the use of low-speed centrifugation versus high-speed centrifugation, as well as variations in centrifugation angles and platelet concentrations [4]. Platelet-rich fibrin was utilized in the management of multiple gingival recessions using the tunnel technique [53]. Platelet-rich fibrin has the potential to contribute to an increase in the percentage of mean root coverage [54]. The positive outcomes indicate that participants receiving platelet-rich fibrin may have benefited from adherence to oral hygiene instructions [55]. Different probing depths could potentially affect the outcomes when using platelet-rich fibrin in conjunction with graft material [56]. Moreover, due to individual differences in the activity of fibrin-rich platelets obtained from participants, standardization may be difficult.

The group that underwent open flap debridement along with the application of platelet-rich fibrin showed a notable reduction in their inflammatory score when compared to both the group that received open flap debridement alone and the group that only had platelet-rich fibrin applied [57]. The combination of platelet-rich fibrin with calcium carbonate nanoparticles has not only slowed down its resorption rate but also heightened its osteogenic and osteoinductive qualities [58]. An earlier publication indicated that the combination of platelet-rich fibrin with bone mesenchymal stem cells had a greater capacity to reduce the expression of Notch1 and Wnt3a while simultaneously activating the Notch1/Wnt3a signaling pathway more efficiently [59]. Furthermore, the use of platelet-rich fibrin also led to a significant decrease in the expression of the inflammatory cytokines TNFA and IL1B [57]. A split-mouth clinical trial conducted across multiple centers, using randomization, demonstrated that the application of platelet-rich fibrin resulted in a reduction in post-surgical swelling and pain [60].

This study contains several limitations. One of the most important aspects to consider is the heterogeneity of the included studies. The studies included in this meta-analysis may vary in terms of design, sample size, and methodological quality, which could affect the generalizability of the findings [61]. Variability in the studies, including variations in the local administration of platelet-rich fibrin, restricts our ability to draw clear conclusions from the data. Secondly, there may be a lack of standardization in the surgical procedures, proficiency level, and outcome measures. Publication bias has to always be considered, too. As with this meta-analyses, there is the potential for publication bias, where studies with positive results are more likely to be published than those with negative or inconclusive results [62]. To investigate publishing bias, we constructed a funnel plot and observed asymmetries that indicated some degree of publishing bias, even within the statistically significant region (Supplementary Figure S1). We evaluated the results after adjusting for publication bias using a trim-and-fill method. Before adjustment, all outcomes were significant, including decreased periodontal probing depth, improved clinical attachment level, and bone fill, but after applying trim and fill, the significance decreased (periodontal probing depth: $p = 0.1316$, clinical attachment level: $p = 0.3189$, and bone fill: $p = 0.0593$). Nevertheless, the initially observed significant results suggest a potential benefit of platelet-rich fibrin, and clinical application cannot be completely ruled out. These findings raise awareness of the impact publication bias can have on results and emphasize the importance of unpublished studies or studies reporting non-significant results. The significant impact of platelet-rich fibrin observed in the initial analysis could still be considered clinically important, suggesting that more extensive clinical studies are needed to provide further evidence.

This study underscores the therapeutic potential of this intervention and its potential to positively impact the fields of probing depth, clinical attachment level enhancement, and bone fill. Drawing from the existing body of literature, it can be inferred that platelet-rich

fibrin is effective as an adjunct to periodontal regeneration if applied in mixture form. Given the promising results observed in this meta-analysis on the efficacy of platelet-rich fibrin in periodontal regeneration, further investigation is needed to expand the understanding and application of platelet-rich fibrin in the dental field. Based on the conclusions obtained in this study, it is expected that the application of platelet-rich fibrin can be further expanded and the range of possible applications can be expanded.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/app14083371/s1, Figure S1: Contour-enhanced funnel plots; Table S1: Search strategy of the online databases; Table S2: Excluded studies from full-text reading; Table S3: Risk of bias. References [63–67] are cited in the supplementary materials.

Author Contributions: Conceptualization, W.-J.P., S.-H.H., N.J.K. and J.-B.P.; formal analysis, W.-J.P., S.-H.H., N.J.K. and J.-B.P.; writing—original draft preparation, W.-J.P., S.-H.H., N.J.K. and J.-B.P.; and writing—review and editing, W.-J.P., S.-H.H., N.J.K. and J.-B.P. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Conflicts of Interest: The authors declare no conflict of interest.

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