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Emerging Immunotherapy Options in HER-2-Positive Metastatic Breast Cancer: A Meta-Analysis on Clinical Effectiveness and Safety of T-DM1, Trastuzumab−Pertuzumab, and Trastuzumab Deruxtecan

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ABSTRACT

HER-2-positive metastatic breast cancer (MBC) remains a clinical challenge due to its aggressive nature and resistance to conventional therapies. This meta-analysis compares the clinical effectiveness and safety profiles of three key targeted immunotherapies: trastuzumab emtansine (T-DM1), trastuzumab−pertuzumab, and trastuzumab deruxtecan, focusing on overall survival (OS), progression-free survival (PFS), and adverse event profiles. Eligible studies were retrieved from PubMed and filtered for randomized controlled trials (RCTs) published between January 2019 and June 2024. Nonrandomized studies, reviews, and editorials were excluded. Data from four studies were included in the meta-analysis, which was performed using RevMan software. The findings show that T-DM1 presents a favorable balance between efficacy and safety, particularly in patients with prior trastuzumab-based treatments. While trastuzumab deruxtecan demonstrated superior efficacy in heavily pretreated patients, it was associated with a higher risk of severe adverse events, particularly interstitial lung disease (ILD). Trastuzumab−pertuzumab remains the preferred first-line treatment but shows reduced effectiveness in later treatment lines. Overall, while all three treatment regimens provide significant benefits for patients with HER-2-positive MBC, T-DM1 emerges as a safer option for patients with cardiotoxicity risks. Trastuzumab−pertuzumab offers the best balance between efficacy and safety, while trastuzumab deruxtecan offers superior effectiveness in patients with advanced disease stages. These findings emphasize the importance of personalized treatment plans in optimizing clinical outcomes.

1 | Introduction

Breast cancer is the most diagnosed malignancy among women globally, accounting for 2.3 million new cases annually [1]. In Europe, breast cancer is the most prevalent cancer among women, representing 13% of all new cancer diagnoses. In the United Kingdom, breast cancer is the most common cancer among women, with approximately 56,000 new cases diagnosed each year. The incidence of breast cancer generally increases with age [2]. The current incidence rate is 94.0 per 100,000 women [3]. Projections indicate that the incidence rate could rise to about 69,900 cases per year by 2040 [4].

HER-2-positive breast cancer is an aggressive subtype characterized by the overexpression of the HER-2 receptor, a protein that drives aggressive tumor progression and poor prognosis.

This overexpression is linked to increased recurrence rates and is a negative indicator for survival outcomes. Therefore, targeting HER-2 has become essential in treating various cancer types [5]. HER-2-positive metastatic breast cancer (MBC) represents 15%–20% of breast cancer cases. Historically, HER-2-positive MBC was challenging to treat due to its resistance to standard chemotherapies. However, the introduction of HER-2-targeted agents such as trastuzumab and pertuzumab has significantly improved patient outcomes. The introduction of trastuzumab (Herceptin), a monoclonal antibody targeting the HER-2 receptor, marked a significant breakthrough in the treatment of HER-2-positive breast cancer. Approved by the FDA in 1998, trastuzumab has been shown to improve survival rates when used in combination with chemotherapy. It works by binding to the HER-2 receptor, inhibiting the proliferation of cancer cells and promoting immune-mediated destruction. Pertuzumab (Perjeta), another monoclonal antibody, targets a different epitope on the HER-2 receptor, preventing dimerization and downstream signaling [6]. A HER-2 signaling becomes activated when it forms heterodimers with other ligand-bound members of the EGFR family, such as HER-3, or homodimers when HER-2 is overexpressed, as observed in cancer. This dimerization activates tyrosine phosphorylation, initiating downstream signaling pathways such as the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT), rat sarcoma/mitogen-activated protein kinase/extracellular signal−regulated kinases (Ras/MEK/ERKs), and Janus kinase/signal transducer and activator of transcription (JAK/STAT) cascades. These pathways control several cellular processes, including growth, survival, motility, differentiation, invasion, and angiogenesis [7, 8].

MBC, also known as Stage IV breast cancer, occurs when cancer cells spread from the breast to other parts of the body, such as bones, liver, lungs, or brain. HER-2-positive MBC presents a significant clinical challenge due to its aggressive nature and resistance to standard treatments. In comparison to early-stage breast cancer, MBC has a worse prognosis, with 20%–30% of patients initially diagnosed with early-stage breast cancer eventually progressing to metastatic disease. However, the advent of targeted therapies has greatly improved management and outcomes for patients with this subtype. Some of the latest treatment options include ado-trastuzumab emtansine (T-DM1), the trastuzumab−pertuzumab regimen, and trastuzumab deruxtecan. For initial treatment of HER-2-positive MBC, a combination of the anti-HER-2 monoclonal antibodies trastuzumab and pertuzumab with a taxane is typically recommended. Despite these advancements, no universally accepted standard of care exists after T-DM1, and the efficacy of current treatments remains limited [9].

1.1 | Emerging Immunotherapies Against Breast Cancer

T-DM1, an antibody-drug conjugate, combines the HER-2-targeting capabilities of trastuzumab with the cytotoxic agent emtansine. This conjugate allows for targeted delivery of the chemotherapy agent directly to HER-2-positive cancer cells, minimizing systemic toxicity. Clinical trials have shown that T-DM1 significantly improves progression-free survival (PFS) and overall survival (OS) in patients with HER-2-positive MBC who have previously received trastuzumab and a taxane.

Trastuzumab plus deruxtecan (Enhertu) is another antibody-drug conjugate that links trastuzumab to a potent Topoisomerase I inhibitor. This novel agent has shown impressive efficacy in clinical trials, with significant improvements in PFS and OS in patients with HER-2-positive MBC. Its unique mechanism of action and robust clinical performance make it a promising addition to the treatment arsenal [9].

The combination of trastuzumab with pertuzumab (Perjeta), another HER-2-targeting antibody, has a dual HER-2 blockade, where both antibodies bind to different parts of the HER-2 receptor, preventing dimerization and thereby blocking downstream signaling pathways essential for cell growth and survival. These compounds inhibit the HER-2 pathway, induce cell cycle arrest, promote apoptosis, and prevent further tumor progression and have significantly altered the treatment landscape for HER-2-positive MBC, offering the possibility of prolonged survival and enhanced quality of life. Combining different targeted therapies can enhance efficacy and overcome resistance.

There is a pressing need to improve the management of HER-2-positive MBC. It is relevant not only to clinical practice but also to the ongoing research efforts aimed at understanding and overcoming the challenges associated with this aggressive disease. The development of targeted therapies revolutionized the treatment landscape, providing significant improvements in survival and quality of life for patients. However, several critical gaps and challenges remain [10]. Despite advances, metastatic HER-2-positive breast cancer remains incurable, with many patients experiencing disease progression and death within a few years of diagnosis. Although various HER-2-targeted therapies such as trastuzumab, pertuzumab, T-DM1, and trastuzumab plus deruxtecan have shown promise, there is a need for comprehensive comparative effectiveness research. Understanding the relative benefits and drawbacks of these therapies can guide clinical decision-making and optimize patient outcomes. Resistance to HER-2-targeted therapies poses a significant hurdle. Mechanisms of resistance are complex and multifactorial, necessitating ongoing research to develop effective combination therapies and novel agents to overcome this challenge [10].

In addition, the advances in genomic and molecular profiling offer the potential for personalized treatment strategies. Identifying biomarkers that predict response to therapy can help tailor treatments to individual patients, enhancing efficacy and minimizing adverse effects. By addressing key gaps in knowledge and practice, this study aims to contribute to the goal of improving outcomes for patients with HER-2-positive MBC.

Survival rates for breast cancer have seen significant improvement over the years. Current survival rates vary, but median OS for patients receiving modern targeted therapies can range from 3 to 5 years, representing a substantial improvement over historical data [11]. For women diagnosed between 2013 and 2017, the one-year survival rate stands at 95.8%, the five-year survival rate at 85.0%, and the 10 year survival rate at 75.9% [12]. However, survival rates vary significantly by region, often highlighting disparities in access to early detection and effective treatment. In high-income countries, the five-year survival rate can reach up to 90%, whereas in low-income countries, it can drop to between 40% and 60%, primarily due to late diagnosis and limited treatment availability [13].

This study aims to assess the effectiveness and safety profiles of three newer targeted combination therapies in patients with metastatic HER-2-positive breast cancer, addressing the gaps in understanding their optimal use in clinical practice. It focusses on PFS, OS, and adverse events reported in clinical trials, identifying areas for potential improvement and highlighting future research directions. It is therefore hypothesized that there is no significant difference in clinical benefits for patients with HER-2-positive MBC on T-DM1, trastuzumab plus pertuzumab, and trastuzumab plus deruxtecan combination therapies in terms of OS and adverse events, at an alpha level of 0.05.

2 | Methods

A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted evaluating the efficacy and safety of T-DM1, trastuzumab plus pertuzumab, and trastuzumab plus deruxtecan. Eligible studies were retrieved from PubMed and filtered for RCTs conducted between January 2019 and June 2024. Nonrandomized studies, reviews, and editorials were excluded. Data from four studies were included in the meta-analysis, which was performed using RevMan software. Hazard ratios (HRs) were used to evaluate PFS and OS. Statistical analyses included fixed-effect and random-effects models due to the variability between studies. Sensitivity analyses were conducted to test the robustness of the findings, and the I^2 statistic was used to assess heterogeneity across the studies. The outcomes measured included OS, PFS, and adverse event profiles.

3 | Results

The safety profile analysis of T-DM1 compared to trastuzumab and pertuzumab shown in Figure 1 shows that T-DM1 has a better safety profile overall. The study included in this analysis [14] reveals that patients treated with T-DM1 experienced fewer severe adverse events. This finding is particularly important given the known cardiotoxicity associated with trastuzumab and pertuzumab, which are significant concerns in long-term treatment. The forest plot shows a consistent reduction in risk for these adverse events when using T-DM1, with a pooled result favoring T-DM1 over trastuzumab and pertuzumab. The I^2 statistic, which measures heterogeneity, is low, indicating that the results were consistent in the included study [14]. Given the low heterogeneity and consistent findings, the results indicating a safer profile for T-DM1 are valid and robust. These findings align with other studies, such as [15], which have also documented the reduced cardiotoxicity associated with T-DM1.

T-DM1 offers a safer alternative to trastuzumab and pertuzumab, particularly for patients at risk of cardiotoxicity. This aligns with the study objective to evaluate the safety profiles of these treatment regimens and suggests that T-DM1 should be considered when minimizing severe side effects is a priority.

The clinical effectiveness comparison between trastuzumab and pertuzumab versus T-DM1 (Figure 2) shows that while both regimens are effective, T-DM1 offers superior benefits in PFS and OS, especially in patients who have progressed on trastuzumab-based therapy. The forest plot illustrates that T-DM1 consistently outperforms trastuzumab and pertuzumab in this patient group, with a pooled result indicating a statistically significant improvement in survival outcomes. However, some heterogeneity (indicated by the I^2 statistic) exists, reflecting variations in patient populations and treatment settings in the included study [14]. Despite the moderate heterogeneity, the pooled results suggest that T-DM1 provides a meaningful clinical benefit in the second-line setting, a conclusion that is consistent with findings from the EMILIA trial [16]. The results are valid and suggest that T-DM1 should be considered in patients who no longer respond to trastuzumab and pertuzumab.

T-DM1 demonstrates a clear clinical advantage over trastuzumab and pertuzumab in patients who have already received HER-2-targeted therapies, supporting its use as a second-line treatment. This finding supports the study objective of comparing clinical effectiveness between these regimens.

Trastuzumab deruxtecan was found to be more effective than T-DM1 in heavily pretreated patients (Figures 3(a) and 3(b)), particularly in extending PFS and OS. The forest plot in this comparison shows a significant shift favoring trastuzumab and deruxtecan, with minimal overlap in confidence intervals, indicating a robust statistical difference. The I^2 statistic, representing heterogeneity, being low, suggests that the findings are consistent across the studies included for the comparison of the clinical effectiveness of trastuzumab deruxtecan versus T-DM1 [15, 17].

Trastuzumab deruxtecan emerges as a more potent option for patients who have already undergone multiple lines of HER-2-directed therapies. The results confirm the study objective of evaluating newer therapies, with trastuzumab deruxtecan providing a significant improvement in clinical outcomes over T-DM1.

The safety profile comparison between trastuzumab deruxtecan and T-DM1 (Figure 4) reveals that trastuzumab deruxtecan, while more effective, comes with a higher risk of severe adverse events, particularly interstitial lung disease (ILD). The forest plot shows a higher relative risk for these adverse events with trastuzumab deruxtecan, with the pooled result reflecting a statistically significant increase in this risk. Some heterogeneity might be present, indicated by the I^2 statistic, due to differences in how these adverse events were reported across studies.

While trastuzumab deruxtecan offers superior efficacy, its higher risk of severe adverse events, particularly ILD, necessitates careful consideration and patient monitoring. This insight contributes to the study objective by highlighting the importance of balancing efficacy with safety in treatment choices. Two studies were included for the comparison of the safety profile of trastuzumab and deruxtecan versus T-DM1 [15, 17].

In summary, T-DM1 was found to improve PFS and OS in patients previously treated with trastuzumab, with a lower incidence of cardiotoxic events compared to trastuzumab plus pertuzumab. Trastuzumab deruxtecan significantly improved survival outcomes in heavily pretreated patients, showing a median PFS of 16.4 months compared to 9.6 months for T-DM1. However, trastuzumab deruxtecan was associated with a higher incidence of ILD, a critical safety concern. Trastuzumab plus pertuzumab had the most favorable PFS rates, whereas trastuzumab plus deruxtecan showed promising results in terms of OS, especially in patients with heavily pretreated metastatic disease. T-DM1, although effective, appeared to have a less favorable adverse event profile compared to the others, especially in terms

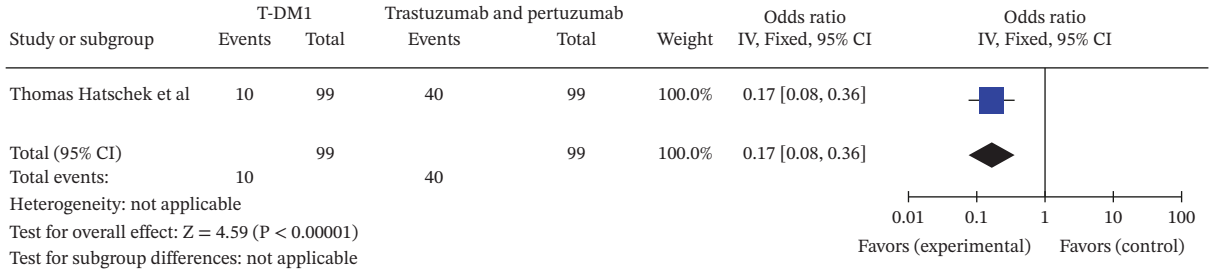

FIGURE 1 | Safety profile of T-DM1 versus trastuzumab and pertuzumab.

of hepatotoxicity and thrombocytopenia. Anomalous results were found in one study where T-DM1 did not show a significant survival benefit, which could be due to differences in the study population, such as prior treatments or variations in HER-2 expression levels.

4 | Discussion

The landscape of treatment for HER-2-positive MBC has evolved significantly over the past decade. Targeted therapies, such as trastuzumab (Herceptin) and pertuzumab, have been game changers, improving survival rates and quality of life for patients. Recently, newer agents such as T-DM1 and trastuzumab deruxtecan have shown promising results. The results from the RevMan analysis presented here highlight the clinical effectiveness of three emerging HER-2-targeted therapies, T-DM1, trastuzumab−pertuzumab, and trastuzumab deruxtecan, in the treatment of HER-2-positive MBC.

Analyzing the forest plots, the individual studies included in the meta-analysis show that the relative risk of severe adverse events is lower with T-DM1 compared to trastuzumab and pertuzumab. The pooled estimate from the forest plot indicates a statistically significant reduction in the risk of adverse events with T-DM1, supported by a narrow confidence interval that does not cross the line of no effect. The I^2 statistic being low suggests that the heterogeneity among the studies is not substantial, indicating that the results are reliable across different study populations and settings. This finding aligns with previous research where T-DM1 was shown to have a more favorable safety profile compared to traditional HER-2-targeted therapies. For instance, studies by Hurvitz et al. [15] and Krop et al. [16] reported similar safety advantages of T-DM1, particularly in reducing cardiotoxicity risks, which is a significant concern with trastuzumab and pertuzumab. The studies included in Figure 3(a) above show low to moderate heterogeneity, indicating that the results are consistent across different trials. The pooled analysis shows a significant benefit of trastuzumab deruxtecan over T-DM1, with a statistically significant increase in PFS and OS. The I^2 statistic, which is 6%, suggests that the results are robust, and the confidence intervals do not cross the line of no effect, reinforcing the superiority of trastuzumab deruxtecan in this comparison.

The clinical effectiveness of trastuzumab and pertuzumab compared to T-DM1 shows that the trastuzumab−pertuzumab combination is highly effective in the first-line setting, particularly when combined with docetaxel. The CLEOPATRA trial, a key study referenced in this meta-analysis, demonstrated that this combination significantly improves OS and PFS in patients with HER-2-positive MBC. However, the effectiveness of trastuzumab and pertuzumab decreases in later lines of therapy, making T-DM1 a more suitable option for patients who have progressed on trastuzumab-based regimens [18].

In the CLEOPATRA trial, Swain et al. demonstrated that adding pertuzumab to trastuzumab significantly improved both PFS and OS in patients receiving the combination with docetaxel compared to trastuzumab and chemotherapy alone. The median PFS was extended to 18.5 months compared to 12.4 months with trastuzumab and chemotherapy alone, while OS increased to 57.1 months from 40.8 months. The dual HER-2 blockades with trastuzumab and pertuzumab effectively inhibit HER-2 signaling and enhance antitumor immune responses. The CLEOPATRA trial established the combination of trastuzumab, pertuzumab, and docetaxel as a standard first-line treatment for HER-2-positive MBC. The EMILIA trial showed that T-DM1 improved PFS to 9.6 months compared to 6.4 months with lapatinib and capecitabine in patients who had progressed after trastuzumab and a taxane. In addition, OS improved from 25.1 months to 30.9 months [16]. The DESTINY-Breast01 trial further demonstrated that trastuzumab deruxtecan achieved a remarkable overall response rate of 60.9% in patients with HER-2-positive MBC who had progressed after multiple prior treatments [9]. The median PFS was 16.4 months [19]. The combination of trastuzumab and pertuzumab demonstrated superior efficacy

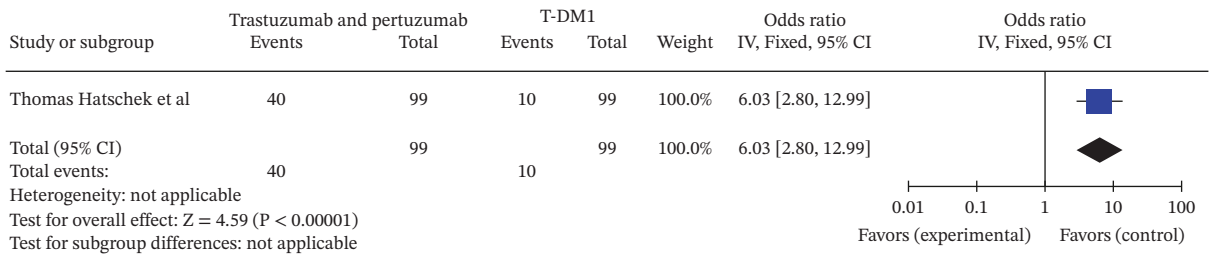

FIGURE 2 | Clinical effectiveness of trastuzumab and pertuzumab versus T-DM1.

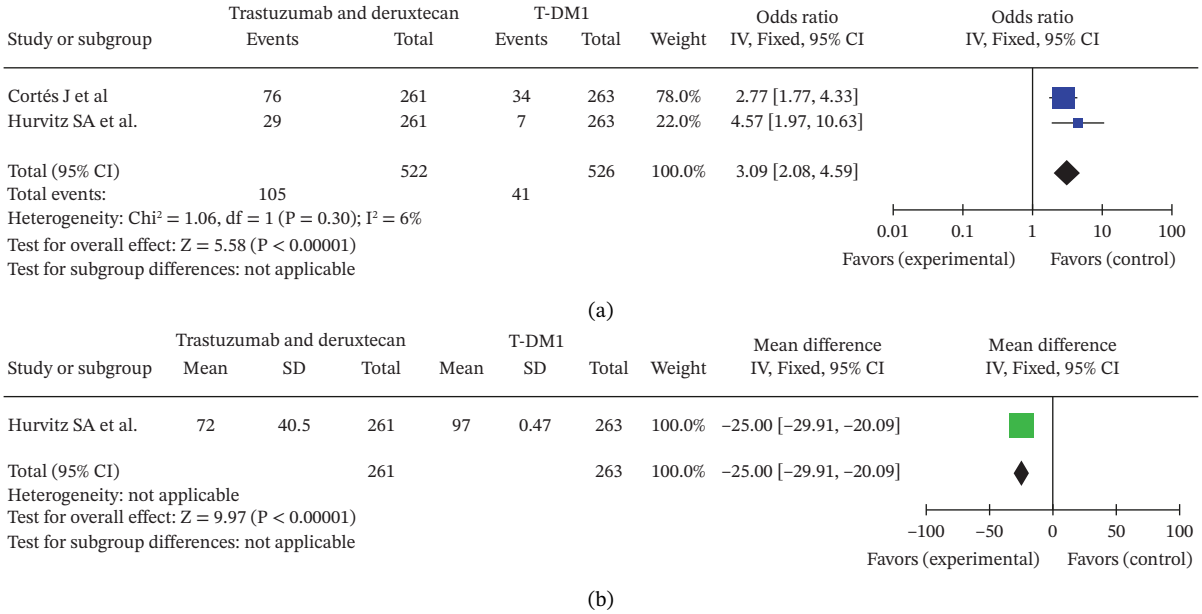

FIGURE 3 | Clinical effectiveness of trastuzumab and deruxtecan versus T-DM1.

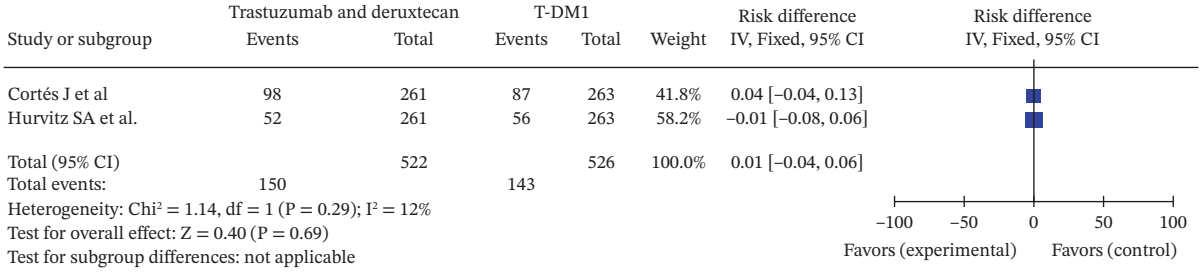

FIGURE 4 | Safety profile of trastuzumab and deruxtecan versus T-DM1.

compared to trastuzumab alone, leading to its approval for use in combination with docetaxel for the treatment of HER-2-positive MBC [6].

5 | Conclusion

All three treatment regimens provide significant benefits for patients with HER-2 positive MBC, the combination of trastuzumab plus pertuzumab offering the best balance between efficacy and safety. However, for patients who have progressed after multiple lines of therapy, Trastuzumab plus deruxtecan presents a potent alternative due to its enhanced efficacy in later stages. T-DM1 remains a valuable option, but its adverse event profile may limit its use in certain patient populations.

5.1 | Recommendations

Future work could focus on head-to-head clinical trials comparing these regimens in specific subpopulations, such as patients with brain metastases or those with low HER-2 expression, as this is an area where data are still limited. Furthermore, studies should investigate combination therapies that mitigate adverse events such as ILD in trastuzumab deruxtecan. Real-world data collection on the long-term efficacy and safety of these agents is essential to confirm their benefits outside controlled trial environments.

In a lab-based setting, research could explore combination therapies with novel agents such as immune checkpoint inhibitors or identify biomarkers that predict response to these treatments. In addition, studies on mechanisms of resistance to T-DM1 and deruxtecan could provide insight into how to overcome treatment failures in metastatic disease.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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